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Synthesis of novel *N*,*O*-planar chiral [2,2]paracyclophane ligands and their application as catalysts in the addition of diethylzinc to aldehydes

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Abstract—A series of novel planar chiral *N*,*O*-[2,2]paracyclophane ligands were synthesised and applied as catalysts in the enantioselective addition of diethylzinc to aldehydes. The results indicate that the planar chirality of [2,2]paracyclophane, not the central chirality of the oxazoline, is the dominant stereocontrolling element.

Planar chiral ligands play an important role in asymmetric synthesis. In comparison with ferrocene derivatives[1] and arene transition metal complexes,[2] little attention has been paid to planar chiral ligands derived from [2,2]paracyclophane and only a limited number of reports have appeared on the study of planar chiral [2,2]paracyclophane,[3] and few of these works focus on the applications of this class of compound as asymmetric catalysts.[3e–h,k,m,n,4] Recently, we reported the synthesis of novel *N*,*S*- and *N*,*Se*-planar chiral [2,2]paracyclophane ligands and their application in palladium-catalysed allylic alkylation reactions.[4] We found that the planar chirality is the dominant factor in controlling the stereoselectivity of the reaction. As part of an ongoing study of chiral cyclophanes and part of a program aimed at the applications of planar chirality in asymmetric catalysis,[5] we have synthesised a series of novel disubstituted planar chiral *N*,*O*-ligands based on the [2,2]paracyclophane backbone and found that they efficiently catalyse the enantioselective addition of diethylzinc to aldehydes. Herein, we communicate the results of this study.

Reaction of the racemic 4-carboxy [2,2]paracyclophane **1**[6] with a number of enantiomerically pure aminoalcohols afforded the amide **2**. Bromination at the aromatic nucleus afforded the diastereoisomeric bromides **3** and **4**,[7] subsequent cyclisation of which[8] provided the diastereoisomeric pairs of oxazolinylcyclophanes **5** and **6**, which were easily separable by column chromatography to give workable yields of the pure compounds.

In separate reactions, bromo-lithium exchange of **5** and **6** at low temperature, followed by trapping of the anion with benzophenone, gave the desired planar chiral *N*,*O*-[2,2]paracyclophanes **7** and **8**, respectively (Scheme 1). The absolute configurations of planar chirality were determined by X-ray diffraction of the precursors **5** and **6** and the X-ray crystal structures of **5d** and **6c** are illustrated in Fig. 1. The configurations of **5d** and **6c** are assigned as ($19R$,$4R_p$,$13S_p$) and ($19S$,$4S_p$,$13R_p$), respectively.

With these ligands in hand, we turned our attention to their application in catalytic asymmetric reactions. To assess the paracyclophanes as catalytic ligands, their effect on the enantioselective addition of diethylzinc to aldehydes was examined. The results are shown in Table 1.

In the presence of a catalytic amount of ligand (5 mol%) the reaction proceeded smoothly to provide the corresponding alcohol (Eq. (1)). Ligands **7a** and **7c** afforded the best yields and enantioselectivities when benzaldehyde was the substrate (Entries 1 and 5). Ligand **8d** also showed good enantioselectivity, but lower

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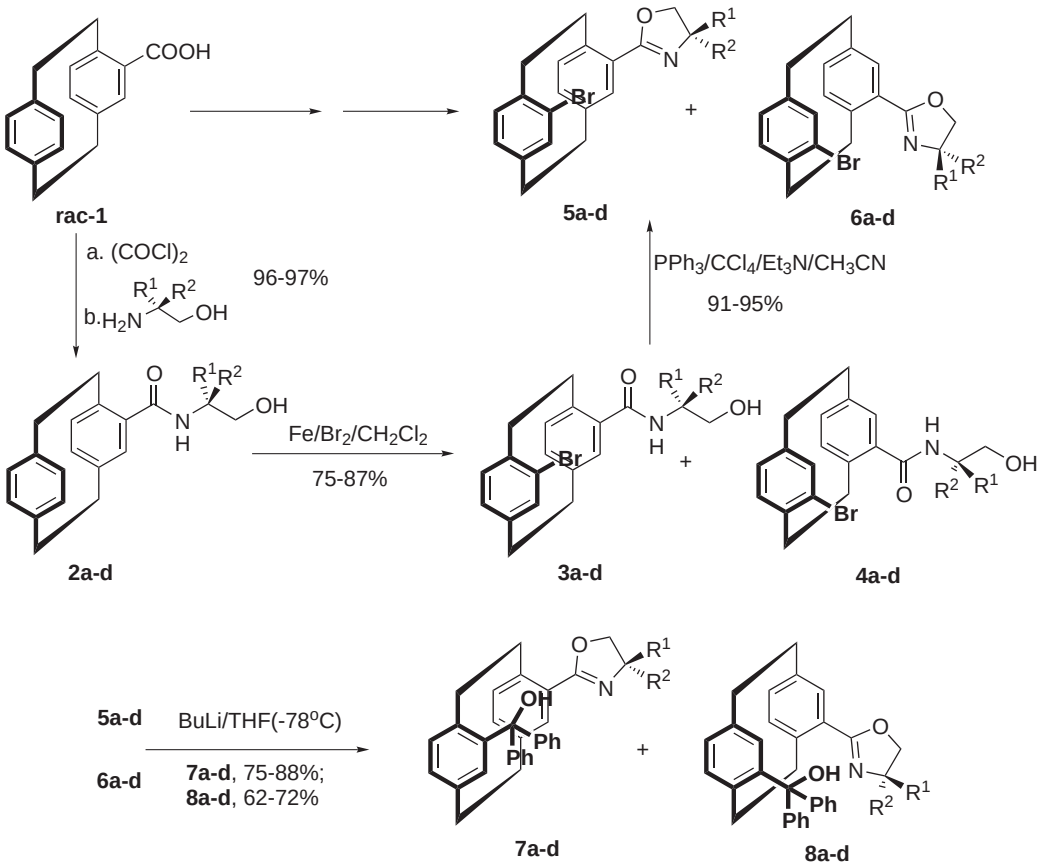


Scheme 1. **a**: $R^1=H$, $R^2=i$Pr; **b**: $R^1=H$, $R^2=t$Bu; **c**: $R^1=H$, $R^2=$Bn; **d**: $R^1=$Ph, $R^2=H$.

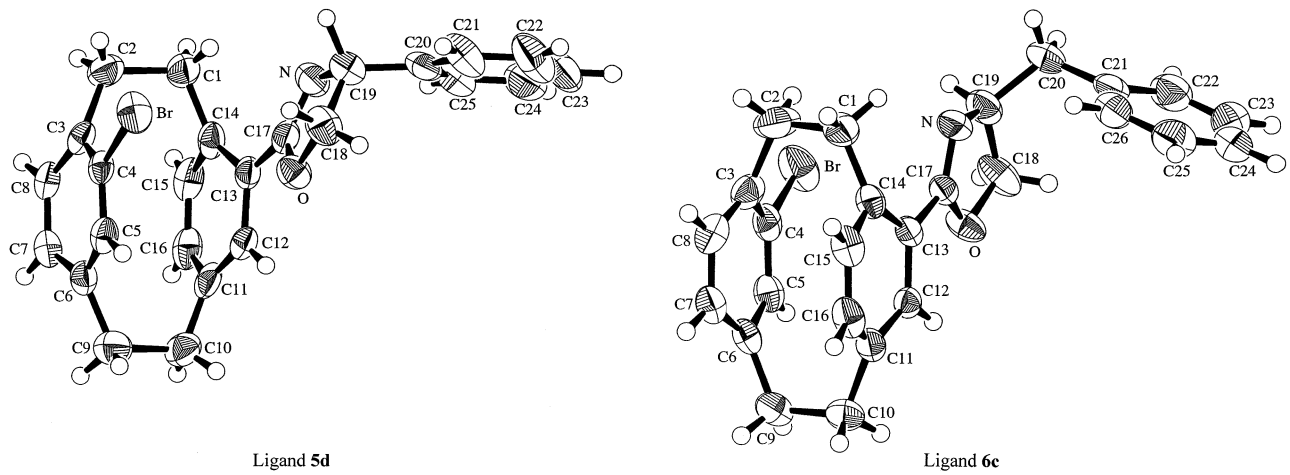
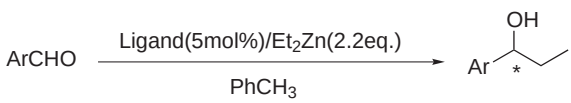


Fig. 1. ORTEP illustrations of **5d** and **6c** with the atomic numbering.

reactivity than ligands **7a** and **7c** (Entry 8), while ligands **7b**, **7d**, **8a**, **8b** and **8c** showed both poor reactivity and enantioselectivity.

When ligand **7c** was used as catalyst, all aromatic aldehydes reacted with diethylzinc to give the products in high yield and e.e. It is interesting to compare the results with those obtained when using ferrocene ligands.[9,10a] The e.e. value obtained from **7c** is higher than that from both 1,2- and 1,1′-disubstituted ferrocene ligands using benzaldehydes with an electron-withdrawing group on the benzene ring as substrates but it is lower than that from 1,2-disubstituted planar ferrocene ligands when the substituent is electron-donating. The difference of the configurations of planar and central chiralities in these ligands markedly affects their reactivity and their capacity for asymmetric induction.[4,5,10] Ligands **7a**, **7b**, **7c** and **8d** showed higher reactivity and



(1)

Table 1. Enantioselective addition of diethylzinc to aldehydes with planar chiral *N*,*O*-ligands **7** and **8**

Entry	Ar	Ligand	Time (h)	Yield (%)[a]	E.e. (%)[b]	Config.[c]
1	Ph	**7a**	9	96	93	*R*
2	Ph	**8a**	24	35	5	*S*
3	Ph	**7b**	24	37	32	*R*
4	Ph	**8b**	24	13	7	*S*
5	Ph	**7c**	7	93	93	*R*
6	Ph	**8c**	24	12	7	*S*
7	Ph	**7d**	24	12	5	*S*
8	Ph	**8d**	18	85	87	*S*
9	*p*-ClC_6H_4	**7c**	8	96	94	*R*
10	*p*-BrC_6H_4	**7c**	9	95	93	*R*
11	*p*-$MeOC_6H_4$	**7c**	24	86	82	*R*
12	*o*-$MeOC_6H_4$	**7c**	4	94	81	*R*
13	α-Naphthyl	**7c**	20	87	86	*R*
14	β-Naphthyl	**7c**	9	95	95	*R*

[a] Isolated yield based on aldehyde.
[b] Determined by HPLC (Chiralcel OD column).
[c] Configurations were assigned by comparison with the sign of the specific rotation of known compounds.

induced higher enantioselectivity than the corresponding diastereomeric ligands **8a**, **8b**, **8c** and **7d**. The configuration of products from the reaction catalysed by **7a**–**7c** differs from that originated from **8a**–**8c**. The only exceptions were **7d** and **8d**, both of which gave the (*S*)-configured product, despite the ligands having opposing planar chirality. These results indicate that the planar chirality and central chirality in **7a**–**7c** and **8d** are matched and act in a co-operative way in this reaction; additionally this indicates that the planar chirality of the [2,2]paracyclophane, not the central chirality of the oxazoline in **7** and **8**, may be the dominant stereocontrolling factor.

In conclusion, we have successfully synthesised a series of novel planar chiral *N*,*O*-ligands based on the [2,2]paracyclophane backbone and demonstrated their efficiency in asymmetric reactions.

The planar chirality of the [2,2]paracyclophane appears to play a dominant role in the stereochemistry of the reaction. The synthesis of similar ligands via introduction of other coordinating atoms and their applications in asymmetric reactions is currently in progress.

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