## $C_2$ -Symmetric S/C/S ligands based on N-heterocyclic carbenes: a new ligand architecture for asymmetric catalysis<sup>†</sup>

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Neutral,  $C_2$ -symmetric S/C/S ligands based on *N*-heterocyclic carbenes and thioether functionalities were incorporated into transition metal complexes characterised by two direct metal-stereogenic sulfur bonds. This new ligand design was applied to 1,3-dipolar cycloadditions as the first example of the use silver of carbenes in asymmetric catalysis.

The design of new types of ligands has been the central strategy that enabled the formidable development of homogeneous catalysis over the past decades. This statement particularly applies to asymmetric catalysis, where the construction of suitable chiral environments around the active centres is essential to discriminate diastereomeric transition states. After the seminal work by Dang and Kagan,<sup>1</sup> one of the most successful catalyst designs exploits the geometrical simplicity associated with a  $C_2$ -symmetry that reduces the number of possible transition states. Though it has been rationalised how and why  $C_1$ -symmetric catalysts provide a better performance in some cases,<sup>2</sup> there is still a high proportion of  $C_2$ -symmetric ligands (BOX, PyBOX, BINAP, BINOL, SALEN, TADDOL, DUPHOS, *etc.*) which have a wide applicability (the so called "privileged ligands").<sup>3</sup>

In most cases, the asymmetric environment is provided by chiral elements (stereogenic centres, chiral axes, *etc.*) separated by at least two bonds from the active centre. Taking transition metal–bis-oxazoline BOX or PyBOX complexes as representative examples, the stereogenic centres on the oxazoline ring are placed at typical distances of *ca.* 3.0-3.2 Å and 3.3-3.5 Å from the metal, respectively (Fig. 1).



Fig. 1 Metal complexes of bidentate BOX and tridentate PyBOX ligands.

A closer asymmetric environment can be provided by ligands bearing heteroatoms (N, P or S) that are able to become stable

stereogenic centres upon coordination to the metal centre. In view of our recent interest in new *N*-heterocyclic carbene (NHC) architectures,<sup>4,5</sup> we have recently reported the synthesis and applications of Pd and Rh complexes containing heterobidentate C/S ligands based on NHCs and thioether functionalities (Fig. 2).<sup>6</sup> In these complexes, the configuration of the sulfur atom is controlled by a neighbour stereogenic centre that forces a relative *trans* configuration in the chelate to avoid severe steric interactions.





On this basis, we designed  $C_2$ -symmetric complexes of structure I (Scheme 1), based on a tridentate S/NHC/S ligand that combines the stabilising properties of the imidazol-2-ylidene or its benzimidazole analogue with two directly bonded stereogenic sulfur atoms. In this communication, we wish to report on the successful development of catalysts based on this new S/C/S-ligand class and the first application of silver NHC carbenes in asymmetric catalysis.



Scheme 1 Retrosynthetic analysis to  $C_2$ -symmetric S/C/S-complexes I.

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Scheme 2 Synthesis of S/C/S pincer ligands and complexes thereof.

The very simple retrosynthetic analysis of compounds I suggests their synthesis from imidazolium(benzimidazolium) salts II, which in turn should be easily accessible by alkylation (twice) of the free heterocycles with appropriate reagents III.

As deduced from previous structural studies on heterobidentate ligands,<sup>6</sup> the isopropyl group appears to be big enough to control the relative configuration of the neighbour S stereogenic centre created upon coordination. Thus, (1-bromo-3-methylbutan-2-yl)[alkyl(aryl)]sulfanes **2a–d** (Scheme 2) were chosen as the reagents. Their synthesis was readily accomplished in good yields by treatment of alcohols **1a–d**<sup>‡7,8,9</sup> with CBr<sub>4</sub> and PPh<sub>3</sub>.

The akylation of imidazole with bromides **2a–d** afforded the desired products **3a–d**, that were further alkylated with the same bromides **2** to afford the required imidazolium salts **4a–d**§ in moderate yields. Stepwise alkylation of benzimidazole with **2a** afforded **5** and **6** in a similar manner. Treatment of bromides **4a–d** and **6** with Ag<sub>2</sub>O afforded the corresponding silver carbenes **7a–d** and **8**, respectively, in excellent yields.

In addition, the cationic palladium complex 10 was obtained in 86% yield by a direct reaction of the azolium chloride 9, [obtained by exchange from 4a with resin Dowex<sup>®</sup> 22 (chloride form)] with PdCl<sub>2</sub> in DMF.¶ Alternatively, the same product was obtained in near quantitative yield by the reaction of the same azolium 9 with Ag<sub>2</sub>O and *in situ* transmetallation with [PdCl<sub>2</sub>(CH<sub>3</sub>CN)<sub>2</sub>]. Suitable crystals for X-ray diffraction analysis were obtained by slow diffusion of hexane into a solution of 10 in CH<sub>2</sub>Cl<sub>2</sub> (Fig. 3). The structure exhibits the expected square-planar geometry with nearly no distortion [C(1)-Pd(1)-S(1) 90.05(14)°, C(1)-Pd(1)-S(2) 88.39(14)°], with the palladium atom being part of two boatlike constrained metallacycles, with a relatively short Pd-C bond of 1.947(5) Å. The two isopropyl groups are arranged in pseudo-equatorial positions, forcing the cyclohexyl groups to accommodate in relative trans pseudo axial positions [torsional angles  $C(14)-S(1)-Pd(1)-C(1) = 82.97^{\circ}$  and  $C(20)-S(2)-Pd(1)-C(1) = 82.97^{\circ}$ 



Fig. 3 Ortep drawing of the cationic Pd(II) complex 10. Thermal ellipsoids are drawn at the 50% probability level. Chloride counteranion and H-atoms are omitted for clarity.

 $C(1) = 67.30^{\circ}$ ] with absolute *S* configuration at the sulfur atoms and Pd–S distances of 2.3060(12) and 2.3215(11) Å.

Silver N-heterocyclic carbenes, commonly used as transfer agents to other transition metals,10 have received little attention as potential catalysts,<sup>11</sup> probably due to its lability. However, the expected stabilising capability of the pincer S/C/S ligands prompted us to explore the possibility of using silver complexes 7 and 8 as catalysts. Taking into account the well established use of silver complexes in asymmetric 1,3-dipolar cycloadditions,<sup>12</sup> the reaction of imino esters 11-16 with t-butyl acrylate was chosen as a model system (Scheme 3). Previously reported silver complexes with heterobidentate C/S ligands 17-216 were incorporated in the preliminary experiments. From these screenings, it was concluded that catalyst 7a based on the new tridentate S/C/S ligands affords a higher selectivity (ee 55%, Table 1, entry 6) than complexes 17-21 from bidentate ligands (ee's up to 35% at rt, entries 1-5). These results are tentatively explained by assuming a hemilabile behavior of the ligand 7.13 Surprisingly, the benzimidazole derivative 8 was not an active catalysts in the model reaction (entry 7).

Table 1	Enantioselective 1	,3-dipolar cycl	oaddition of	f azomethine	ylides (from	imino esters	11-16) with te	ert-butyl acrylate <sup>a</sup>
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Entry	Imine	Ar	Cat.	Solvent	T∕°C	t/h	Prod.	Yield <sup>b</sup>	ee <sup>c</sup>
1	11	Ph	17	Toluene	25	8	22	70	30
2	11	Ph	18	Toluene	25	8	22	62	33
3	11	Ph	19	Toluene	25	8	22	33	10
4	11	Ph	20	Toluene	25	8	22	50	0
5	11	Ph	21	Toluene	25	8	22	85	35
6	11	Ph	7a	Toluene	25	8	22	75	55
7	11	Ph	8	Toluene	25	48		_	
8	11	Ph	7a	$Et_2O$	-25	84	22	52	74
9	12	2-Tolyl	7a	$Et_2O$	-25	84	23	89	76
10	12	2-Tolyl	7b	$Et_2O$	-25	84	23	84	48
11	12	2-Tolyl	7c	$Et_2O$	-25	84	23	90	26
12	12	2-Tolyl	7d	$Et_2O$	-25	84	23	85	6
13	13	4-Methoxyphenyl	7a	$Et_2O$	$-10^{d}$	84	24	62	70
14	14	4-Bromophenyl	7a	$Et_2O$	-25	84	25	93	76
15	15	4-Chlorophenyl	7a	$Et_2O$	-25	84	26	70	80
16	16	2-Naphthyl	7a	$Et_2O$	-25	84	27	66	74

<sup>*a*</sup> Reactions were performed with 1.2 equiv. of *t*-butyl acrylate on a 0.15 mmol scale. <sup>*b*</sup> Isolated yields of pure *endo* isomers. *Endo/exo* ratios  $\geq$  95:5 were determined by <sup>1</sup>H NMR of crude reaction mixtures in all cases. <sup>*c*</sup> Determined by HPLC on chiral stationary phases. <sup>*a*</sup> Reaction carried out at -25 °C afforded < 10% of product after prolonged reaction times.



Scheme 3 1,3-Dipolar cycloaddition of azomethine ylides from imino esters 11–16 with *tert*-butyl acrylate.

Under optimized conditions (-25 °C, Et<sub>2</sub>O as the solvent and catalysts loading of 5 mol%), complex **7a** proved to be a better catalyst than its analogues **7b–d** (entries 10–12), affording cycloadducts **22–27** with excellent *endo* selectivities and enantios-electivities up to 80% (Table 1, entries 8–9, 13–16).

In summary, pincer type,  $C_2$ -symmetric S/C(NHC)/S neutral ligands provide an unprecedented geometry characterised by a direct bonding of two stereogenic S atoms to the metal centre. As a first application for this ligand topology, their silver complexes were successfully used as catalysts in the asymmetric 1,3-dipolar cycloaddition of imino glycinates. The development of different applications in asymmetric catalysis is a current object of study in our laboratories.

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## Notes and references

**‡ 1a** and **1d** were prepared according to literature procedures: see ref. 6 and 7. **1b** was prepared from (*R*)-*tert*-butyl *tert*-butanethiosulfinate by the reaction with *i*-BuMgCl according to the procedure described in ref. 8. The resulting sulfoxide was transformed into **1b** by the reaction with chloromethyl benzyl ether according to the procedure described in ref. **1c** was prepared by organocatalytic  $\alpha$ -sulfenylation of isovaleraldehyde and subsequent reduction (see ref. 7); the product had spectroscopical and analytical data in agreement with those reported in ref. 6.

§ The direct alkylation of imidazole with two equivalents of bromides 2 afforded lower yields of products 4. Moreover, compounds 3 are interesting intermediates that could also be used to build asymmetric salts by alkylation with different reagents.

**¶** The same treatment from bromide **4a** afforded a similar product, but its X-ray analysis revealed the presence of a mixture of chloride and bromide anions.

∥ Crystal data for **10**: C<sub>51</sub>H<sub>94</sub>Cl<sub>6</sub>N<sub>4</sub>O<sub>2</sub>Pd<sub>2</sub>S<sub>4</sub> [2(C<sub>25</sub>H<sub>44</sub>ClN<sub>2</sub>PdS<sub>2</sub>), CH<sub>2</sub>Cl<sub>2</sub>, 2(H<sub>2</sub>O), 2(Cl)], triclinic, space group *P*1, *Z* = 1, *a* = 10.2385(4) Å, *b* = 25.066(9) Å, *c* = 17.2053(7) Å, *α* = 84.804(2)°, *β* = 82.038(2)°, *γ* = 61.151(1)°, *V* = 1568.82(11) Å<sup>3</sup>, μ(Mo Kα) = 1.001 mm<sup>-1</sup>, *T* = 100(2) K, 57 350 reflections measured, 12 767 unique (*R*<sub>int</sub> = 0.039) which were used in all calculations. *R*<sub>1</sub>(*F*<sup>2</sup>) = 0.0414 [for 11 768 reflections with *F*<sub>0</sub> > 4σ(*F*<sub>0</sub>)], w*R* = 0.0977 for all data, GOF = 1.027. CCDC 712595. Flack parameter: −0.01(2).

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