## Novel *N*,*S*- and *N*,*Se*-planar chiral [2,2]paracyclophane ligands: synthesis and application in Pd-catalyzed allylic alkylation

## Xue-Long Hou,\*ab Xun-Wei Wu,a Li-Xin Dai,a Bo-Xun Caoa and Jie Suna

<sup>a</sup> Laboratory of Organometallic Chemistry, Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences, 354 Fenglin Lu, Shanghai 200032, China. E-mail: xlhou@pub.sioc.ac.cn

<sup>b</sup> Shanghai-Hong Kong Joint Laboratory in Chemical Synthesis, Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences, 354 Fenglin Lu, Shanghai 200032, China

Received (in Cambridge, UK) 4th April 2000, Accepted 19th May 2000

Novel N,S- and N,Se-ligands with planar chirality derived from [2.2]paracyclophane have been synthesized and applied in palladium-catalyzed allylic alkylation reaction, in which ligands 5 and 9 with the two substituents at benzylic and benzene ring positions give the highest ee values.

The design and synthesis of new chiral ligands play a crucial role in transition metal catalyzed asymmetric reactions.<sup>1</sup> Recently, ligands possessing planar chirality have attracted greater interest amongst various chiral ligands in asymmetric catalysis. In comparison with ferrocene derivatives<sup>2</sup> and arene transition metal complexes,<sup>3</sup> little attention has been paid to ligands derived from [2.2]paracyclophane, a structural framework capable of introducing planar chirality, and only a limited number of reports have appeared on studies of chiral [2.2]paracyclophanes,<sup>4</sup> especially their uses in asymmetric catalysis, 4e-h,k although these ligands are linearly chiral,5 chemically stable<sup>6</sup> and undergo racemization only at relatively high temperature.7 As part of a program aimed at the applications of planar chirality in asymmetric synthesis<sup>8</sup> we studied the role of [2.2]paracyclophane-type planar chirality in asymmetric induction. Herein we disclose our results on the synthesis of novel N,S- and N,Se-ligands with planar chirality and central chirality based on the [2.2]paracyclophane backbone and their use in the palladium-catalyzed allylic alkylation reaction.9

From racemic 4-carboxy[2.2]paracyclophane 1 as starting material<sup>10</sup> and by using literature procedures<sup>11</sup> oxazoline **3** was obtained as a mixture of two diastereoisomers. Direct ortholithiation of oxazoline 3 with BunLi and an equimolar amount of TMEDA followed by quenching with PhSSPh gave rise to the expected products 4a and 4b (Scheme 1). To our surprise, a third product 5 was obtained in addition to the expected ortholithiation/electrophile quenching products 4a and 4b. The structure of 5 was determined by <sup>1</sup>H NMR spectroscopy and confirmed by X-ray crystallography.<sup>†</sup> The planar chirality of these three products were readily determined by comparison with that of products obtained by using optically pure 1a and 1b<sup>10</sup> as starting materials and repeating the same procedure. In addition, the absolute configuration of C-2 in 5 was assigned as (R) based on the (S)-configuration of C-19 in the oxazoline moiety (Fig. 1). Possibly the benzylic substituted cyclophane 5 was produced owing to the nonplanarity of benzene ring of the cyclophane<sup>12</sup> and the steric effect of isopropyl group of the oxazoline.13

To examine the efficiency of these planar chiral *N*,*S*-ligands in asymmetric synthesis, palladium-catalyzed allylic alkylation was chosen as the model reaction (Scheme 2). The experiment was carried out at r.t. in the presence of  $[Pd(\eta^3-C_3H_5)Cl]_2$  and the ligands. A nucleophile was generated from dimethyl malonate in the presence of *N*,*O*-bis(trimethylsilyl)acetamide (BSA) and a catalytic amount of salt. The results were summarized in Table 1. It was found that all ligands **4a**, **4b** and **5** can catalyze the reaction to afford the substitution product **7** in almost quantitative yields. In comparison with the results

он i (COCI)<sub>2</sub>/CH<sub>2</sub>CI NH Et<sub>3</sub>N/CH<sub>2</sub>Cl<sub>2</sub> 2 97% PPha/EtaN 96% CCI<sub>4</sub>/MeCN i BuLi(4.2 eq) TMEDA(4.2 eq) Et<sub>2</sub>O, 0 °C, 12 h ii PhSSP (S,S<sub>o</sub>)-4a, 28% SPh 2-(R)-19-(S)-(Sp)-5, 12% (S,R<sub>p</sub>)-4b, 19% i Bul i(4.2 eo) TMEDA(4.2 eq) Et<sub>2</sub>O, 0 °C, 12 h 3 ii PhSeSePh (S,Sp)-8a, 31% SePt ∕∕SePh 2-(R)-19-(S)-(So)-9, 15% (S,R<sub>n</sub>)-8b, 18% Scheme 1

obtained by using benzene ring substituted compounds 4a and 4b as ligands, the reaction using the benzylic substituted cyclophane 5 provided far better enantioselectivity, and the reactivity of 5 was also much higher than that of 4a and 4b (entries 4, 5 *cf.* entry 6).

The structure of ligand **5** is unique in the planar chiral cyclophane family. Its enantioselectivity and reactivity are also notable. Therefore similar *N*, *Se*-ligands **8a**, **8b** and **9**, with the latter having the same skeleton as **5**, were prepared by using similar procedures from intermediate **3** (Scheme 1) and tested further for the efficiency of planar chiral ligands with the two



Fig. 1 ORTEP drawing of  $2-(R)-19-(S)-(S_p)-5$  with the atomic numbering.



**Table 1** The effect of different ligands on the enantioselective palladiumcatalyzed allylic substitution reaction using planar chiral N,S- and N,Seligands<sup>*a*</sup>

Entry	Ligand	Solvent	Salt	t/h	Yield (%) <sup>b</sup>	Ee (%) <sup>c</sup>	Config- uration <sup>d</sup>
1	4a	PhMe	LiOAc	40	98	54	R
2	4a	$CH_2Cl_2$	LiOAc	24	98	50	R
3	4a	$CH_2Cl_2$	KOAc	36	98	53	R
4	4a	MeCN	KOAc	32	98	54	R
5	4b	MeCN	KOAc	21.5	98	63	S
6	5	MeCN	KOAc	1.5	98	94	S
7	8a	MeCN	KOAc	20	98	57	R
8	8b	MeCN	KOAc	30	98	73	S
9	9	MeCN	KOAc	2	98	93	S

<sup>*a*</sup> Molecular ratio:  $[Pd(\eta^3-C_3H_5)Cl]_2$ : ligand: **6**: dimethyl malonate: BSA :salt = 2:6:100:300:300:3. <sup>*b*</sup> Isolated yield after flash chromatography. <sup>*c*</sup> Ee determined by HPLC (chiralel OJ column). <sup>*d*</sup> Absolute configuration of the product **7** was assigned by comparison with the sign of specific rotation according to literature data.<sup>14</sup>

coordinating atoms at benzylic and benzene ring positions in asymmetric synthesis. It can be seen that a higher ee value was obtained for benzylic substituted ligand 9 relative to 8a and 8b (entry 9 cf. entries 7,8 in Table 1). As for the N, S-ligand, the reactivity of the benzylic derivative (9) as ligand is higher than that using ring-substituted cyclophanes 8a and 8b as ligands. These results clearly show that the ligand with the two coordinating atoms at benzylic and benzene ring-positions is more effective than that with both the coordinating atoms at benzene ring-positions. This is presumably due to the increased tether length between the donor atoms which coordinate palladium in 5 and 9, bringing the asymmetric environment closer to the allyl species during the reaction.<sup>15</sup> Interestingly, 4a and **8a** with the same  $S_p$  planar chirality afforded **7** in (*R*)-configuration, whereas **4b**, **8b** with  $R_p$  planar chirality gave rise to 7 in (S)-configuration, even though all of these ligands showed the same central chirality at the oxazoline. It seems that the central chirality is not a decisive factor in controlling the absolute configuration of the product in our reaction.<sup>8b,e</sup>

In summary, novel *N*,*S*- and *N*,*S*e-ligands bearing the two coordinating atoms at benzylic and benzene ring positions showed excellent enantioselectivity and reactivity in palladium-catalyzed allylic alkylation reaction. The synthesis of further similar ligands *via* introduction of other coordinating atoms at

the benzylic position and further investigations on the role of these in asymmetric reactions in more detail are in progress.

Financial support from the National Natural Science Foundation of China (Project 29790127 and 29872045), National Outstanding Youth Fund, Chinese Academy of Sciences, and Shanghai Committee of Science and Technology is gratefully acknowledged.

## Notes and references

† *Crystal data* for **5**: M = 427.60, orthorhombic, space group *P*2,2,2, a = 14.633(2), b = 19.668(4), c = 7.749(2) Å, V = 2230.0(8) Å<sup>3</sup>, Z = 4,  $D_c = 1.274$  g cm<sup>-3</sup>, T = 293 K,  $\lambda$ (Mo-Kα) = 0.7107 Å,  $\mu = 1.657$  cm<sup>-1</sup>, 2938 measured reflections, 2555 observed reflections, R = 0.0430,  $R^1 = 0.0540$ , S = 1.800,  $p_{\text{max}}$ ,  $p_{\text{min}} = 0.431$ , -0.344 e Å<sup>-3</sup>. CCDC 182/1650. See http://www.rsc.org/suppdata/cc/b0/b0026790/ for crystallographic files in .cif format.

- Catalytic Asymmetric Synthesis, ed. I. Ojima, VCH, New York, 1993;
  R. Noyori, Asymmetric Catalysis In Organic Synthesis, Wiley, New York, 1994.
- 2 For reviews, see: *Ferrocenes*, ed. A. Togni and T. Hayashi, VCH, Weinheim, 1995; C. J. Richards and A. J. Locke, *Tetrahedron:* Asymmetry, 1998, **9**, 2377.
- 3 C. Bolm and K. Muniz, Chem. Soc. Rev., 1999, 28, 51.
- 4 (a) H. J. Reich and K. E. Yelm, J. Org. Chem., 1991, 56, 5672; (b) R. Yanada, M. Higashikawa, Y. Miwa, T. Taga and F. Yoneda, Tetrahedron: Asymmetry, 1992, 11, 1387; (c) D. Y. Antonov, Y. N. Belokon, N. S. Ikonnikov, S. A. Orlova, A. P. Pisarevsky, N. I. Raevski, V. I. Rozenberg, E. V. Sergeeva, Y. T. Struchkov, V. I. Tararov and E. V. Vorontsov, J. Chem. Soc., Perkin Trans. 1, 1995, 1873; (d) V. V. Sergeeva, V. I. Rozenberg, E. V. Vorontsov, T. D. Danilova, Z. A. Starikova, A. I. Yanovsky, Y. N. Belokon and H. Hopf, *Tetrahedron: Asymmetry*, 1996, **12**, 3445; (*e*) Y. Belokon, M. Moscalenko, N. Ionnikov, L. Yashkina, D. Antonov, E. Vorontsov and V. Rozenberg, Tetrahedron: Asymmetry, 1997, 19, 3245; (f) P. J. Pye, K. Rossen, R. A. Reamer, N. N. Tsou, R. P. Volante and P. J. Reider, J. Am. Chem. Soc., 1997, 119, 6207; (g) K. Rossen, P. J. Pye, A. Maliakal and R. P. Volante, J. Org. Chem., 1997, 62, 6462; (h) A. H. Vetter and A. Berkessel, Tetrahedron Lett., 1998, 39, 1741; (i) P. J. Pye, K. Rossen, R. A. Reamer, R. P. Volante and P. J. Reider, Tetrahedron Lett., 1998, 39, 4441; (j) V. I. Rozenberg, N. V. Dubrovina, E. V. Vorontsov, E. V. Sergeeva and Y. N. Belokon, Tetrahedron: Asymmetry, 1999, 10, 511; (k) U. Wörsdörfer, F. Vögtle, M. Nieger, M. Waletzke, S. Grimme, F. Glorius and A. Pfaltz, Synthesis, 1999, 4, 597
- 5 R. S. Cahn, C. K. Ingold and V. Prelog, *Experientia*, 1956, **12**, 81; *Angew. Chem., Int. Ed. Engl.*, 1966, **5**, 385.
- 6 D. J. Cram and N. Allinger, J. Am. Chem. Soc., 1955, 77, 6289.
- 7 H. J. Reich and D. J. Cram, J. Am. Chem. Soc., 1969, 91, 3517.
- 8 (a) X. D. Du, L. X. Dai, X. L. Hou, L. J. Xia and M. H. Tang, Chin. J. Chem., 1998, 16, 90; (b) S. L. You, Y. G. Zhou, X. L. Hou and L. X. Dai, Chem. Commun., 1998, 2765; (c) W. P. Deng, X. L. Hou and L. X. Dai, Tetrahedron: Asymmetry 1999, 10, 4689; (d) L. X. Dai, X. L. Hou, W. P. Deng, S. L. You and Y. G. Zhou, Pure Appl. Chem., 1999, 71, 1401; (e) W. P. Deng, X. L. Hou, L. X. Dai, Y. H. Yu and W. Xia, Chem. Commun., 2000, 285; (f) S. L. You, X. L. Hou and L. X. Dai, Tetrahedron: Asymmetry, 2000, 11, 1495.
- 9 For reviews, see: B. M. Trost and D. L. Van Vranken, *Chem. Rev.*, 1996, 96, 395; B. M. Trost, *Acc. Chem. Res.*, 1996, 29, 355; G. J. Helmchen, *J. Organomet. Chem.*, 1999, 576, 203.
- 10 V. Rozenberg, N. Dubrovvina, E. Sergeeva, D. Antonov and Y. Belokon, *Tetrahedron: Asymmetry*, 1998, 9, 653.
- 11 H. Vorbruggen and K. Krolikliewicz, *Tetrahedron Lett.*, 1981, 22, 4471.
- 12 P. M. Keehn and S. M. Rosenfeld, *Cyclophanes*, Academic Press, New York, 1983, p. 71.
- 13 A similar result was obtained in the diastereomeric deprotonation of chiral ferrocenyl oxazolines: see: C. J. Richards, T. Damalidis, D. E. Hibbs and M. B. Hursthouse, *Synlett*, 1995, 74; T. Sammakia and H. A. Latham, *J. Org. Chem.*, 1995, **60**, 6002.
- 14 P. Wimmer and M. Widhalm, Tetrohedron: Asymmetry, 1995, 6, 657.
- 15 B. M. Trost and D. L. Van Vranken, *Angew. Chem., Int. Ed. Engl.*, 1992, 31, 228; G. J. Dawson, C. G. Frost, C. J. Martin, J. M. J. Williams and S. J. Coote, *Tetrahedron Lett.*, 1993, 34, 7793; A. Chesney, M. R. Bryce, R. W. J. Chubh, A. S. Batsancy and J. A. K. Howard, *Tetrahedron: Asymmetry*, 1997, 8, 2337.