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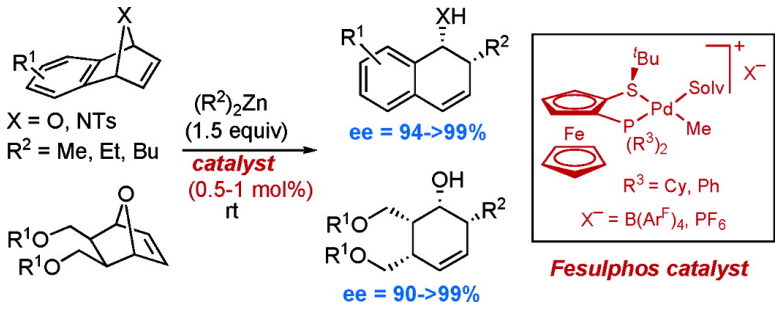
J. Am. Chem. Soc., **2005**, 127 (50), 17938-17947• DOI: 10.1021/ja055692b • Publication Date (Web): 23 November 2005



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Fesulphos-Palladium(II) Complexes as Well-Defined Catalysts for Enantioselective Ring Opening of Meso Heterobicyclic Alkenes with Organozinc Reagents

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Abstract: The air-stable and readily available cationic methyl palladium(II) complexes of planar chiral Fesulphos ligands [(Fesulphos)Pd(Me)(PhCN)]$^+$ X$^-$ are highly efficient catalysts for the alkylative ring opening of oxa- and azabicyclic alkenes with dialkylzinc reagents, showing broad scope with regards to both the bicyclic substrate and the dialkylzinc reagent. Catalyst loading as low as 0.5 mol % is sufficient to achieve good yields and enantioselectivities ranging 94 → 99% ee in most cases. {Fesulphos = (1-phosphino-2-sulfenylferrocene); X$^-$ = tetrakis[3,5-bis(trifluoromethyl)phenyl]borate or PF_6^-].} The origin of the high asymmetric induction has been rationalized by mechanistic studies combining computational calculations and X-ray structural analysis.

Introduction

Two main structural concepts have proved to be greatly successful in the design of chiral ligands for asymmetric catalysis.[1] The first concept is the reduction of the number of possible diastereomeric transition states by using bidentate C_2-symmetrical chiral ligands with P/P, N/N, or O/O coordination (e.g., BINAP, bisoxazolines, salen, or BINOL based ligands), some of which have reached the status of "privileged ligands" because of their broad applicability.[2] The second strategy relies on mixed bidentate structures equipped with a strong and weak donor heteroatom pair, taking advantage of the different electronic properties associated with each heteroatom−metal bond (e.g., the trans influence). This electronic differentiation, together with appropriate steric effects around the metal coordinating heteroatoms, may create an asymmetric environment capable of inducing high levels of enantiocontrol. Some bidentate P/N chiral ligands such as phosphine−oxazoline systems and QUINAP constitute excellent examples of the latter strategy.[3]

Although much less developed than the mixed P/N ligands, in recent years considerable effort has been devoted to the synthesis of chiral ligands based on a P/S coordination mode.[4] In addition to the strong electronic differentiation imposed by the phosphorus and sulfur bonding to the metal, a key structural feature makes phosphine-thioether chiral ligands very appealing structures: the sulfur atom becomes stereogenic upon coordination to the metal, which imposes a unique asymmetric environment very close to the reactive metal center. Despite this, P/S ligands reported to date have been successfully applied only to a limited range of asymmetric transformations, being their asymmetric reaction scope far away from that of the best ligands based on P/P, N/N, or P/N coordination modes.

Within this context, we have recently developed a highly tunable family of P/S ligands having only planar chirality, the 1-*phos*phino-2-*sul*fenyl*fe*rrocenes (*Fesulphos* ligands **1**, Chart 1).[5] These compounds are readily prepared following a modular three-step approach from commercially available ferrocene: sulfinylation of ferrocenyllithium, fully diastereoselective *ortho*-

(1) For excellent overviews on asymmetric catalysis, see: (a) *Comprehensive Asymmetric Catalysis*; Jacobsen, E. N., Pfaltz, A., Yamamoto, H., Eds.; Springer-Verlag: Berlin, 1999. (b) Williams, J. M. J. *Catalysis in Asymmetric Synthesis*; Academic Press: Sheffield, 1999. (c) *Catalytic Asymmetric Synthesis*, 2nd ed.; Ojima, I., Ed.; Wiley-VCH: New York, 2000. See also: (d) Trost, B. M. *PNAS* **2004**, *101*, 5348.

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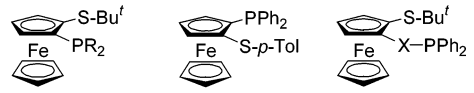
10.1021/ja055692b CCC: $30.25

Chart 1. Fesulphos Family of Ligands (ee >99%)



(*R*)-**1** (*S*)-**1h** (*R*)-**1i**, X=CH_2 (*R*)-**1j**, X=NH

1a, R = Ph
1b, R = (*p*-F)C_6H_4
1c, R = *o*-Tol
1d, R = 1-Naph
1e, R = Cy
1f, R = 2-Fur
1g, R = (*p*-CF_3)C_6H_4

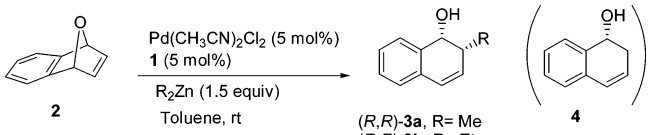
deprotonation/phosphonation of the resulting enantiopure sulfinylferrocene, and subsequent sulfoxide to thioether reduction. Interestingly, a very bulky substitution at sulfur (*tert*-butyl group) leads to a single epimer at sulfur upon coordination to a transition metal such as Pd(II),[5,6] Pt(II),[6] or Cu(I)[6,7] that orients the *tert*-butyl group on sulfur in anti arrangement with regard to the ferrocene unit. By fine-tuning the steric and electronic properties at phosphorus, these ligands have proved to afford very high enantioselectivities in a variety of reactions such as the palladium-catalyzed allylic substitution,[5] the Diels−Alder reaction of cyclopentadiene with *N*-acryloyl oxazolidinones,[6] and the formal aza Diels−Alder reaction of sulfonyl aldimines with activated dienes.[7] As an extension of the applicability of Fesulphos ligands in asymmetric catalysis, herein we describe that these P,S-ligands, in combination with a palladium(II) source, act as extremely efficient catalysts in the alkylative ring-opening reaction of meso oxa- and azabicyclic alkenes with organozinc reagents.[8] In particular, their isolable, air-stable, and structurally well-defined cationic methyl-palladium complexes feature low catalyst loading, very high enantioselectivity, easy fine-tuning, mild reaction conditions, and broad structural scope.[9]

Results and Discussion

Desymmetrization of Meso Oxabenzonorbornadienes in the Presence of a Combination of $PdCl_2(CH_3CN)_2$ and Fesulphos Ligands. One of the most recent and interesting enantioselective processes mediated by palladium catalysts is the nucleophilic alkylative ring opening of meso oxabicyclic and azabicyclic alkenes with dialkylzinc reagents reported by Lautens et al.[8] For this transformation, chiral phosphino-oxazolines (especially *t*-Bu-PHOX),[8a−d] Tol-BINAP,[8a−d] MeOBiphep,[8e] and the P-chiral diphosphine QuinoxP*[8f] proved to be highly efficient ligands, affording the final alcohols with excellent enantioselectivities (up to 97.6% ee).

To check the feasibility of Fesulphos ligands in this transformation, we chose as a model reaction the ring-opening addition of Et_2Zn to 7-oxabenzonorbornadiene (**2**) under the standard reported reaction conditions:[8] Et_2Zn (150 mol %), Pd-

Table 1. Asymmetric Ring Opening of 7-Oxabenzonorbornadiene with Me_2Zn and Et_2Zn Using Fesulphos Ligands **1**



2 (*R*,*R*)-**3a**, R= Me (*R*,*R*)-**3b**, R= Et **4**

entry	ligand	R	*t* (h)	product	yield[a] (%)	ee[b] (%)
1	**1a**	Me	48	**3a**	72	88
2	**1a**	Et	24	**3b**	70	88
3	**1b**	Me	48	**3a**	63	82
4	**1b**	Et	24	**3b**	20[c]	81
5	**1c**	Me	96	**3a**	15	74
6	**1c**	Et	96	**3b**	15	31
7	**1d**	Me	96	**3a**	15	55
8	**1d**	Et	96	**3b**	27	14
9	**1e**	Me	24	**3a**	73	94
10	**1e**	Et	96	**3b**	68	93
11	**1f**	Me	96	**3a**	68	73
12	**1f**	Et	96	**3b**	33	57
13	**1g**	Me	24	**3a**	65	67
14	**1g**	Et	18	**3b**	16[d]	70
15	**1h**	Et	96	**3b**	30	6
16	**1i**	Et	96	**4**	*e*	
17	**1j**	Et	96	**3b**	NR	

[a] In pure product after chromatography. [b] Determined by chiral HPLC (Chiralpak AD column). [c] Product **4** was also obtained in 37% yield. [d] Product **4** was also obtained in 40% yield. [e] Alcohol **4** was formed as the main product.

$(CH_3CN)_2Cl_2$ (5 mol %), Fesulphos **1a** (5 mol %) in CH_2Cl_2 at room temperature. Pleasingly, the reaction was complete in 24 h, providing selectively the cis-dihydronaphthol (*R*,*R*)-**3b**[10] in 86% yield with 80% ee. With this promising preliminar result in hand, a brief study of solvents led us to find that the enantioselectivity was somewhat higher in toluene (88% ee) and 1,2-dichloroethane (84% ee), while xylene (60% ee), chloroform (42% ee), and diisopropyl ether (32% ee) produced a substantial decrease of asymmetric induction.

Having established toluene as an optimal solvent, Table 1 shows the results obtained in the reaction of **2** with Et_2Zn and Me_2Zn in the presence of Fesulphos ligands with different substitutions at phosphorus and sulfur (ligands **1a**−**j**). Some relevant conclusions can be drawn from this study:

(a) By far, the best reactivity profile was observed with ligands **1a** and **1e**, which led to complete conversions within 24 h of reaction (entries 1−2 and 9−10). In contrast, low yields were obtained in the case of the bulky phosphines **1c** and **1d** (entries 5−8), the difurylphosphine **1f** (entries 11 and 12), and the *p*-tolylsulfenyl ligand **1h** (entry 15), due to incomplete conversions after 24 h. The addition of Et_2Zn to **2** in the presence of the electron poor phosphines **1b** and **1g** resulted in the formation of dihydronaphthol **4** as the main product, via a reductive ring-opening process (entries 4 and 14).

(b) With ligands **1i** (entry 16), homologous with regard to **1a**, and **1j** (entry 17) either no reaction or formation of the reductive ring-opened product **4** was observed, suggesting that the formation of six-membered palladacycle intermediates instead of five-membered ones preclude the alkylative ring opening process.

(c) As in previously studied reactions with Fesulphos ligands,[5−7] the presence of the bulky *tert*-butyl group at sulfur

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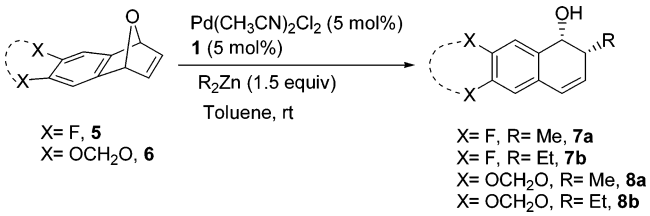
(10) The absolute configuration of the alcohols **3a**−**b**, **7a**−**b**, **8a**−**b**, and **16a** was established by comparison with the chiral HPLC data reported for both enantiomers of these compounds (see refs 8a−d).

Table 2. Asymmetric Ring Opening of Substituted Oxabenzonorbornadienes with Me_2Zn and Et_2Zn Using Fesulphos Ligands **1**



entry	substrate	ligand	R	*t* (h)	product	yield[a] (%)	ee[b] (%)
1	**5**	**1a**	Me	96	**7a**	43	92
2	**5**	**1a**	Et	24	**7b**	72	80
3	**5**	**1b**	Me	96	**7a**	30	88
4	**5**	**1b**	Et	96	**7b**	<15	
5	**5**	**1e**	Me	48	**7a**	38	88
6	**5**	**1e**	Et	96	**7b**	<10	
7	**6**	**1a**	Me	96	**8a**	47	88
8	**6**	**1a**	Et	24	**8b**	70	82
9	**6**	**1b**	Me	96	**8a**	35	>99
10	**6**	**1b**	Et	48	**8b**	53	76
11	**6**	**1e**	Me	96	**8a**	42	86
12	**6**	**1e**	Et	96	**8b**	38	76

[a] In pure product after chromatography. [b] Determined by chiral HPLC.

was essential for achieving high asymmetric inductions. Thus, it was not surprising that nearly racemic product **3b** was isolated in the reaction catalyzed by the *p*-tolylsulfenyl ligand **1h** (entry 15), whereas the corresponding *tert*-butylsulfenyl ligand **1a** provided **3b** with 88% ee.

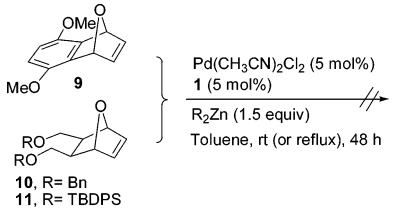
(d) The dicyclohexylphosphine **1e** provided the highest asymmetric inductions, affording the alcohols **3a** and **3b** with excellent 94% and 93% ee, respectively (entries 9 and 10). The rest of the ligands showed lower asymmetric inductions than the parent diphenylphosphino ligand **1a**.

Next, to evaluate the substrate compatibility of our catalyst system, we performed the reaction of the meso electron-poor substrate **5**[11] and the electron-rich alkene **6**[12] with Et_2Zn and Me_2Zn in the presence of the three Fesulphos ligands (**1a**, **1b**, and **1e**) that showed the best asymmetric inductions in the model reaction with **2** (Table 2). From a stereoselectivity point of view, the three ligands behaved rather homogeneously, leading to the cis dihydronaphthols **7** and **8** with enantioselectivities in the range 76−92% ee. The exception to this behavior was found in the reaction of **6** with Me_2Zn promoted by ligand **1b**, in which a single enantiomer of **8a** was isolated (ee >99%, entry 9).

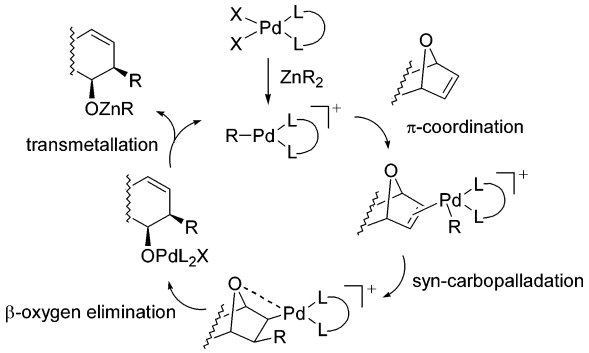
However, compared to the results obtained with the parent substrate **2**, an important drawback associated with the ring-opening of **5** and **6** was the usually low to moderate reaction conversions and/or the competitive formation of reductive ring-opened byproducts. Even prolonged reaction times (4 days instead of 24 h) or higher temperatures did not significantly improve the chemical yields.

A more dramatic example of this insufficient reactivity was observed from the bicyclic substrates **9**, **10**, and **11**, which were recovered unaltered after 48 h of reaction with Et_2Zn or Me_2Zn in the presence of $PdCl_2(CH_3CN)_2$ and ligands **1a** or **1e** (Scheme 1).

Scheme 1. Unreactive Substrates in the Presence of Ligands **1**



Scheme 2. Proposed Catalytic Cycle



Mechanistic studies described by Lautens et al. support the enantioselective carbopalladation of the C−C double bond of the bicyclic alkene by a presumed cationic alkyl palladium intermediate $[L_2PdR]^+$ generated in situ from $PdCl_2(CH_3CN)_2$ and R_2Zn as the key step of the reaction pathway. The subsequent fast β-oxygen elimination of the resulting σ-alkyl palladium species would afford the observed cis-substituted product (Scheme 2).[8c] In agreement with this proposal, it has been recently described that the cationic μ-hydroxo complex $[\{Pd((R)\text{-BINAP})(\mu\text{-OH})\}_2]^{2+}(OTf^-)_2$ is a much more active catalyst than BINAP in the reaction of oxabicycle **2** with Et_2Zn.[8d] Inspired by this mechanistic work, we envisaged the preparation of cationic methylpalladium complexes of Fesulphos $[(\mathbf{1})PdMe]^+$ with the aim of developing much more active catalysts. In fact, if these cationic palladium complexes act as the actual active catalytic species in this process, a great enhancement of the reaction rate and enantioselectivity could derive from their use. Additionally, a careful structural analysis of these cationic methyl palladium complexes and their precursors, coupled with a comparative study of their catalytic activity, would provide important mechanistic insights on the origin of the enantioselectivity during the presumed key carbopalladation step.

Synthesis of Cationic Methyl-Palladium Fesulphos Complexes and Their Precursors. DFT Calculations of Neutral Methylpalladium(II) Complex (1a)Pd(Cl)(Me). Treatment of enantiopure ligands **1a**−**e** with a stoichiometric amount of $PdCl_2(CH_3CN)_2$ in CH_2Cl_2 at room temperature afforded in very high or nearly quantitative yields the dichloro complexes $(\mathbf{1})PdCl_2$, which were readily isolated as air-stable orange solids. As expected, these complexes were obtained in all cases as single epimers at sulfur, thus orienting the *tert*-butyl group at the sterogenic sulfur atom in anti arrangement with regard to the ferrocene backbone. This fact had previously been confirmed by X-ray analysis of several $(\mathbf{1})PdCl_2$ complexes[5,6] (see also Figure 1a).

Interestingly, the transmetalation reaction of $(\mathbf{1})PdCl_2$ with either Me_4Sn[8d] (3.0 equiv) in CH_2Cl_2 at room temperature or, preferably, Me_2Zn (1.5 equiv) in CH_2Cl_2 at room temperature was completely stereoselective, presumably as a result of the

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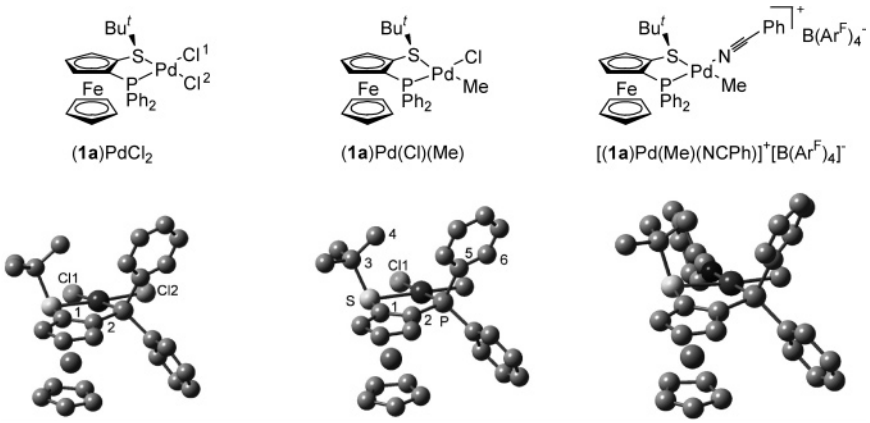


Figure 1. Crystal structures of (**1a**)$PdCl_2$, (**1a**)Pd(Cl)(Me), and [(**1a**)Pd(Me)(PhCN)]$^+$[$B(Ar^F)_4$]$^-$. The hydrogen atoms and the [$B(Ar^F)_4$]$^-$ counterion have been omitted for clarity.

Table 3. Selected Bond Distances (Å) and Angles (deg)

	(**1a**)$PdCl_2$	(**1a**)Pd(Cl)(Me)	(**1a**)Pd(Cl)(Me) (DFT calculations)[a]	[(**1a**)Pd(Me)(PhCN)]$^+$-[$B(Ar^F)_4$]$^-$
d (Pd−Cl1)	2.346	2.359	2.409	
d (Pd−Cl2)	2.302			
d (Pd−S)	2.314	2.444	2.587	2.464
d (Pd−P)	2.242	2.218	2.294	2.217
d (Pd−Me)		2.049	2.065	2.039
θ (S−Pd−P)	90.8	90.2	87.4	90.1
θ (S−Pd−Cl1)	89.4	91.6	91.6	
θ (P−Pd−Cl2)	88.3			
θ (P−Pd−Me)		90.5	93.1	90.8
τ (Pd−S−C1−C2)	0.1	1.8	3.5	8.6
τ (Pd−P−C1−C2)	−12.6	−11.9	−19.5	−15.3
τ (C1−S−C3−C4)	79.0	67.5	73.4	64.4
τ (C2−P−C5−C6)	172.5	170.6	−165.9	−165.6

[a] B3LYP with a combination of basis sets and polarization functions for atoms attached to the metal (see computational details within the Supporting Information).

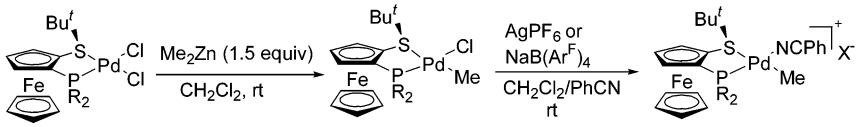
strong electronic differentiation exerted by the phosphane and thioether moieties, affording a single complex (**1**)Pd(Cl)(Me).[13] These air-stable highly crystalline yellow-orange complexes were readily purified by standard silica gel chromatography and proved to be moisture and air-stable at room temperature. The cis stereochemistry between the methyl group and the phosphane moiety was established by ^{1}H and ^{13}C NMR spectra, the low coupling constants $^2J_{P,C(Me)}$ (<2.1 Hz) and $^3J_{P,H(Me)}$ (2.2−2.8 Hz) being of great diagnostic value and similar to the values reported for achiral methyl P,S-palladium complexes.[14] Single-crystal X-ray analysis of (**1a**)Pd(Cl)(Me) confirmed this stereochemistry (Figure 1b). DFT calculations on (**1a**)Pd(Cl)(Me) complex provides structural parameters very close to their X-ray data (Table 3), giving us confidence in the reliability of the computational approach used (see computational details in the Supporting Information). Moreover, the complex with trans relative orientation between the methyl group and the phosphane moiety was optimized by the same method, resulting to be much less stable (5.8 kcal mol^{-1}) than the cis isomer, which is the only one observed.

The cationic methyl-palladium complex was readily prepared and isolated from (**1a**)Pd(Cl)(Me). The chloride ion abstraction was effected by its treatment with stoichiometric amounts of $AgPF_6$ or $NaB(Ar^F)_4$ [Ar^F= 3,5-bis(trifluoromethyl)phenyl, Brookhart's reagent][15] in a 6:1 CH_2Cl_2−benzonitrile mixture. Filtration of the resulting AgCl or NaCl precipitate, followed by evaporation of the solvent and trituration with hexanes−Et_2O, led to the cationic methyl-palladium benzonitrile-coordinated complexes as stable yellow-orange solids (Scheme 3). The coupling constants $^2J_{P,C(Me)}$ (<1.0 Hz) and $^3J_{P,H(Me)}$(1.3−1.6 Hz) were very similar to those of the precursor (**1a**)Pd(Cl)(Me), reflecting that the methyl group on palladium is positioned cis with respect to the phosphorus atom. Pleasingly, careful recrystallization of the tetraarylborate complex [(**1a**)Pd(Me)(PhCN)][$B(Ar^F)_4$] afforded suitable crystals for X-ray analysis, allowing confirmation of the anti arrangement of the benzonitrile ligand to the phosphorus atom[16] (Figure 1c).

The following structural features are worthy of consideration: (a) All compounds exhibit a perfect square planar geometry of the ligands around the metal center (sum of bond angles around Pd in the range of 360.0−360.2°), with very similar bond angles θ S−Pd−P, θ S−Pd−Cl(1), and θ S−Pd-Me. (b) The five-membered palladacycle slightly deviates from planarity, having dihedral angles close to zero for Pd−S−C(1)−C(2) (somewhat higher in the cationic complex, 7.98°) and 12°−

(13) Dimethylation of (**1**)$PdCl_2$ was not observed even with an excess of Me_2-Zn (over 5.0 equiv) under prolonged reaction times.
(14) For achiral cationic methyl P,S-palladium complexes, see: (a) Suranna, G. P.; Mastrorilli, P.; Nobile, C. F.; Keim, W. *Inorg. Chim. Acta* **2000**, *305*, 151. (b) Daugulis, O.; Brookhart, M.; White, P. S. *Organometallics* **2002**, *21*, 5935.
(15) (a) Brookhart, M.; Grant, B.; Volpe, A. F., Jr. *Organometallics* **1992**, *11*, 3920. (b) Brookhart, M.; Wagner, M. *J. Am. Chem. Soc.* **1994**, *116*, 3641.
(16) Two slightly different structures were detected in the crystal, differing mainly in the orientation of the counterion.

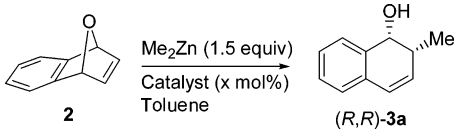
Scheme 3. Synthesis of Fesulphos Palladium Complexes



R = Ph, (**1a**)PdCl$_2$, 94% (**1a**)Pd(Cl)(Me), 93%
R = (*p*-F)C$_6$H$_4$, (**1b**)PdCl$_2$, 99% (**1b**)Pd(Cl)(Me), 95%
R = *o*-Tol, (**1c**)PdCl$_2$, 99% (**1c**)Pd(Cl)(Me), 87%
R = 1-Naph, (**1d**)PdCl$_2$, 78% (**1d**)Pd(Cl)(Me), 70%
R = Cy, (**1e**)PdCl$_2$, 99% (**1e**)Pd(Cl)(Me), 95%

[(**1a**)Pd(Me)(NCPh)]$^+$X$^-$
X$^-$ = PF$_6^-$, 81%
X$^-$ = BAr$^F{}_4^-$, 71%

Table 4. Asymmetric Ring Opening of 7-Oxabenzonorbornadiene with Me$_2$Zn Catalyzed by Palladium(II) Complexes of Ligands **1**



2 (*R*,*R*)-**3a**

entry	cat. (*x* mol %)	additive (*x* mol %)	*T* (°C)	*t* (min)	yield[a] [%]	ee[b] [%]
1	(**1a**)PdCl$_2$ (5)		25	1440	80[c]	81
2	(**1a**)Pd(Cl)(Me) (5)		25	1440	74[c]	87
3	(**1a**)Pd(Cl)(Me) (5)	AgPF$_6$ (5)	25	420	83	83
4	[(**1a**)PdMePhCN]$^+$(PF$_6$)$^-$ (5)		25	360	68	61
5	(**1a**)Pd(Cl)(Me) (5)	NaB(Ar^F)$_4$ (5)	25	10	86	78
6	(**1a**)Pd(Cl)(Me) (0.5)	NaB(Ar^F)$_4$ (0.5)	25	30	78	78
7	[(**1a**)PdMePhCN]$^+$(BAr$^F{}_4$)$^-$ (0.5)		25	30	82	72
8	(**1b**)Pd(Cl)(Me) (5)	NaB(Ar^F)$_4$ (5)	25	15	71	69
9	(**1c**)Pd(Cl)(Me) (5)	NaB(Ar^F)$_4$ (5)	25	30	74	64
10	(**1d**)Pd(Cl)(Me) (5)	NaB(Ar^F)$_4$ (5)	25	360	80	46
11	(**1e**)Pd(Cl)(Me) (5)	NaB(Ar^F)$_4$ (5)	25	10	77	83
12[d]	(**1e**)Pd(Cl)(Me) (5)	NaB(Ar^F)$_4$ (5)	−25	30	88	95
13[d]	(**1e**)Pd(Cl)(Me) (1)	NaB(Ar^F)$_4$ (1)	−25	60	87	97
14[d]	(**1e**)Pd(Cl)(Me) (0.2)	NaB(Ar^F)$_4$ (0.2)	−25	300	88	97

[a] In pure product after chromatography. [b] Determined by chiral HPLC (Chiralpak AD column). [c] Conversion yield calculated by ^{1}H NMR. [d] Reaction performed in 1,2-dichloroethane.

13° for Pd−P−C(2)−C(1). This geometry determines that one of the phenyl groups at phosphorus and the bulky *tert*-butyl group on sulfur are oriented in an almost parallel diaxial arrangement, generating a sterically very congested area in the upper face of the palladacycle moiety. (c) Some subtle differences are observed in the bond lengths around palladium. The most significant is the elongation of the Pd−S bond in the methyl-palladim complexes (**1a**)Pd(Cl)(Me) (2.444 Å) and [(**1a**)-Pd(Me)(PhCN)]$^+$ (2.464 Å) compared to that of the starting dichloro complex (**1a**)PdCl$_2$ (2.314 Å), as result of the strong trans influence of the highly σ-donating methyl group. On the other hand, both methyl-palladium complexes are geometrically very similar around the metal center, the cationic complex possessing a Pd−Me bond somewhat shorter (2.039 vs 2.049 Å) and the Pd−S somewhat longer (2.464 vs 2.444 Å) than the neutral species, likely as a result of the enhanced σ-donation of the methyl group to the more electron-deficient cationic Pd atom.

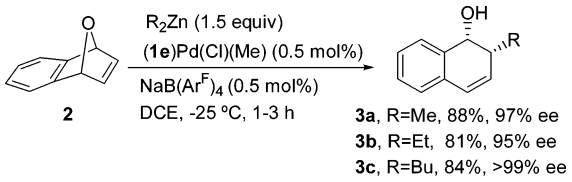
Reaction of Oxabicycle 2 with Me$_2$Zn Catalyzed by Fesulphos-Palladium Complexes. To test the efficiency of the well-defined Fesulphos-palladium catalysts previously synthesized, we studied the reaction of oxabicycle **2** with Me$_2$Zn. As the starting point we used similar experimental conditions to those previously employed when combining PdCl$_2$(CH$_3$CN)$_2$+Fesulphos ligand (5 mol % of catalyst in toluene at room temperature). The reactions were monitored by TLC until disappearance of the starting alkene **2**, except for very slow transformations which were stopped after 24 h. The results are summarized Table 4.

The reaction in the presence of catalyst (**1a**)PdCl$_2$ exhibited a similar result to that of the combination **1a**+PdCl$_2$(CH$_3$CN)$_2$ (see Table 1), reaching 80% conversion after 24 h to give the alcohol (*R*,*R*)-**3a** in 81% ee (entry 1). A very similar reactivity was observed in the case of using the complex (**1a**)Pd(Cl)(Me), which provided 74% conversion after 24 h, leading to **3a** in 87% ee (entry 2). Interestingly, a significant increase in the reaction rate occurred when a stoichiometric amount of AgPF$_6$ (5 mol %) was added to dissociate the chloride ligand, with the consequent formation of a cationic palladium complex[17] (entry 3). The reaction was finished in 7 h, providing **3a** in 83% yield and similar enantioselectivity (83% ee). This acceleration effect was confirmed in the absence of silver, by using a sample of the isolated salt [(**1a**)Pd(Cl)(PhCN)]$^+$PF$_6^-$ as catalyst (entry 4), instead of the in situ generated complex (entry 3).

However, the most dramatic enhancement in the reaction rate was produced when NaB(Ar^F)$_4$ (5 mol %) was used as chloride scavenger (entry 5). Under these conditions a complete conversion was observed within just 10 min, suggesting that the reactivity of the presumed key cationic palladium catalyst greatly depends on the nature of the anionic counterion, the bulky noncoordinating B(Ar^F)$_4^-$ anion being optimal. This outstanding reactivity allowed a dramatic decrease of the catalyst loading: 0.5 mol % of catalyst was sufficient to observe complete disappearance of the starting material within 30 min without loss of enantioselectivity (entry 6). As expected, a similar result in terms of reactivity, chemical yield, and enantioselectivity was

(17) A similar reactivity was observed using AgSbF$_6$ instead of AgPF$_6$.

Scheme 4. Ring-Opening Reaction of **2** with Several Dialkylzinc Reagents



obtained using 0.5 mol % of the corresponding isolated cationic complex [(**1a**)Pd(Me)(PhCN)]$^+$[B(Ar^F)$_4$]$^-$ (entry 7), instead of the in situ generated catalyst (entry 6).

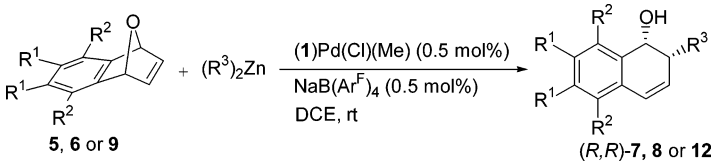
To fine-tune the enantioselectivity of the process, we next studied the effect of the substitution at phosphorus in the in situ generated cationic Fesulphos-palladium complexes [(**1b**−**e**)Pd(Me)]$^+$. For comparison purposes all reactions were conducted in the presence of 5 mol % of (**1**)Pd(Cl)(Me) and NaB(Ar^F)$_4$ (entries 8−11). With the exception of the complex containing the bulky naphthylphosphane ligand **1d** (entry 10), very high reactivity was observed again in all cases, the reaction reaching completion within just 10−30 min.

The observed enantioselectivities nicely parallel those found with the couple $PdCl_2(CH_3CN)_2$+ligand **1** as the catalyst system (Table 1). Thus, complexes derived from ligands **1b**, **1c**, and **1d** provided a lower enantioselectivity (46−69% ee) than that achieved from the complex of **1a** (78% ee, entry 6), while the palladium complex containing the dicyclohexyl phosphine **1e** afforded the highest asymmetric induction (entry 11, 83% ee). The combination (**1e**)Pd(Cl)(Me)+NaB(Ar^F)$_4$ proved to be so effective that the reaction could be conducted at a much lower temperature (−25 °C), which resulted in a remarkable enhancement in the enantioselectivity (95% ee, entry 12). Outstandingly, this catalytic system also admits a severe reduction in the catalyst loading, maintaining very reasonable reaction times. For instance, the reactions of **2** with Me_2Zn in 1,2-dichloroethane at −25 °C in the presence of 1 mol % of this optimal catalyst afforded alcohol **3a** in an excellent 97% ee within 60 min (entry 13), while a 0.2 mol % of catalyst led to the same enantioselectivity after 5 h (entry 14).

Interestingly, Et_2Zn and Bu_2Zn did also efficiently participate in the ring opening reaction of **2** using 0.5 mol % of catalyst (Scheme 4). Particular attention deserves the addition of Bu_2Zn, wich led to alcohol **3c** with complete enantiocontrol (>99% ee).

Scope of the Alkylative Ring-Opening Catalyzed by (1)-Pd(Me)$^+$. Once developed a very active and enantioselective catalyst for the alkylative ring opening of compound **2** with several dialkylzinc reagents, we turned our efforts toward studying the scope and generality of the process with regard to the alkene substrate. We focused our attention in the reaction of Me_2Zn, Et_2Zn and Bu_2Zn with the meso oxabicyclic compounds **5**, **6** and **9**, which showed modest or very poor reactivity with the standard combination of $PdCl_2(CH_3CN)_2$ and Fesulphos ligand (Table 2). To confirm the feasibility of using a low catalyst loading and the influence of the substitution at phosphorus, we systematically explored the addition of the dialkylzinc reagent in the presence of 0.5 mol % of the in situ formed cationic methyl-Pd complex of the three ligands that provided the best results in the opening of the model substrate **2** [(**1a**)PdMe$^+$, (**1b**)PdMe$^+$, and (**1e**)PdMe$^+$]. All reactions were carried out in DCE at room temperature by addition of dialkylzinc reagent to a mixture of the corresponding complex (**1**)Pd(Cl)(Me) (0.5 mol %), NaB(Ar^F)$_4$ (0.5 mol %), and the oxabicyclic alkene. The results are collected in Table 5.

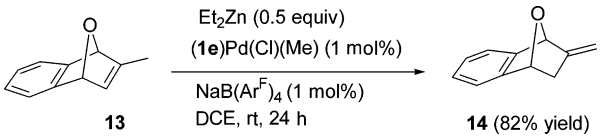
Table 5. Asymmetric Ring Opening of Oxabenzonorbornadienes with R_2Zn Catalyzed by Cationic Pd-Complexes of **1a**, **1b**, and **1e**



ent.	substrate	R^1	R^2	R^3	catalyst	*t* (min)	product	yield[a] (%)	ee[b] (%)
1	**5**	F	H	Me	**1a**·PdMe$^+$	60	**7a**	87	83
2	**5**	F	H	Et	**1a**·PdMe$^+$	60	**7b**	80	81
3	**5**	F	H	Me	**1b**·PdMe$^+$	600	**7a**	43[c]	77
4	**5**	F	H	Et	**1b**·PdMe$^+$	600	**7b**	74	87
5	**5**	F	H	Me	**1e**·PdMe$^+$	30	**7a**	95	95
6	**5**	F	H	Et	**1e**·PdMe$^+$	30	**7b**	79	96
7	**5**	F	H	Bu	**1e**·PdMe$^+$	60	**7c**	75	96
8	**6**	OCH_2O	H	Me	**1a**·PdMe$^+$	10	**8a**	62	90
9	**6**	OCH_2O	H	Et	**1a**·PdMe$^+$	30	**8b**	77	88
10	**6**	OCH_2O	H	Me	**1b**·PdMe$^+$	120	**8a**	58	88
11	**6**	OCH_2O	H	Et	**1b**·PdMe$^+$	1440	**8b**	45	81
12	**6**	OCH_2O	H	Me	**1e**·PdMe$^+$	10	**8a**	71	>99
13	**6**	OCH_2O	H	Et	**1e**·PdMe$^+$	30	**8b**	61	94
14	**6**	OCH_2O	H	Bu	**1e**·PdMe$^+$	*d*	**8c**	*d*	
15	**9**	H	OMe	Me	**1a**·PdMe$^+$	30	**12a**	80	91
16	**9**	H	OMe	Et	**1a**·PdMe$^+$	180	**12b**	90	89
17	**9**	H	OMe	Me	**1b**·PdMe$^+$	1200	**12a**	89	95
18	**9**	H	OMe	Et	**1b**·PdMe$^+$	1440	**12b**	54	66
19	**9**	H	OMe	Me	**1e**·PdMe$^+$	15	**12a**	98	97
20	**9**	H	OMe	Et	**1e**·PdMe$^+$	60	**12b**	85	94
21	**9**	H	OMe	Bu	**1e**·PdMe$^+$	30	**12c**	91	98

[a] In pure product after chromatography. [b] Determined by chiral HPLC (Chiralpak AS, Chiralcel AS and Chiralpak AD columns). [c] Conversion yield. [d] Rapid aromatization of the addition product was observed.

Scheme 5. Attempt of Kinetic Resolution of Trisubstituted Alkene **13**



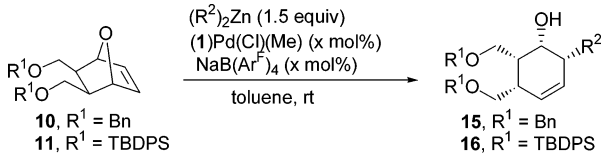
To our delight, all ring-opening processes occurred with good chemical yields and high enantioselectivities, leading to the known cis-dihydronaphthols **7a**−**b**[8a] and **8a**−**b**,[8a] and the new compounds **7c** and **12a**−**c**, without formation of significant amounts of side products. However, the most outstanding result was the astonishing great stereochemical fidelity displayed by this family of Fesulphos ligands. Again, as for substrate **2**, in all cases the catalyst containing the electron-rich phosphine **1e** provided the best asymmetric induction, allowing a very high enantiocontrol of the process (94→99% ee, entries 5−7, 12, 13, and 19−21). The second most efficient catalyst proved to be the diphenylphosphino complex (**1a**)Pd(Me)$^+$ (81−91% ee, entries 1, 2, 8, 9, 15, and 16), while the electron-poor bis(*p*-fluorophenyl)phosphino complex (**1b**)Pd(Me)$^+$ was both less stereoselective and sharply less reactive (66−88% ee, entries 3, 4, 10, 11, 17, and 18).

As a last oxa-benzonorbornadiene substrate, we attempted the kinetic resolution of racemic **13**, having a methyl group at the alkene moiety. Unexpectedly, in this case the reaction with Et_2Zn in the presence of (**1e**)Pd(Me)$^+$ promoted the endo to exo isomerization of the C−C double bond (product **14**) instead of the alkylative ring-opening reaction (Scheme 5).

Alkylative Ring-Opening of Less Reactive Substrates. From a synthetic point of view, meso nonaromatic [2.2.1]-oxabicyclic alkenes are particularly interesting substrates for enantioselective alkylative ring-opening reactions, since they lead to substituted cyclohexenols having four contiguous stereogenic centers. However, the use of these compounds is much more restricted than that of their oxabenzonorbornadiene counterparts due to their low reactivity. For instance, this transformation promoted by Pd(Tol-BINAP)Cl_2 requires either high reaction temperatures and/or the addition of stoichiometric amounts of additives such as Lewis acid [e.g., Zn(OTf)$_2$] or EtMgBr.[8d] Pleasingly, in our case, 5 mol % of catalysts (**1a**)-PdMe$^+$ and (**1e**)PdMe$^+$ induced the ring opening of **10** with Me_2Zn in toluene at room temperature in the absence of any additive, to give the cis-cyclohexenol **15a** with reasonable yields and excellent enantioselectivities (92→99% ee, Table 6, entries 1 and 2). Interestingly, the silyl ether derivative **11** was even more reactive, the reaction reaching completion within 2 h at room temperature in the presence of only 1 mol % of catalyst, affording **16a** with 96−97% ee (entries 3 and 4).[10] The ring-opening of alkene **11** with other dialkylzinc reagents such as Et_2Zn and Bu_2Zn in the presence of 1 mol % of catalyst (**1e**)-PdMe$^+$was next studied. The reaction with Et_2Zn was even faster, leading to alcohol **16b** with 70% yield and 83% ee after 25 min at room temperature (90% ee at −20 °C, entry 5). On the other hand, the butyl derivative **16c** was similarly obtained with 67% yield and 90% ee by addition of Bu_2Zn to **10** (1 h, rt, entry 6).

This protocol was finally extended to the desymmetrization of azabenzonorbornadiene derivatives, a kind of alkene whose opening reaction with Me_2Zn had been described in refluxing DCE due to their decreased reactivity.[8b] In this transformation, unlike the behavior of the oxa-analogue **2**, complex (**1a**)PdMe$^+$ with the hexafluorophosphate anion was more reactive than the corresponding tetraarylborate complex (Table 7). In addition, the complex [(**1a**)Pd(Me)(PhCN)](PF$_6$) (5 mol %) afforded the corresponding ring-opened product **18a** in good isolated yield (73%) and virtually complete enantioselectivty (>99% ee, entry 4).[18] The use of 1 mol % of [(**1a**)PdMe](PF$_6$) resulted in a much slower reaction (60% conversion after 48 h), although without loss of enantioselectivity (99% ee, entry 4). The reaction with Et_2Zn was surprisingly much less enantioselective, giving **18b** in 65% yield with only 33% ee (entry 5).

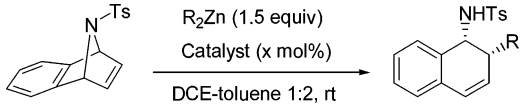
Table 6. Enantioselective Ring Opening of Nonaromatic [2.2.1]Oxabicyclic Alkenes with R_2Zn Catalyzed by Cationic Methyl−Pd Complexes of **1a** and **1e**



entry	R^1	R^2	*x*	ligand	time	product	yield[a] (%)	ee[b] (%)
1	Bn	Me	5	**1a**	20 h	**15a**	68	>99
2	Bn	Me	5	**1e**	22 h	**15a**	79	92
3	OTBDPS	Me	1	**1a**	2 h	**16a**	70	96
4	OTBDPS	Me	1	**1e**	2 h	**16a**	61	97
5	OTBDPS	Et	1	**1e**	25 min	**16b**	70(71)[c]	83(90)[c]
6	OTBDPS	Bu	1	**1e**	1 h	**16c**	67	90

[a] In pure product after chromatography. [b] Determined by chiral HPLC. [c] Reaction performed at −20 °C.

Table 7. Enantioselective Ring-Opening of Azabenzonorbornadiene with R_2Zn



entry	R	catalyst	*x*	*t* (h)	product	yield[a] (%)	ee[b] (%)
1	Me	(**1a**)Pd(Cl)(Me) + NaB(Ar^F)$_4$	5	25	**18a**	79	98
2	Me	[(**1a**)Pd(Me)(PhCN)]$^+$[B(Ar^F)$_4$]$^-$	5	24	**18a**	70[c]	97
3	Me	[(**1a**)Pd(Me)(PhCN)]$^+$(PF$_6$)$^-$	5	0.5	**18a**	73	>99
4	Me	[(**1a**)Pd(Me)(PhCN)]$^+$(PF$_6$)$^-$	1	48	**18a**	60[c]	99
5	Et	[(**1a**)Pd(Me)(PhCN)]$^+$(PF$_6$)$^-$	5	24	**18b**	65	33

[a] In pure product after chromatography. [b] Determined by chiral HPLC. [c] Conversion yield determined by ^{1}H NMR from the crude reaction mixture.

Mechanistic Hypothesis. The X-ray structures of palladium complexes of **1** (Figure 1), together with computational studies gave us strong insights on the mechanistic forces behind the high performance displayed by these P,S-palladium catalysts. Considering that, according to the general mechanism proposed by Lautens et al., the stereogenic carbon centers are created in the *syn*-carbopalladation step on the key cationic palladium−π-alkene complex; we studied theoretically this reaction by DFT (B3LYP) method. As model structures in our theoretical study we chose the parent ligand **1a** and oxanorbornadiene as alkene.

(18) The cis stereochemistry of (+)-**17a** was confirmed by comparison of its physical and spectroscopical data with those reported in the literature for racemic *cis*-**17a** and *trans*-**17a** (see, for instance: Gómez Arrayás, R.; Cabrera, S.; Carretero, J. C. *Org. Lett*. **2005**, *7*, 219). The absolute stereochemistry of (+)-**17a** was assumed as (1*R*,2*R*) according to the reaction mechanism.

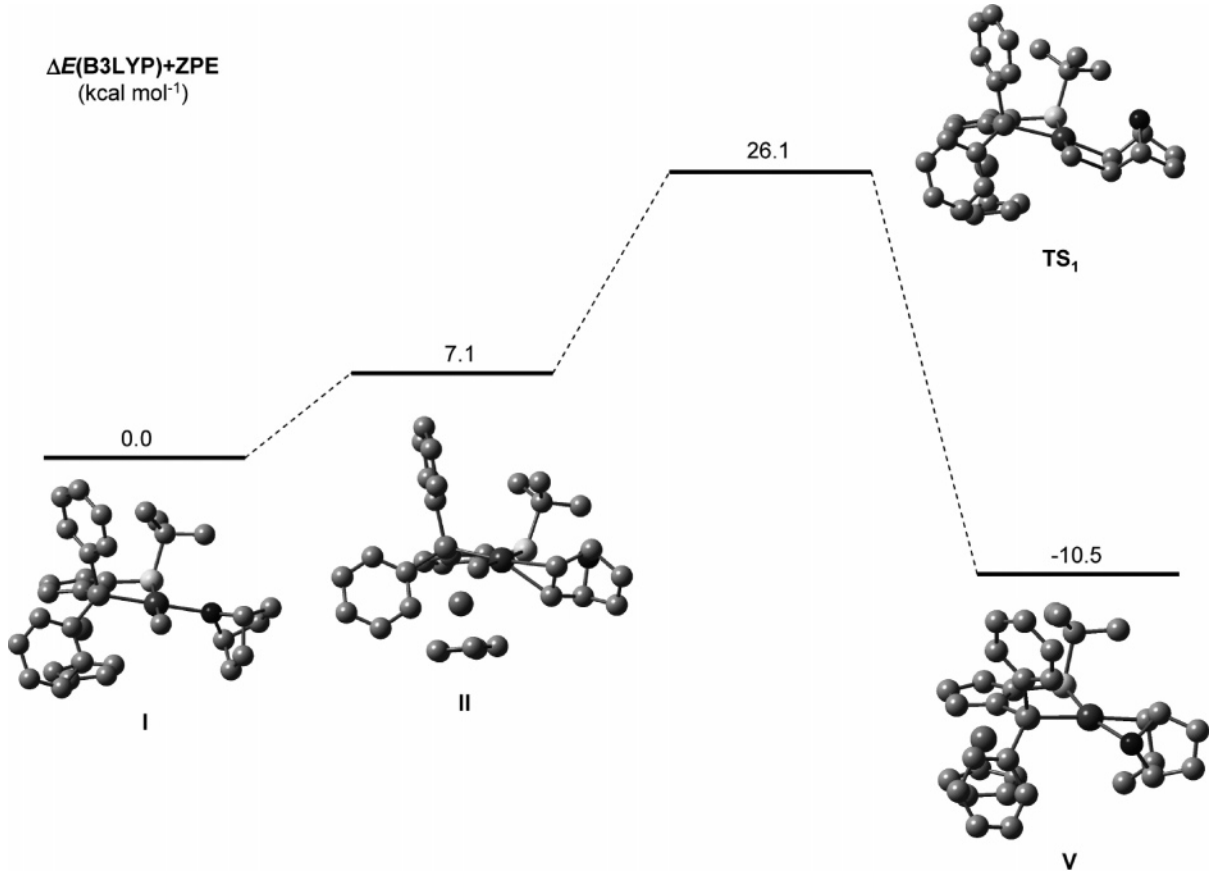


Figure 2. Reaction coordinate of carbopalladation to give the minor enantiomer (*S*,*S*)-**3a**. Hydrogen atoms have been omitted for clarity.

The reaction coordinates of the carbopalladation step to afford the minor enantiomer (*S*,*S*)-**3a** and the major enantiomer (*R*,*R*)-**3a** are presented in Figures 2 and 3, respectively, along with the relative energies of the optimized geometries for each intermediate and transition state. After considering several geometries for the coordination of oxanorbornadiene with the complex (**1a**)Pd(Me)$^+$, structures **I**−**IV** were found as the minimum of energy according to their harmonic frequencies. The four structures exhibit a perfect square planar geometry of the ligand around palladium ($\sum\theta$[Pd] = 359.8°−360.6°). Since **I** (in which only the oxygen atom is coordinated to the metal [*d*(Pd−O) = 2.214 Å]) resulted the most stable structure, the formation of this complex was considered the initial stage of the carbopalladation step. A η^2-coordination of the C=C double bond to palladium was found in complexes **II**−**IV**, as deduced from the Pd−C distances (2.39−2.53 Å) and the slight elongation of the C=C bond (1.360−1.365 Å) compared to the same bond length in intermediate **I** (1.334 Å). In complex **II** the alkene moiety is in perpendicular arrangement with regard to the coordination plane [(C=C)−Pd−Me dihedral angle = −70.4°], the oxygen atom pointing opposite to the methyl group. Almost the opposite orientation of the alkene was found in structure **III**, though a deviation from perpendicularity was observed [(C=C)−Pd−Me dihedral angle = −56.3°], likely to avoid steric interactions between the oxygen and the methyl group. However, complex **IV**, formed by rotation of the alkene, showed a quasi coplanar arrangement of the alkene, both carbon atoms of the C=C double bond being almost within the coordination plane of palladium [(C=C)−Pd−Me dihedral angle = −10.4°].[19] Considering the distances between the methyl group and the closest alkene carbon, complex **II** can be envisaged as an intermediate in the formation of the minor enantiomer of the carbopalladation product (**V**), whereas complex **IV** would be involved in the formation of the major enantiomer **VI**.

In addition, carbopalladation products **V** and **VI**, as well as the transition states leading to them (**TS$_1$** and **TS$_2$**, respectively), were optimized. Complex **V** [*d*(Pd−C) = 2.109 Å; *d*(Pd−O) = 2.226 Å] was found to be somewhat more stable than **VI** [*d*(Pd−C) = 2.105 Å; *d*(Pd−O) = 2.251 Å], the latter having the methyl group oriented to the more sterically hindered up face of the ligand. Both transition states **TS$_1$** and **TS$_2$** have the Pd−C σ-bond almost completely formed (2.111 Å). However, while the Me−C bond (2.145 and 2.163 Å, respectively) is being formed, the Pd−Me bond (2.295 and 2.303 Å, respectively) and C=C bond (1.435 and 1.431 Å, respectively) are being broken. The transition state **TS$_1$**, in which the oxygen atom is directed to the more sterically hindered up face of the ligand, was found to be 3.3 kcal mol^{-1} less stable than **TS$_2$**, being this large difference in energy consistent with enantioselectivities greater than 90% observed experimentally.

These studies suggest that there are two key structural aspects that determine the enantioselectivity in the carbopalladation step: (a) coordination of the bicyclic alkene trans to phosphorus

(19) Perpendicular and coplanar arrangements of alkene ligands with respect to the coordination plane have been reported for alkene−platinum complexes. The actual orientation of the alkene has been proposed to be governed by steric factors. See, for instance: Collman, J. P.; Norton, J. R.; Finke, R. G. In *Principles and Applications of Organotransition Metal Chemistry*; University Science Books, Mill Valley, CA, 1987; pp 41−42.

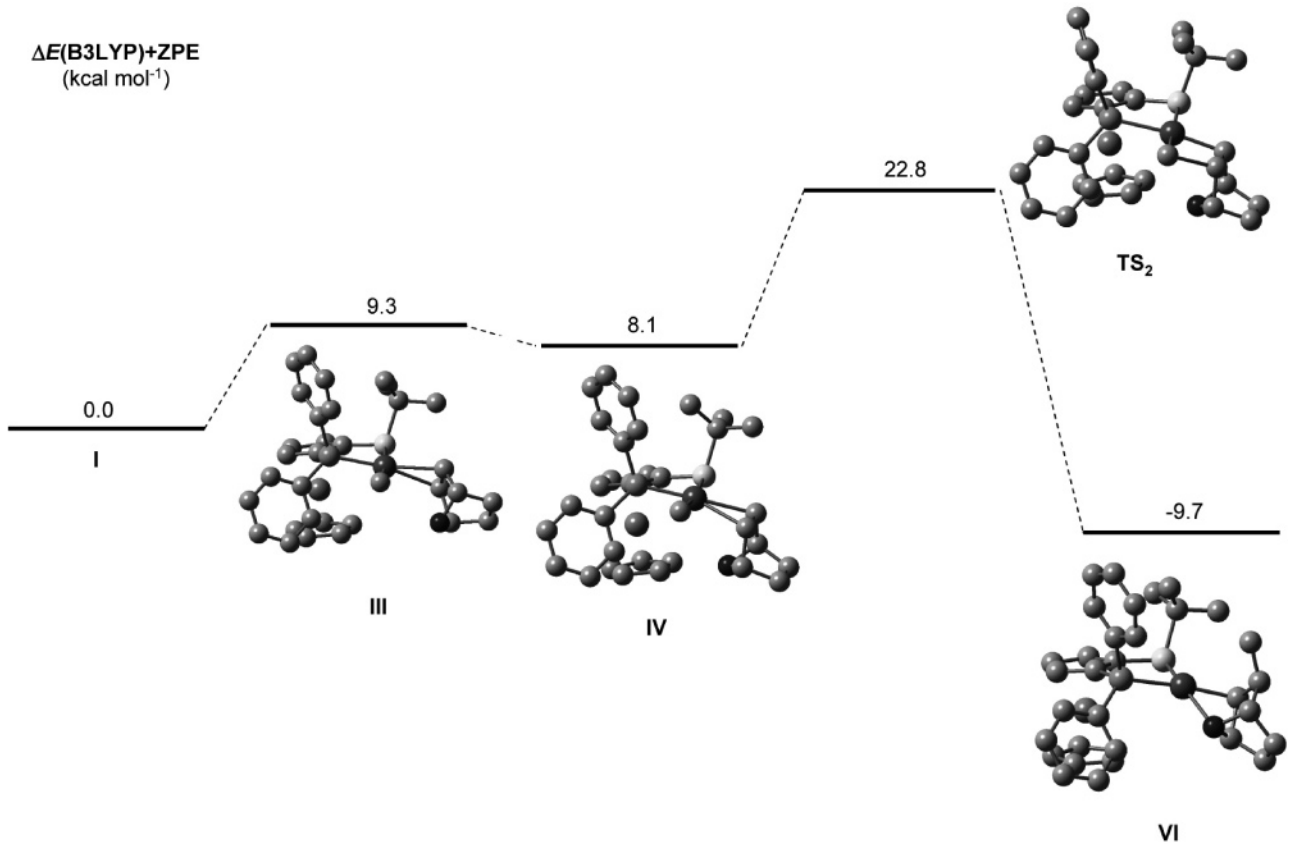
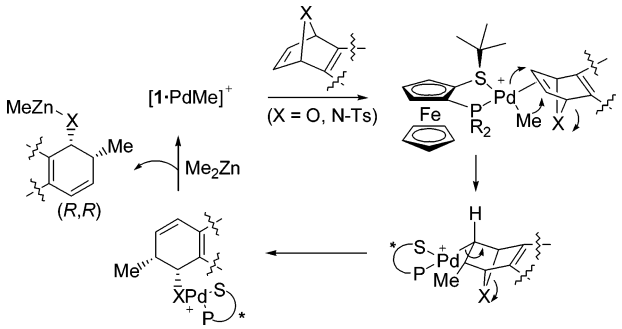


Figure 3. Reaction coordinate of carbopalladation to give the major enantiomer (*R*,*R*)-**3a**. Hydrogen atoms have been omitted for clarity.

Scheme 6. Mechanistic Proposal



on the palladium atom and (b) coordination of the alkene from its less hindered exo face, orienting the oxygen (or nitrogen) bridge to the opposite side of the very bulky *tert*-butyl group (intermediate **IV**). Therefore, we can conclude that the synergistic effect derived from the strong electronic trans effect of the phosphorus moiety, together with the great steric control exerted by the close bulky stereogenic sulfur substitution, would be responsible for the high asymmetric induction displayed by Fesulphos catalysts in this transformation (Scheme 6).

Conclusions

In summary, the highly tunable family of Fesulphos ligands (**1**), owing P,S-coordination mode and exclusively planar chirality, act as very efficient ligands in the enantioselective alkylative ring opening of oxa- and azabicyclic alkenes with dialkylzinc reagents. In particular, their readily available cationic methylpalladium complexes display an unprecedented high reactivity with regard to a variety of substrates. After fine-tuning of the substitution at phosphorus, the optimal catalyst (**1e**)Pd(Me)$^+$ combines a broad scope, low catalyst loadings (0.5 mol % in most cases), and smooth reaction conditions (−25 °C or rt), affording the corresponding ring-opened products in good yields (65−95%) and with homogeneously high enantioselectivities (90→99% ee). A combination of computational studies at DFT (B3LYP) level and a complete X-ray structural analysis of palladium complexes, including the presumed catalytically active cationic methyl−Pd complex, shows that Fesulphos ligands fulfill unique structural and electronic requirements to provide high asymmetric induction in the key carbopalladation step. Specifically, the high asymmetric performance of these ligands in this transformation could rely on the strong trans effect of the phosphine moiety, acting in combination with the great sterically demanding environment imposed by the stereogenic sulfur atom directly bonded to the palladium atom.

Acknowledgment. This work was supported by the *Ministerio de Educación y Ciencia* (*MEC*, Project BQU2003-0508) y *Consejería de Educación de la Comunidad de Madrid* (Project GR/MAT/0016/2004). S.C. thanks the *Universidad Autónoma de Madrid* (*UAM*) for a predoctoral fellowship. R.G.A. thanks the *MEC* for a Ramón y Cajal Contract. We acknowledge the skilled assistance of Dr. Jaime Rodríguez González in solving the X-ray crystal structure of the cationic palladium complex. Prof. José L. García-Ruano is gratefully acknowledged for unrestricted access to the HPLC equipment of his group. We also thank the Centro de Computación Científica (*UAM*) for computation time, and Dr. M. Alcamí (*UAM*) and Dr. Feliu Maseras (Institute of Chemical Research of Catalonia) for

helpful discussions. Johnson Matthey PLC is gratefully acknowledged for a generous loan of $PdCl_2$.

Supporting Information Available: Detailed experimental procedures and characterization data. Copies of ^1H NMR and ^{13}C NMR of new compounds. Computational details. Cartesian coordinates for all optimized structures and their absolute energies. This material is available free of charge via the Internet at http://pubs.acs.org.

JA055692B