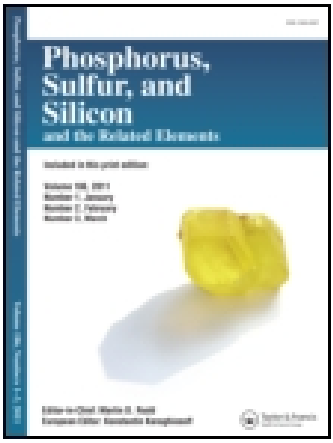



Phosphorus, Sulfur, and Silicon and the Related Elements
Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/gpss20

# Transition Metal Complexes of Fesulphos Ligands in Enantioselective Catalytic Transformations

Juan Carlos Carretero [a], Ramón Gómez Arrayás [a], Olga García Mancheño [a] & Silvia Cabrera [a]
[a] Departamento de Química Orgánica, Facultad de Ciencias, Universidad Autónoma de Madrid, Madrid, Spain
Published online: 16 Aug 2006.

To cite this article: Juan Carlos Carretero, Ramón Gómez Arrayás, Olga García Mancheño & Silvia Cabrera (2005) Transition Metal Complexes of Fesulphos Ligands in Enantioselective Catalytic Transformations, Phosphorus, Sulfur, and Silicon and the Related Elements, 180:5-6, 1259-1265, DOI: 10.1080/10426500590911458

To link to this article: http://dx.doi.org/10.1080/10426500590911458

*Phosphorus, Sulfur, and Silicon*, 180:1259–1265, 2005

ISSN: 1042-6507 print / 1563-5325 online
DOI: 10.1080/10426500590911458



# Transition Metal Complexes of Fesulphos Ligands in Enantioselective Catalytic Transformations

**Ramón Gómez Arrayás**
**Olga García Mancheño**
**Silvia Cabrera**
**Juan Carlos Carretero**
Departamento de Química Orgánica, Facultad de Ciencias, Universidad Autónoma de Madrid, Madrid, Spain

*Metal complexes of 1-phosphino-2-sulfenylferrocene (fesulphos ligands) act as highly efficient catalysts in Pd-catalyzed desymmetrization of meso heterobicyclic alkenes and in Cu-catalyzed formal aza Diels–Alder reaction of Danishefsky diene to* N*-sulfonyl imines.*

**Keywords** Aza Diels–Alder; planar chirality; ring-opening; sulfonyl imines; sulfur ligands



## INTRODUCTION

Thioether-based chiral ligands hold great promise in enantioselective catalysis because the sulfur atom becomes stereogenic upon coordination to a metal, which imposes a unique asymmetric environment next to the reactive metal center. We have recently developed a novel family of P,S-bidentate ligands possessing planar chirality as the only element of asymmetry: *Fesulphos* **1** (1-phosphino-2-sulfenylferrocenes).[1] The modular approach to their synthesis enables easy fine-tuning of their asymmetric performance by simple modification of the electronic and steric properties of the groups attached to phosphorus and sulfur. Ligands **1** proved to be highly efficient in the Pd-catalyzed allylic substitutions of 1,3-diphenylpropenyl acetate (96–99.5% ee).[1] Described herein

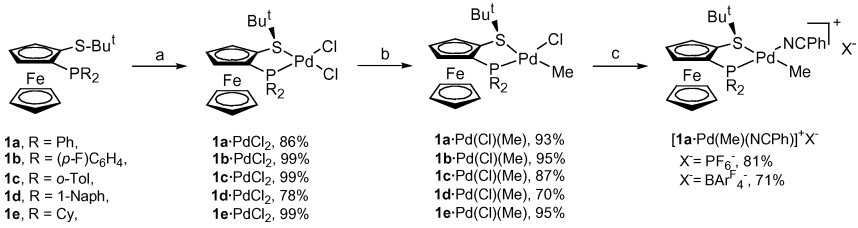
Received July 9, 2004; accepted October 5, 2004.
Financial support by MEC (BQU2003-0508) is gratefully acknowledged. R. G. A. thanks the MEC for a Ramon y Cajal contract. O. G. M. and S. C. thank MEC and UAM, respectively, for predoctoral fellowships.
Address correspondence to Juan Carlos Carretero, Departamento de Química Orgánica, Facultad de Ciencias, Universidad Autónoma de Madrid, Cantoblanco, 28049 Madrid, Spain. E-mail: juancarlos.carretero@uam.es

is the behavior of metal complexes of these ligands as chiral catalysts in other asymmetric transformations such as the Pd-catalyzed ring-opening reaction of meso bicyclic alkenes,[2] and the Cu-catalyzed aza Diels–Alder cycloaddition of electron-rich dienes to *N*-sulfonyl imines.[3]

## RESULTS

### Cationic Palladium Complexes of Fesulphos in the Asymmetric Ring-Opening Reaction of Meso Heterobicyclic Alkenes

The Pd-catalyzed enantioselective ring opening of meso oxabicyclic alkenes with dialkylzinc reagents is a powerful C—C bond-forming reaction recently reported by Lautens.[4] Inspired by mechanistic studies evidencing enantioselective carbopalladation of the alkene with cationic alkyl palladium species $[L_2PdR]^+$ as the key step, we envisioned that the cationic methylpalladium complexes of Fesulphos $[(\mathbf{1})PdMe]^+$ could function as very active catalysts in this reaction. Scheme 1 shows the preparation of such cationic complexes. Treatment of **1** with $PdCl_2(CH_3CN)_2$ afforded in very high yield the corresponding complexes $[(\mathbf{1})PdCl_2]$ as single epimers at sulfur. Interestingly, the transmetallation reaction of these complexes with $Me_2Zn$ was completely stereoselective, affording a single complex $[(\mathbf{1})Pd(Cl)(Me)]$ in 70–95% yield. The cis arrangement of the methyl group and the phosphine was unequivocally established by X-ray crystal diffraction analysis of the complex [(**1a**)Pd(Cl)(Me)].




**1a**, R = Ph,
**1b**, R = (*p*-F)$C_6H_4$,
**1c**, R = *o*-Tol,
**1d**, R = 1-Naph,
**1e**, R = Cy,

**1a**·$PdCl_2$, 86%
**1b**·$PdCl_2$, 99%
**1c**·$PdCl_2$, 99%
**1d**·$PdCl_2$, 78%
**1e**·$PdCl_2$, 99%

**1a**·Pd(Cl)(Me), 93%
**1b**·Pd(Cl)(Me), 95%
**1c**·Pd(Cl)(Me), 87%
**1d**·Pd(Cl)(Me), 70%
**1e**·Pd(Cl)(Me), 95%

[**1a**·Pd(Me)(NCPh)]$^+$X$^-$
X$^-$= $PF_6^-$, 81%
X$^-$= $BAr^F{}_4^-$, 71%

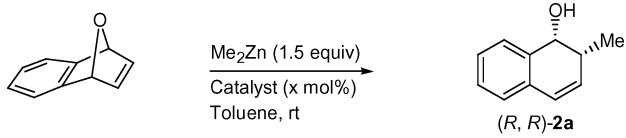
**SCHEME 1** a) $PdCl_2(CH_3CN)_2$, $CH_2Cl_2$, rt; b) $Me_2Zn$ (1.5 equiv.), $CH_2Cl_2$, rt; c) $AgPF_6$ or $NaBAr^F_4$, PhCN, $CH_2Cl_2$, rt.

The ring-opening reaction of oxabenzonorbornadiene with $Me_2Zn$ in the presence of a 5 mol% of neutral palladium complexes $[(\mathbf{1a})PdCl_2]$ and [(**1a**)Pd(Cl)(Me)] in toluene at room temperature (rt) led to about 80% conversion after 24 h, affording the ring-opened product in 81–85% ee (Scheme 2 and Table I). Remarkably, a complete conversion was observed within 10 min when 5 mol% of the air-stable cationic complex

**TABLE I**

| Catalyst(× mol%) | Time | Yield (%) | ee (%) |
|---|---|---|---|
| **1a**·$PdCl_2$ (5.0) | 24 h | 80 | 81 |
| **1a**·Pd(Cl)(Me) (5.0) | 24 h | 75 | 85 |
| [**1a**·Pd(Me)(NCPh)] + $NaBAr^F_4$(5.0) | 10 min | 86 | 78 |
| [**1a**·Pd(Me)(NCPh)] + $NaBAr^F_4$(0.2) | 5 h | 88 | 97 |

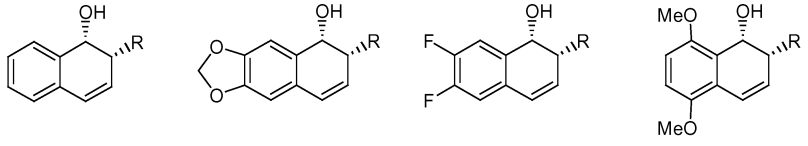
[(**1a**)Pd(Me)(PhCN)]$BAr^F_4$ [$Ar^F$ = 3,5-bis(trifluoromethyl)phenyl] was used (78% ee). To fine-tune the reactivity and enantioselectivity of the process we next studied the effect of the substitution at the phosphorus atom (complexes of ligands **1b–e**), the complex of the electronically rich dicyclohexyl phosphane **1e** providing best results. In fact, the combination of [(**1e**)Pd(Cl)(Me)] +$NaB(Ar^F)_4$ proved to be so effective that catalyst loading as low as 0.2 mol% was sufficient to reach quantitative conversion within 5 h at −25°C, which afforded alcohol **2a** in 88% yield with 97% ee.




**SCHEME 2**

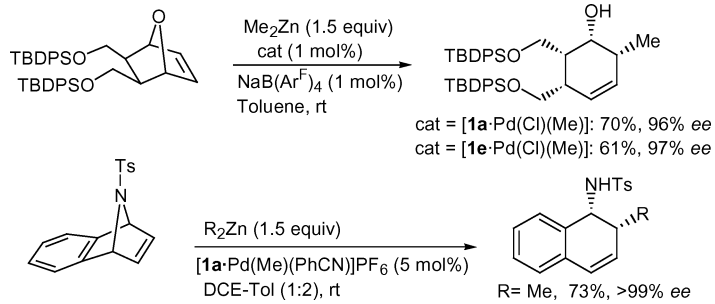
Figure 1 highlights the scope of the process. Complete conversions within 10–30 min, good chemical yields (61–98%), and excellent enantioselectivities (94–99% ee, HPLC) were obtained in the ring opening of a variety of substituted meso oxabenzonorbornadienes with both $Me_2Zn$ and $Et_2Zn$ in DCE at room temperature by using 0.5 mol% [(**1e**)Pd(Cl)(Me)] in combination with $NaB(Ar^F)_4$ (0.5 mol%) as catalyst.

The efficiency of these highly active catalysts toward much less reactive bicyclic substrates was also studied (Scheme 3). Thus, 1 mol%




R = Me, 88%, 97% *ee* R = Me, 71%, >99% *ee* R = Me, 95%, 95% *ee* R = Me, 98%, 97% *ee*
R = Et, 81%, 95% *ee* R = Et, 61%, 94% *ee* R = Et, 79%, 96% *ee* R = Et, 85%, 94% *ee*

**FIGURE 1**




**SCHEME 3**

of both [(**1a**)Pd(Me)]$^+$ and [(**1e**)Pd(Me)]$^+$ induced the ring-opening reaction of nonaromatic [2.2.1]-oxabicyclic alkene with $Me_2Zn$ in 3 h at rt, providing the corresponding cyclohexenol in 96–97% ee. On the other hand, a 5 mol% of the complex [(**1a**)Pd(Me)(PhCN)]$^+(PF_6)^-$ catalyzed the opening of the *N*-tosyl azabenzonorbornadiene with $Me_2Zn$ in 30 min at room temperature, the corresponding (*R*,*R*)-2-methyl-1-tosylaminodihydronaphthalene being obtained with virtually complete enantiocontrol (>99% ee).

The X-ray structure of palladium complexes shown in Scheme 1 suggests that the high asymmetric induction displayed by these catalysts 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.

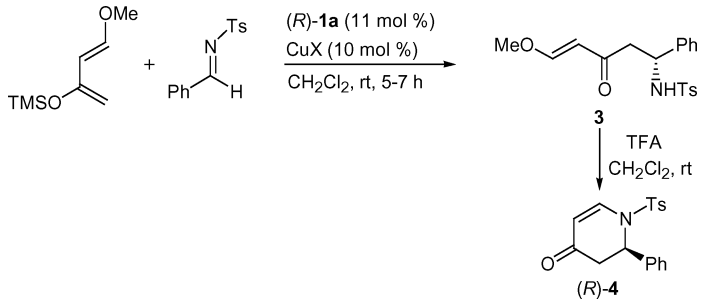
## Copper Complexes of Fesulphos as Chiral Lewis Acids for Enantioselective Aza Diels–Alder Reactions of *N*-Sulfonyl Imines

The catalytic enantioselective aza Diels–Alder reaction of electron-rich dienes with aldimines[5] is conceptually an extremely powerful strategy for the construction of dihydropyridones, which are key intermediates in the synthesis of biologically active alkaloids.[6] Initially, we performed

**TABLE II**

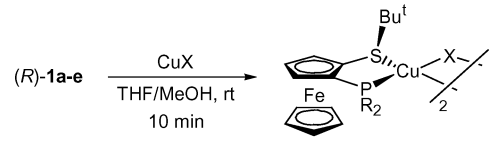
| | 4 | |
|---|---|---|
| Cu salt | Yield (%) | ee (%) |
| $Cu(MeCN)_4ClO_4$ | 83 | 74 |
| $Cu(MeCN)_4PF_6$ | 72 | 77 |
| CuOTf | 80 | 76 |

the reaction of Danishefsky's diene with the *N*-tosylimine of benzaldehyde in the presence of a 10 mol% of ligand **1a** and $Cu(CH_3CN)_4ClO_4$ in $CH_2Cl_2$ at rt. Complete conversion was observed within 5 h to afford the Mannich-type addition product **3**, which was readily transformed into the cycloadduct **4** upon addition of TFA to the reaction mixture (Scheme 4 and Table II). Similar results were obtained with other Cu(I) salts.




**SCHEME 4**

We turned our attention towards the isolation and structural study of Cu(I) complexes of Fesulphos ligands, whose preparation was achieved by simple combination of equimolar amounts of ligands **1a–e** and CuX (X = Cl, Br) in THF/MeOH (Scheme 5). The tetrahedral coordination at copper and the absolute (*R*) configuration at sulfur of the single epimer obtained in all cases were unambiguously established by X-ray analysis of **5a**.




**5a**, R=Ph, X=Cl, 99%
**6a**, R=Ph, X=Br, 94%
**5b**, R=(*p*-F)$C_6H_4$(X=Cl), 99%
**5c**, R=*o*-Tol, X=Cl, 99%
**5d**, R=1-Naph, X=Cl, 61%
**6d**, R=1-Naph, X=Br, 90%
**5e**, R=Cy, X=Cl, 61%

**SCHEME 5**

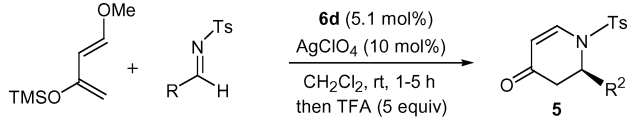
The evaluation of this set of copper complexes (5.1 mol%), combined with $AgClO_4$ (10 mol%) as chiral catalysts in the model aza Diels–Alder reaction, led us to find that both reactivity and enantioselectivity were deeply influenced by the substitution at phosphorus. Complex **6d**, having the bulky $\alpha$-naphthylphosphine moiety, exhibited highest values of reactivity and asymmetric induction, affording (*R*)-**4** in 87% yield and 97% ee at $-20^\circ$C (90% yield and 93% ee at room temperature).

**TABLE III**

| R | Yield (%)[a] | ee (%)[b] |
|---|---|---|
| Ph | 90 | 93 (97)[c] |
| o-Tol | 82 | 93 |
| ($p$-F)$C_6H_4$ | 78 | 88 (93)[c] |
| ($p$-OMe)$C_6H_4$ | 76 | 91 |
| ($p$-$NMe_2$)$C_6H_4$ | 39 | 93 |
| 2-Naph | 85 | 86 (93)[c] |
| PhCH=CH | 66 | 83 (96)[c] |
| $n$-Pr | 65[c] | 73[c] (82)[d] |

[a]Isolated yield; [b]Determined by HPLCs; [c]AT-20°C; [d]At-78°C.

With optimized catalyst **6d** in hand, the scope of the reaction was next explored with a variety of other *N*-sulfonyl imines (Scheme 6 and Table III). A high degree of stereochemical fidelity was observed with




**SCHEME 6**

a number of electronically varied aromatic imines (entries 1–6, 86–93% ee at rt; 93–97% ee at −20°C). It is also noteworthy that the high reactivity and enantioselectivity displayed by the tosyl imine of cinnamaldehyde, the reaction being complete within 1 h at –20°C to afford the cycloadduct with 82% yield and 96% ee. As far as we know, this is the first example of a catalytic enantioselective aza Diels–Alder reaction of $\alpha,\beta$-unsaturated imino dienophiles. The applicability of this protocol to aldimines of enolizable aliphatic aldehydes, a kind of heterodienophiles scarcely studied in this reaction, was demonstrated with the tosylimine of butyraldehyde, which reacted in 30 min at −20°C to provide the corresponding dihydropyridone in 65% yield and 73% ee (82% ee at −78°C).

Finally, from a practical point of view, it is important to note that these *N*-sulfonyl dihydropyridones are crystalline solids, giving rise to enantiopure samples (>99.5% ee) upon a single recrystallization.

## REFERENCES

[1] O. García Mancheño, J. Priego, S. Cabrera, R. Gómez Arrayás, T. Llamas, and J. C. Carretero, *J. Org. Chem.*, **68,** 3679 (2003).

[2] a) S. Cabrera, R. Gómez Arrayás, and J. C. Carretero, *Angew. Chem., Int. Ed. Engl.*, **43,** 3944 (2004); b) J. Priego, O. García Mancheño, S. Cabrera, R. Gómez Arrayás, T. Llamas, and J. C. Carretero, *Chem. Commun.*, 2512 (2002).

[3] O. García Mancheño, R. Gómez Arrayás, and J. C. Carretero, *J. Am. Chem. Soc.*, **126,** 456 (2004).

[4] a) M. Lautens and S. Hiebert, *J. Am. Chem. Soc.*, **126,** 1437 (2004); b) M. Lautens, S. Hiebert, and J.-L. Renaud, *J. Am. Chem. Soc.*, **123,** 6834 (2001). For a review, see: c) M. Lautens, K. Fagnou, and S. Hiebert, *Acc. Chem. Res.*, **36,** 48 (2003).

[5] For previous catalytic asymmetric aza Diels–Alder reactions: a) N. S. Josephsohn, M. L. Snapper, and A. H. Hoveyda, *J. Am. Chem. Soc*., **125,** 4018 (2003); b) S. Kobayashi, K.-I. Kusakabe, and H. Ishitani, *Org. Lett.*, **2,** 1225 (2000); c) S. Yao, S. Saaby, R. G. Hazell, and K. A. Jorgensen, *Chem. Eur. J.*, **6,** 2435 (2000).

[6] a) J. P. Michael, in *The Alkaloids*, G. A. Cordell (Ed.) (Academic Press: San Diego, 2001), Vol. 55. For the potential of enantiopure dihydropyridones in alkaloid synthesis, see D. L. Comins, S. Huang, C. L. McArdle, and C. L. Ingalls, *Org. Lett*., **3,** 469 (2001).