1-Phosphino-2-sulfenylferrocenes: efficient ligands in enantioselective palladium-catalyzed allylic substitutions and ring opening of 7-oxabenzonorbornadienes†

Julián Priego, Olga García Mancheño, Silvia Cabrera, Ramón Gómez Arrayás, Tomás Llamas and Juan C. Carretero*

Departamento de Química Orgánica, Facultad de Ciencias, Universidad Autónoma de Madrid, Cantoblanco, 28049 Madrid, Spain. E-mail: juancarlos.carretero@uam.es; Fax: +34 913973966; Tel: +34 913973925

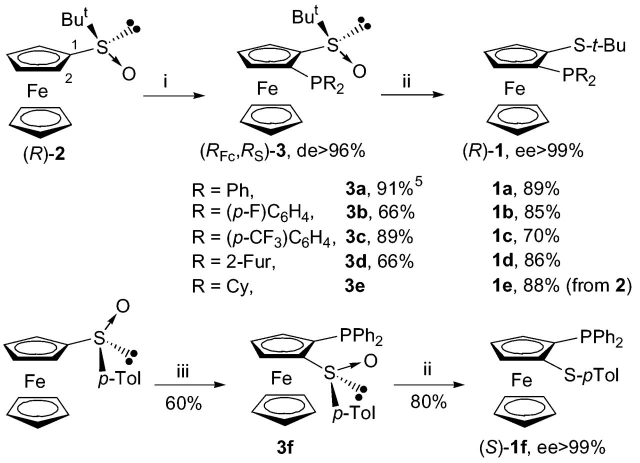
Received (in Cambridge, UK) 26th July 2002, Accepted 20th September 2002
First published as an Advance Article on the web 7th October 2002

The readily available 1-phosphino-2-sulfenylferrocenes 1 provide very high enantioselectivities in Pd-catalyzed allylic substitution reactions and alkylative ring opening of 7-oxabenzonorbornadiene with dialkylzinc reagents.

The use of mixed bidentate ligands equipped with strong and weak donor heteroatom pairs has proved to be one of the most useful concepts in asymmetric catalysis. Although much less studied than the mixed P,N-coordination mode, some recent reports indicate that P,S-bidentate ligands based on chiral thioethers can also lead to high enantioselectivities in C–C bond forming metal-catalyzed reactions.[1] However, P,S-bidentate ligands possessing planar chirality as the only source of chirality have not been previously studied. We describe herein that the readily available enantiopure P,S-bidentate ferrocenes **1** act as very efficient ligands in Pd-catalyzed allylic substitutions and alkylative ring opening of 7-oxabenzonorbornadiene.

The preparation of the starting sulfinylferrocene **2** had been previously reported either by sulfinylation of ferrocenyllithium with enantiopure *tert*-butylsulfinates, or by asymmetric oxidation of *tert*-butylsulfenylferrocene.[2] Alternatively, we have recently reported[3] that (*R*)-**2** can be readily prepared in multigram scale by sulfinylation of ferrocenyllithium with (*R*)-S-*tert*-butyl *tert*-butanethiosulfinate.[4] It was well established from the work of Kagan and coworkers [2] and Hua and coworkers[5] that the *ortho*-lithiation of (*R*)-**2** occurs with nearly complete diastereocontrol at C-2. Accordingly, the treatment of (*R*)-**2** with *tert*-butyllithium and a chlorophosphine led to the corresponding (R_{Fc}, R_S) sulfinylferrocenyl phosphine **3** in good yield[6] (66–91%) and complete diastereoselectivity (de > 96%). The further reduction of the sulfoxide to the sulfide moiety was cleanly achieved with $HSiCl_3$–Et_3N in refluxing toluene, affording the enantiopure planar chiral ferrocenes **1a**–**e** (ee > 99%; HPLC, Chiralcel OD) (Scheme 1). The enantiopure *p*-tolylsulfenyl ferrocene (*S*)-**1f** was readily prepared from (*S*)-*p*-tolylsufinylferrocene[2,7] following the same synthetic approach.

These sterically and electronically varied ferrocenes **1a**–**f** were evaluated as chiral ligands in the standard Pd-catalyzed allylic substitution[8] of dimethyl malonate with 1,3-diphenyl-2-propenyl acetate (Table 1). Interestingly, we found that this transformation was deeply accelerated by addition of a catalytic amount of Bu_4NCl[9] (10 mol%), which allows us to carry out the reaction at −20 °C, therefore improving the enantioselectivity (values in brackets). Remarkably, the parent ligand **1a** and the phosphines **1b** and **1c**, having electron-withdrawing substituents, provided (*R*)-**4** with very high enantioselectivity (ee up to 96–97% at −20 °C). In contrast, a decrease in the asymmetric induction was observed with the more electron-rich phosphines **1d** and **1e** (entries 4 and 5). A much more dramatic effect was found in the case of the *p*-tolylsulfenylferrocene **1f** (entry 6), which afforded **4** in low ee. This suggests that a high sterically demanding substitution at the sulfur atom in ligands **1** is crucial for reaching a high stereochemical control.

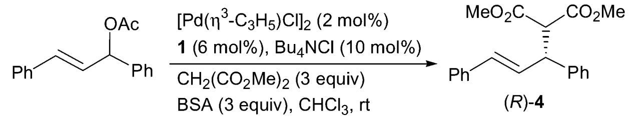


Scheme 1 Reagents and conditions: i, *t*-BuLi, THF, −78 °C; R_2PCl; ii, $HSiCl_3$, Et_3N, toluene, 110 °C; iii, LDA, THF, −78 °C; Ph_2PCl (ref. 7).

Ligands **1a**–**f** were next tested in Pd-catalyzed allylic substitution with nitrogen nucleophiles, such as benzylamine and potassium phthalimide (KPhth) (Table 2). In the presence of **1a** the reaction with $BnNH_2$ afforded (*S*)-**5** in 97% ee and the reaction with phthalimide gave (*S*)-**6** in 91% ee. Interestingly, the electronically poor phosphines **1b** and **1c** provided again the best results (ee up to 99%).

The behavior of ferrocenes **1** as P,S-bidentate ligands was demonstrated by X-ray crystallographic study[10] of the complex (**1a**)$PdCl_2$ (Fig. 1), which was readily prepared by treatment of **1a** with $Pd(CH_3CN)_2Cl_2$ in CH_2Cl_2 (72% yield). Important structural information deduced from this study is the anti

Table 1 Pd-catalyzed reaction of 1,3-diphenyl-2-propenyl acetate with dimethyl malonate in the presence of ligands **1**



Entry	Ligand	Yield (%)[a]	Ee (%)[b]
1	**1a**	92	93 (96)[c]
2	**1b**	94	92 (97)[c]
3	**1c**	90	92 (96)[c]
4	**1d**	60	90
5	**1e**	96	84
6	**1f**	92	40[d]

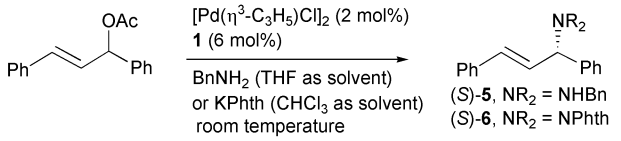
[a] In pure product after chromatography. [b] Determined by HPLC (Chiralcel OD). [c] Enantiomeric excess at −20 °C. [d] Enantiomeric excess of (*S*)-**4**.

---

† Electronic supplementary information (ESI) available: experimental details and determination of enantiomeric excesses. See http://www.rsc.org/suppdata/cc/b2/b207344g/

DOI: 10.1039/b207344g

Table 2 Pd-catalyzed reaction of 1,3-diphenyl-2-propenyl acetate with benzylamine and phthalimide in the presence of ligands **1**



Entry	Ligand	Nu	Product	Yield (%)[a]	Ee (%)[b]
1	**1a**	$BnNH_2$	**5**	80	97 (97)[c]
2	**1a**	KPhth	**6**	74	91
3	**1b**	$BnNH_2$	**5**	89	98 (99)[c]
4	**1b**	KPhth	**6**	90	92.5 (96)[c]
5	**1c**	$BnNH_2$	**5**	91	98
6	**1d**	$BnNH_2$	**5**	60[d]	94
7	**1e**	$BnNH_2$	**5**	50[e]	40
8	**1f**	$BnNH_2$	**5**	88	41[f]

[a] In pure product after chromatography. [b] Determined by HPLC (Chiralcel OD). [c] Enantiomeric excess at −20 °C. [d] Conversion yield after 15 h. [e] Conversion yield after 96 h. [f] Enantiomeric excess of (*R*)-**5**.

orientation of the *tert*-butyl group with regard to the iron atom and that the Pd–Cl bond *trans* to the phosphorus is longer than *trans* to sulfur (2.35 Å *vs.* 2.30 Å), reflecting the stronger *trans* effect of the phosphine moiety. Taking into account these data, the high asymmetric efficiency of ligands **1** could be explained by the preferential attack of the nucleophile *trans* to phosphorus[1] on the presumed key π-allylpalladium complex intermediate **I**.

To investigate the application of ligands **1** in other palladium-catalyzed reactions, we studied the alkylative ring opening of 7-oxabenzonorbornadiene with dialkylzinc reagents, recently reported by Lautens *et al.*,[11] in which the efficiency of P,S-bidentate ligands had not been previously explored. The results obtained using $Pd(CH_3CN)_2Cl_2$ as catalyst are shown in Table 3.

The reaction of 7-oxabenzonorbornadiene with Et_2Zn and Me_2Zn in the presence of **1a** provided the known alcohols[11] **7a** and **7b** in 90% ee and 88% ee, respectively. In contrast, the electron-deficient phosphines **1b** and **1c**, which gave optimal results in the allylic substitutions, exhibited only modest performance in the Pd-catalyzed alkylative ring opening process, affording the racemic alcohol **8**[12] as the major product in several cases (Table 3, entries 3 and 5). Interestingly, in this reaction the best results were obtained with the electron-rich dialkylphosphine **1e** (93–94% ee, entries 7 and 8). These enantioselectivities are among the best reported for this transformation.[11]

In summary, the readily available bidentate P,S-ligands **1**, having solely planar chirality, provide high enantioselectivities in Pd-catalyzed allylic substitutions and in the ring opening of 7-oxabenzonorbornadiene with dialkylzinc reagents. The modular approach for the preparation of this ligand system allows its electronic and steric properties to be easily fine-tuned.

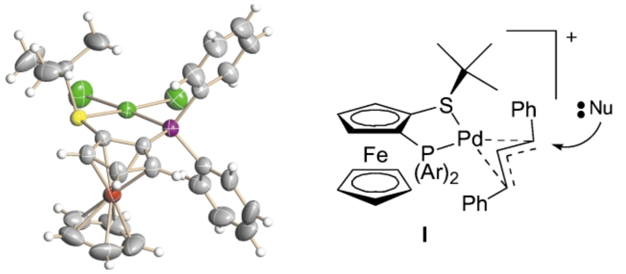
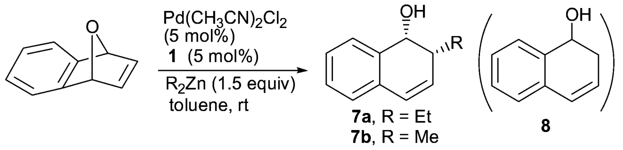


Fig. 1 Crystal structure of (**1a**)$PdCl_2$ and proposed key π-allylpalladium complex intermediate **I**.

Table 3 Pd-catalyzed reaction of oxabenzonorbornadiene with dialkylzinc reagents in the presence of ligands **1**



Entry	Ligand	R	Product	Yield (%)[a]	Ee (%)[b]
1	**1a**	Et	**7a**	70	90
2	**1a**	Me	**7b**	72	88
3	**1b**	Et	**7a**	20[c]	81
4	**1b**	Me	**7b**	63	82
5	**1c**	Et	**7a**	16[d]	70
6	**1c**	Me	**7b**	65	67
7	**1e**	Et	**7a**	68	93
8	**1e**	Me	**7b**	73	94
9	**1f**	Et	**7a**	22[e]	6

[a] In pure product after chromatography. [b] Determined by HPLC (Chiralcel OD column). [c] Compound **8** was also obtained in 37% yield. [d] Compound **8** was also obtained in 40% yield. [e] Conversion yield after 3 days.

Financial support of this work by the M.C.Y.T. is gratefully acknowledged (project BQU2000-0266). R. G. A. thanks the M.C.Y.T. for a 'Contrato Ramón y Cajal'. J. P. and O. G. M. thank the M.E.C. for a predoctoral fellowship. We acknowledge Johnson Matthey PLC for a generous loan of $PdCl_2$.

Notes and references

1 For recent examples, see: A. Albinati, P. S. Pregosin and K. Wick, *Organometallics*, 1996, **15**, 2419; J. Spencer, V. Gramlich, R. Häusel and A. Togni, *Tetrahedron: Asymmetry*, 1996, **7**, 41; D. A. Evans, K. R. Campos, J. S. Tedrow, F. E. Michael and M. R. Gagné, *J. Am. Chem. Soc.*, 2000, **122**, 7905; Y.-Y. Yan and T. V. RajanBabu, *Org. Lett.*, 2000, **2**, 199; D. Enders, R. Peters, R. Lochtman, G. Raabe, J. Runsink and J. W. Bats, *Eur. J. Org. Chem.*, 2000, 3399; H. Nakano, Y. Okuyama, M. Yanagida and H. Hongo, *J. Org. Chem.*, 2001, **66**, 620; H. Nakano, Y. Suzuki, C. Kabuto, R. Fujita and H. Hongo, *J. Org. Chem.*, 2002, **67**, 5011.

2 F. Rebière, O. Riant, L. Ricard and H. B. Kagan, *Angew. Chem., Int. Ed. Eng.*, 1993, **32**, 568; P. Diter, O. Samuel, S. Taudien and H. B. Kagan, *Tetrahedron: Asymmetry*, 1994, **5**, 549.

3 J. Priego, O. García Mancheño, S. Cabrera and J. C. Carretero, *J. Org. Chem.*, 2002, **67**, 1346.

4 D. A. Cogan, G. Liu, K. Kim, B. J. Backes and J. A. Ellman, *J. Am. Chem. Soc.*, 1998, **120**, 8011.

5 N. M. Lagneau, Y. Chen, P. M. Robben, H.-S. Sin, K. Takasu, J.-S. Chen, P. D. Robinson and D. H. Hua, *Tetrahedron*, 1998, **54**, 7301.

6 In solution, the phosphines **3** slowly evolve to the corresponding sulfenylferrocenyl phosphine oxides by an intramolecular oxygen transfer process. For a similar behaviour, see: K. Hiroi, Y. Suzuki, I. Abe and R. Kawagishi, *Tetrahedron*, 2000, **56**, 4701.

7 O. Riant, G. Argouarch, D. Guillaneux, O. Samuel and H. B. Kagan, *J. Org. Chem.*, 1998, **63**, 3511.

8 For a review, see: B. M. Trost and D. L. van Vranken, *Chem. Rev.*, 1996, **96**, 395.

9 For a review on halide effects in transition metal catalysis, see: K. Fagnou and M. Lautens, *Angew. Chem., Int. Ed.*, 2002, **41**, 26.

10 *Crystal data* for $C_{26}H_{27}Cl_2FePPdS$ [(**1a**)$PdCl_2$]: crystal size $0.08 \times 0.25 \times 0.25$ mm, $M_w = 635.66$, monoclinic, space group $P2_1/n$, $a = 9.7541(5)$, $b = 15.9433(8)$, $c = 16.9386(8)$ Å, $\beta = 94.8180(10)°$, $V = 2624.9(2)$ Å^3, $Z = 4$, $D_c = 1.609$ g cm^{-3}, $\mu = 1.595$ mm^{-1}, $T = 296(2)$ K, Mo-Kα radiation ($\lambda = 0.71073$ Å), 17617 reflections measured, 7447 independent ($R_{int} = 0.0810$). Refinement on F^2 for 7447 reflections and 293 parameters gave $GOF = 1.067$, $R = 0.0515$, $R_w = 0.1076$ for $I > 2\sigma(I)$. CCDC reference number 185296. See http://www.rsc.org/suppdata/cc/b2/b207344g/ for crystallographic data in CIF or other electronic format.

11 M. Lautens, J.-L. Renaud and S. Hiebert, *J. Am. Chem. Soc.*, 2000, **122**, 1804; M. Lautens, S. Hiebert and J.-L. Renaud, *J. Am. Chem. Soc.*, 2001, **123**, 6834.

12 M. Lautens and T. Rovis, *Tetrahedron*, 1998, **54**, 1107.