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

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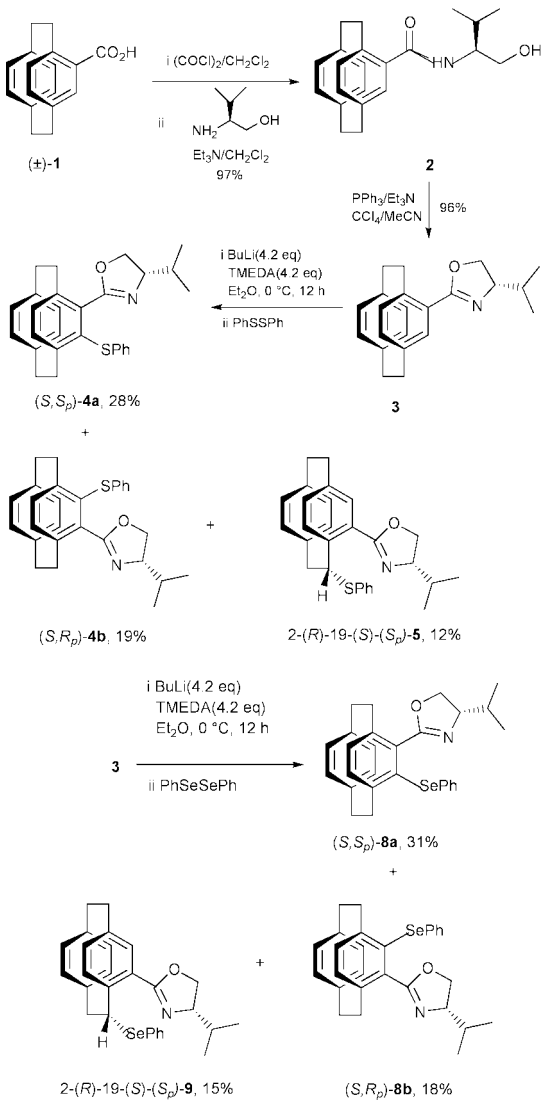
Novel *N,S*- and *N,Se*-ligands with planar chirality derived from [2.2]paracyclophane have been synthesized and applied in palladium-catalyzed allylic alkylation reaction, in which ligands 5 and 9 with the two substituents at benzylic and benzene ring positions give the highest ee values.

The design and synthesis of new chiral ligands play a crucial role in transition metal catalyzed asymmetric reactions.[1] Recently, ligands possessing planar chirality have attracted greater interest amongst various chiral ligands in asymmetric catalysis. In comparison with ferrocene derivatives[2] and arene transition metal complexes,[3] 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,[4] especially their uses in asymmetric catalysis,[4e–h,k] although these ligands are linearly chiral,[5] chemically stable[6] and undergo racemization only at relatively high temperature.[7] As part of a program aimed at the applications of planar chirality in asymmetric synthesis[8] 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[10] and by using literature procedures[11] oxazoline **3** was obtained as a mixture of two diastereoisomers. Direct *ortho*-lithiation of oxazoline **3** with Bu^{n}Li 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 *ortho*-lithiation/electrophile quenching products **4a** and **4b**. The structure of **5** was determined by ^{1}H NMR spectroscopy and confirmed by X-ray crystallography.† The planar chirality of these three products were readily determined by comparison with that of products obtained by using optically pure **1a** and **1b**[10] 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[12] 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 $[Pd(\eta^3\text{-}C_3H_5)Cl]_2$ 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



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

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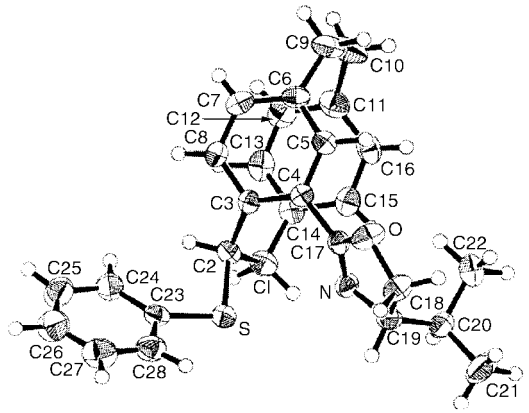
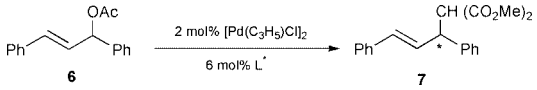


Fig. 1 ORTEP drawing of 2-(*R*)-19-(*S*)-(S_p)-**5** with the atomic numbering.



Scheme 2

Table 1 The effect of different ligands on the enantioselective palladium-catalyzed allylic substitution reaction using planar chiral *N,S*- and *N,Se*-ligands[a]

Entry	Ligand	Solvent	Salt	*t*/h	Yield (%)[b]	Ee (%)[c]	Configuration[d]
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*

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

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.[15] 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.[8b,e]

In summary, novel *N,S*- and *N,Se*-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.

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Notes and references

† *Crystal data* for **5**: M = 427.60, orthorhombic, space group $P2_12_12$, a = 14.633(2), b = 19.668(4), c = 7.749(2) Å, V = 2230.0(8) Å^3, Z = 4, D_c = 1.274 g cm^{-3}, T = 293 K, λ(Mo-Kα) = 0.7107 Å, μ = 1.657 cm^{-1}, 2938 measured reflections, 2555 observed reflections, R = 0.0430, R^1 = 0.0540, S = 1.800, p_{max}, p_{min} = 0.431, −0.344 e Å^{-3}. CCDC 182/1650. See http://www.rsc.org/suppdata/cc/b0/b002679o/ for crystallographic files in .cif format.

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