Ring-Opening Catalysts

Cationic Planar Chiral Palladium P,S Complexes as Highly Efficient Catalysts in the Enantioselective Ring Opening of Oxa- and Azabicyclic Alkenes**

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A huge effort has been devoted to the development of highly efficient asymmetric transition-metal-catalyzed reactions using chiral ligands based on P,P, P,N or N,N coordination modes,[1] some of which have reached the status of privileged ligands.[2] In sharp contrast, thioether-based chiral ligands[3] have received much less attention, despite a key structural feature that makes them very attractive in asymmetric catalysis: the sulfur atom becomes stereogenic upon coordination to the metal, thus imposing a unique asymmetric environment next to the reactive metal center. In this context, we recently reported that the planar chiral Fesulphos ligands **1** (1-phosphanyl-2-sulfenylferrocenes) behave as very efficient P,S ligands in Pd-catalyzed allylic substitutions and in Cu-catalyzed additions to imines.[4]

Among recently described new Pd-catalyzed enantioselective reactions, the ring opening of *meso* oxabicyclic alkenes with dialkyl zinc reagents in the presence of chiral P,P and P,N ligands reported by Lautens et al. constitutes a synthetically outstanding C–C bond forming desymmetrization reaction.[5] According to mechanistic evidence[5b] this alkylative ring-opening reaction proceeds by coordination and subsequent enantioselective carbopalladation of the alkene, with a cationic alkyl palladium intermediate $[L_2PdR]^+$ formed in situ under the reaction conditions employed.[6] Inspired by this work, we envisaged that the cationic methylpalladium complexes of Fesulphos ligands $[(\mathbf{1})PdMe]^+$ could act as very active catalysts in this type of reaction. Herein, we report that this robust and readily available catalyst system combines low catalyst loading, high enantioselectivity, easy fine-tuning, mild reaction conditions, and broad structural scope.

Treatment of ligands **1** with $[PdCl_2(CH_3CN)_2]$[7] afforded in very high yield the corresponding complexes $[(\mathbf{1})PdCl_2]$ as single epimers at the sulfur atom.[4b] Interestingly, the transmetalation reaction of these complexes with Me_2Zn was completely stereoselective, affording a single complex [(**1**)Pd(Cl)(Me)] in 70–95% yield (Scheme 1). The *cis* arrangement of the methyl group and the phosphane moiety was established by analysis of their ^1H, ^{13}C, and ^{31}P NMR spectra; the low coupling constants $^2J_{P,C(Me)}$ (< 1.0 Hz) and $^3J_{P,H(Me)}$ (2.4 Hz) were of great diagnostic value.[8] This stereochemical assignment was unequivocally confirmed by X-ray crystal diffraction analysis[9] of [(**1a**)Pd(Cl)(Me)] (Figure 1). Additional relevant structural information includes the preservation of the *anti* arrangement of the *tert*-butyl group with respect to the iron atom ($R_P R_S$ configuration), and the elongation of the Pd–S bond (2.444 Å) compared to that of the starting dichloro complex (2.314 Å)[4b] as result of the strong *trans* effect of the highly σ-donating methyl group. The removal of the chloride ion in [(**1a**)Pd(Cl)(Me)] by treatment with $AgPF_6$ (CH_2Cl_2, room temperature) or $NaB(Ar^F)_4$ [Ar^F = 3,5-bis(trifluoromethyl)phenyl][10] in the presence of benzonitrile afforded a single cationic benzonitrile-coordinated palladium species $[(\mathbf{1a})Pd(Me)(PhCN)]^+X^-$. The crystal structure of this complex[11] (Figure 1) is very similar to that of its precursor [**1a**·Pd(Cl)(Me)] although, as expected, the Pd–Me bond is even shorter (2.011 versus 2.048 Å) and the Pd–S bond is longer (2.461 versus 2.444 Å) as a result of the enhanced σ donation of the methyl group to the cationic Pd atom.

Table 1 summarizes the most significant results obtained with this set of potential P,S catalysts in the model reaction of 7-oxabenzonorbornadiene with Me_2Zn.

As the starting point we used similar experimental conditions to those previously described: 5 mol% of catalyst in toluene or 1,2-dichloroethane (DCE) at room temperature

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Supporting information for this article is available on the WWW under http://www.angewandte.org or from the author.

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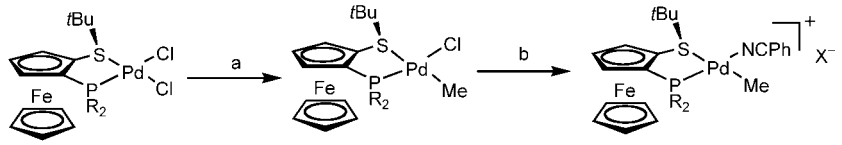


R = Ph, [(**1a**)$PdCl_2$], 86% — [(**1a**) Pd(Cl)(Me)], 93% — [(**1a**) Pd(Me)(NCPh)]$^+X^-$

R = (*p*-F)C_6H_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%

X^- = PF_6^-, 81%

X^- = $BAr^F{}_4^-$, 71%

Scheme 1. Synthesis of Fesulphos palladium complexes. a) Me_2Zn (1.5 equiv), CH_2Cl_2, RT; b) $AgPF_6$ or $NaBAr^F{}_4$, PhCN, CH_2Cl_2, RT. Cy = cyclohexyl.

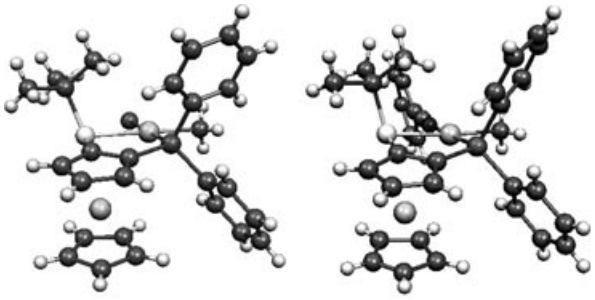


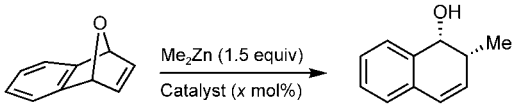
Figure 1. X-Ray crystal structures of [(**1a**)Pd(Cl)(Me)] and [(**1a**)Pd(Me)(PhCN)]$B(Ar^F)_4$ (the $B(Ar^F)_4^-$ anion has been omitted for clarity).

(RT).[5] Catalyst [(**1a**)$PdCl_2$] led to 80% conversion in 24 hours (entry 1) to give the *cis* alcohol (*R*,*R*)-**2a**[12] with a remarkable 81% *ee*. A similar result was achieved using the methyl complex [(**1a**)Pd(Cl)(Me)] (entry 2), which supports the proposal that both complexes evolve to the same active catalyst under the reaction conditions used. A significant increase in the reaction rate occurred when a catalytic amount of $AgPF_6$ was added to dissociate the chloride ligand (entry 3). However, the greatest acceleration effect was produced by adding $NaB(Ar^F)_4$ (entry 4). A complete conversion was observed within 10 minutes with this noncoordinating counterion. This outstanding reactivity allowed a dramatic decrease of the catalyst loading: 0.5 mol% of catalyst drove the reaction to completion in 30 minutes (entry 5). As expected, a similar result was obtained using 0.5 mol% of the isolated air-stable cationic complex (entry 6) instead of catalyst generated in situ.

To fine-tune the reactivity and enantioselectivity of the process, we next studied the effect of the substitution at the phosphorus atom (complexes of ligands **1b–e**). With the exception of the complex containing the bulky naphthylphosphane ligand **1d** (entry 9), the reactions were complete in 10–30 minutes, with the electronically rich phosphane **1e** providing the best enantioselectivity (entry 10). The combination [(**1e**)Pd(Cl)(Me)]+$NaB(Ar^F)_4$ proved to be so effective that the reaction could be performed with severely decreased catalyst loading and temperature, which resulted in an enhancement of the enantioselectivity. Thus, 0.2 mol% of catalyst was sufficient to reach quantitative conversion within 5 h at −25 °C, which afforded alcohol **2a** in 88% yield with 97% *ee* (entry 11).

With these optimized P,S catalysts in hand, we turned our attention toward the substrate generality of the process. The use of 0.5 mol% [(**1e**)Pd(Cl)(Me)][13] in combination with $NaB(Ar^F)_4$ (0.5 mol%) as a halogen scavenger catalyzed the enantioselective opening of a variety of substituted *meso* oxabenzonorbornadienes with both Me_2Zn and Et_2Zn in DCE[14] at room temperature. As shown in Scheme 2, complete conversions within 10–30 minutes, good chemical yields (61–98%), and excellent enantioselectivities (94–>99% *ee*, HPLC) were obtained for all products **2–5**.

Table 1: Ring opening of 7-oxabenzonorbornadiene with Me_2Zn catalyzed by palladium complexes of ligands **1**.



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

Entry	Catalyst (*x* mol%)	Additive (*x* mol%)	*t* (min)	Yield [%][a]	*ee* [%][b]
1	[(**1a**)$PdCl_2$] (5)	–	1440	80[c]	81
2	[(**1a**)Pd(Cl)(Me)] (5)	–	2880	75[c]	85
3	[(**1a**)Pd(Cl)(Me)] (5)	$AgPF_6$ (5)	420	83	83
4	[(**1a**)Pd(Cl)(Me)] (5)	$NaBAr^F{}_4$ (5)	10	86	78
5	[(**1a**)Pd(Cl)(Me)] (0.5)	$NaBAr^F{}_4$ (0.5)	30	78	78
6	[(**1a**)Pd(Me)(PhCN)]$^+(BAr^F{}_4)^-$ (0.5)	–	30	82	72
7	[(**1b**)Pd(Cl)(Me)] (5)	$NaBAr^F{}_4$ (5)	15	71	69
8	[(**1c**)Pd(Cl)(Me)] (5)	$NaBAr^F{}_4$ (5)	30	74	64
9	[(**1d**)Pd(Cl)(Me)] (5)	$NaBAr^F{}_4$ (5)	360	80	46
10	[(**1e**)Pd(Cl)(Me)] (5)	$NaBAr^F{}_4$ (5)	10	77	83
11[d]	[(**1e**)Pd(Cl)(Me)] (0.2)	$NaBAr^F{}_4$ (0.2)	300	88	97

[a] In pure product. [b] HPLC (Chiralpak AD column). [c] Conversion yield. [d] In 1,2-dichloroethane at −25 °C.

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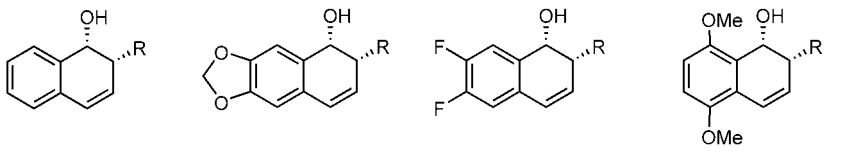
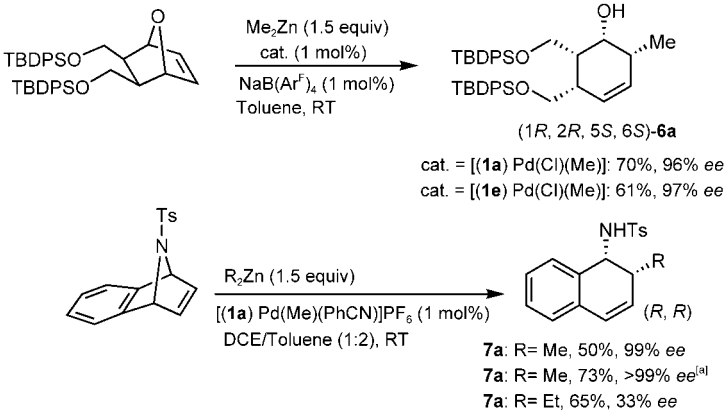


2a: R = Me, 88%, 97% *ee*[a] **3a**: R = Me, 71%, >99% *ee* **4a**: R = Me, 95%, 95% *ee* **5a**: R = Me, 98%, 97% *ee*
2b: R = Et, 81%, 95% *ee* **3b**: R = Et, 61%, 94% *ee* **4b**: R = Et, 79%, 96% *ee* **5b**: R = Et, 85%, 94% *ee*

Scheme 2. Alcohols **2**–**5** resulting from the reaction of substituted oxabenzonorbornadienes with Me_2Zn and Et_2Zn catalyzed with $[(\mathbf{1e})PdMe]^+$. [a] The reaction was carried out at −25 °C.

Finally, to test the efficiency of these highly active catalysts toward much less reactive bicyclic substrates, we studied the opening reaction of nonaromatic [2.2.1]oxabicyclic alkenes and azabenzonorbornadienes, which usually require harsher reaction conditions.[5c] Notably, $[(\mathbf{1a})PdMe]^+$ and $[(\mathbf{1e})PdMe]^+$ (1 mol%) induced the ring opening of the [2.2.1]oxabicyclic alkene with Me_2Zn within three hours at room temperature, which led to cyclohexenol **6a**[12] in 96–97% *ee* (Scheme 3).

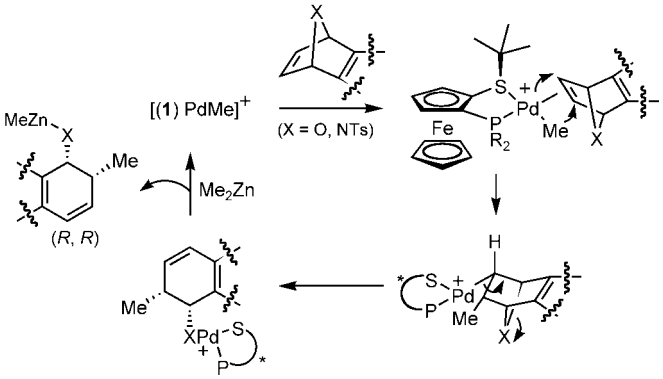


Scheme 3. Ring opening of less reactive *meso* substrates. TBDPS = *tert*-butyldiphenylsilyl, Ts = toluene-4-sulfonyl. [a] The reaction was carried out with 5 mol% of catalyst.

The most reactive catalyst for the opening of the azabenzonorbornadiene derivative was the complex $[(\mathbf{1a})Pd(Me)(PhCN)]^+(PF_6)^-$. In the reaction with Me_2Zn the ring-opened product (*R*,*R*)-**7a** was obtained within 30 minutes (73% yield) with virtually complete enantiocontrol (> 99% *ee*) by using 5 mol% of catalyst. The use of 1 mol% of catalyst resulted in a much slower reaction (60% conversion after 48 h). The reaction with Et_2Zn was faster, but surprisingly much less enantioselective, and gave **7b** in 33% *ee*.

According to the X-ray structures shown in Figure 1, the high enantioselectivity displayed by these P,S-palladium species could be explained by assuming a combination of electronic and steric factors: a) coordination of the bicyclic alkene *trans* to the phosphorus atom on the palladium center; and b) coordination of the alkene from its less hindered *exo* face, with orientation of the oxygen (or nitrogen) bridge to the opposite side of the very bulky *tert*-butyl group. Thus, the synergetic effect derived from the strong electronic *trans* effect of the phosphorus moiety and the great steric control exerted by the close, bulky stereogenic sulfur substituent would be responsible for the high asymmetric induction in the key carbopalladation step (Scheme 4).

In summary, the cationic methylpalladium species derived from the readily available planar chiral P,S ligands **1** display an excellent profile as catalysts for the enantioselective alkylative ring



Scheme 4. Mechanistic proposal.

opening of oxa- and azabicyclic alkenes with dialkyl zinc reagents. The structure of these catalysts suggests that the high asymmetric induction relies on the strong *trans* effect of the phosphane moiety that acts in combination with the sterically demanding environment imposed by the stereogenic sulfur atom directly bonded to the palladium atom.

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Keywords: alkenes · asymmetric catalysis · ferrocenyl ligands · palladium · S ligands

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[7] For the use of the parent ligands **1** in the Pd-catalyzed desymmetrization of oxabenzonorbornadiene, see reference [4c].

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[9] Crystal structure for $C_{27}H_{30}ClFePPdS$ [(**1a**)Pd(Cl)(Me)]: crystal size $0.35 \times 0.34 \times 0.32$ mm, hexagonal, space group $P6_1$, $a = 18.3144(2)$, $b = 18.3144(2)$, $c = 15.7573(2)$ Å, $\gamma = 120°$, $V = 4577.18(9)$ Å^3, $Z = 6$, $\rho_{calcd} = 1.339$ Mg m^{-3}, $\mu = 10.583$ mm^{-1}, $2\theta_{max} = 70.25°$, $Cu_{K\alpha}$ radiation, $\lambda = 1.54178$ Å, $2\theta/\omega$ scans, $T = 296(2)$ K, absorption correction: none, 29638 reflections collected, 5709 independent. Refinement on F^2 for 5709 reflections and 293 parameters gave GOF = 0.996, $R1 = 0.0334$, $wR2 = 0.0992$ for $I > 2\sigma(I)$. Residual electron density $-0.391 < \Delta\rho < 0.775$ e Å^{-3}. Absolute structure parameter −0.008(5).

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[11] Crystal structure for $C_{66}H_{47}BF_{24}FeNPPdS$ {[(**1a**)Pd(Me)(NC-Ph)]$^+$[$(Ar^F{}_4)B$]$^-$}: crystal size $0.23 \times 0.14 \times 0.10$ mm, monoclinic, space group $P2_1$, $a = 17.372(3)$, $b = 23.423(4)$, $c = 18.140(3)$ Å, $\beta = 110.615(3)°$, $V = 6909(2)$ Å^3, $Z = 4$, $\rho_{calcd} = 1.487$ Mg m^{-3}, $\mu = 0.628$ mm^{-1}, $2\theta_{max} = 56.56°$, $Mo_{K\alpha}$ radiation, $\lambda = 0.71073$ Å, $2\theta/\omega$ scans, $T = 293$ K, absorption correction: none, 24303 reflections collected, 10937 independent. Refinement on F^2 for 24303 reflections and 1739 parameters gave GOF = 1.002, $R1 = 0.0895$, $wR2 = 0.2353$ for $I > 2\sigma(I)$. Residual electron density $-1.655 < \Delta\rho < 0.944$ e Å^{-3}. Absolute structure parameter −0.01(3). CCDC-231878 and CCDC-229828 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/conts/retrieving.html (or from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: (+44) 1223-336-033; or deposit@ccdc.cam.ac.uk).

[12] The absolute configuration of the alcohols **2**–**4** and **6a** was established by comparison with the data obtained by HPLC using a chiral stationary phase for both enantiomers of these compounds (see references [5c] and [5d]).

[13] In all these reactions the enantioselectivity achieved from [(**1e**)Pd(Cl)(Me)] was significantly higher than that from the parent diphenylphosphanyl catalyst [(**1a**)Pd(Cl)(Me)].

[14] A higher reactivity was found in DCE than in toluene, probably as a result of the increased solubility of the cationic Pd complex in the former.

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