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A one-step, modular route to optically-active diphos ligands[†]

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A chlorosilane elimination reaction has been developed that allows the efficient synthesis of optically pure C1-symmetric, C1-backboned diphosphines with a wide variety of stereoelectronic characteristics.

Asymmetric hydrogenation, catalyzed by metal complexes of optically active phosphines, was a landmark discovery in chemistry.^{1,2} Numerous diphosphines³⁻⁹ have been invented for the enantioselective hydrogenation of alkenes, ketones and imines and several have found industrial applications.^{10,11} The diphos ligands A-F shown in Fig. 1 represent milestones en route to the current understanding of the features that create an effective ligand for asymmetric catalysis and they continue to inspire the design of new ligands.¹²

The high enantioselectivity obtained with catalysts based on C_2 - or C_1 -symmetric diphosphines has been rationalized in terms of the degree of control of the metal binding site offered by the chelates involved.¹³ For example the rigid 4-membered rings formed by the C₁-backboned E and F (Fig. 1) have been



Fig. 1 Phosphorus ligands for asymmetric hydrogenation. $A = diop;^3$ $\mathbf{B} = \text{dipamp};^{4} \mathbf{C} = \text{binap};^{5} \mathbf{D} = \text{DuPhos};^{6} \mathbf{E} = \text{miniphos};^{7} \mathbf{F} = \text{trichicken-}$ $footphos;^{8} G = monophos.^{9}$

spectacularly effective for asymmetric hydrogenation,^{7,8,14} and it is the rigidity of the metal chelates that appears to be a critical feature of these catalysts. Despite the multitude of diphos ligands that have been prepared, there continues to be a need for new ones because, as several authors have noted, ligand discovery remains largely an empirical rather than a rational endeavour.¹⁵ A disadvantage of diphos ligands is that their synthesis is often multistep and/or requires an optical resolution step, making systematic refinement of their structures time-consuming and laborious.¹⁶ A major reason why monophos ligands such as G have attracted attention¹⁷ is that their synthesis is simple, modular and so reliable that they have been employed in high-throughput experimentation (HTE). Here we report a simple, one-step route to C1-linked diphos ligands that has the capacity to create a library of optically-active diphos ligands rapidly.

The construction of achiral C1-linked diphosphines by an Si-P exchange reaction such as that shown in eqn (1) has been previously reported.^{18,19} The attraction of this route is that the volatile by-product is readily removed and therefore we have investigated its potential as the basis for a general route to optically active, C1-linked diphos ligands.

$$(p-\text{Tol})_2\text{PCl} + \text{Me}_3\text{Si} \frown \text{PPh}_2 \xrightarrow{-\text{ClSiMe}_3} (p-\text{Tol})_2\text{P} \frown \text{PPh}_2 (1)$$

The reaction of chlorophosphite 1a with the trimethylsilylmethyl-phosphine 2a gave the diphos ligand La quantitatively (eqn (2)).



The reactants in eqn (2) are readily varied and easily prepared.¹⁹⁻²² Thus L_{b-f} are produced in high yields from the reactions of trimethylsilylmethylphosphines 2b-d with the

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	* P-X + M	le₃Si′	PR'2	-XSiMe ₃
	1a R=H	2a	R' = Ph	L _a
	1a R=H	2b	R = ⁱ Pr	L _b
	• 1a R=H	2c	R = Cy	L _c
	1a R = H	2d	R = ^t Bu	L _d
	1b R = Ph	2d	R = ^t Bu	L _e
	1c R = Mes	2d	R = ^t Bu	L _f
Ph	1d	2a	R = Ph	Lg
P	1d	2b	R = ⁱ Pr	L _h
	1d	2c	R = Cy	L _i
Ph	1d	2d	R = ^t Bu	Lj

Scheme 1 Synthesis of the diphos ligands L_{a-i} . X = Cl in all cases except for 1b and 1c where X = Br.

corresponding optically-pure halophosphites **1a-c** (Scheme 1). A significant extension of this process was achieved by employing the optically pure chlorophosphacycle 1d (Scheme 1) to produce L_{g-i} . The crude products L_{a-i} were sufficiently pure to be used in catalysis without further purification.

The complexes [Rh(diene)L] (3) where diene = 1,5-cyclooctadiene or norbornadiene were generated by the addition of La-i to $[Rh(diene)_2][BF_4]$ in CH_2Cl_2 and in each case the product was identified from the characteristic AMX pattern in its ³¹P NMR spectrum (see ESI[†] for details). Representative examples of 3, where $L = L_d$ or L_{g-j} , have been isolated and fully characterised. The ligands were screened for the asymmetric hydrogenation of the three benchmark substrates DMI, MAA and MAC (structures shown below) and the results are given in Table 1 and depicted graphically in Fig. 2 from which it is clear that significant variation in selectivity occurs for ostensibly small changes in ligand structure.



For the complexes of the binol-derived L_{a-d} with DMI and MAA, the highest ee was obtained with the PCy_2 derivative: $L_a < L_b < L_c > L_d$ (entries 1–12 in Table 1). For the complexes of the 3,3'-substituted ligands L_{d-f}, the highest ee was obtained when the 3,3'-substituents were Ph: $L_d < L_e > L_f$ (entries 10–18 in Table 1). With complexes of the phospholane-derived ligand L_{g-i} , the enantioselectivity was greatest for the P^tBu₂ ligand: $L_g < L_h < L_i < L_j$ (entries 19–30). It is apparent from Fig. 2 that the performance of any particular ligand can be highly substrate-dependent.

The absolute configuration of the asymmetric hydrogenation products obtained with Rh-diphos complexes generally obey the quadrant-blocking rule; that is, blocked upper left quadrant leads to R-configuration for MAC and MAA and S-configuration for DMI.13 The nature of the quadrant blocking is best discerned

Entry	Ligand	DMI	MAA	MAC	Conv. (%)
1	La	68 (S)			100
2	La		46 (R)		100
3	La			35 (R)	100
4	Lb	90 (S)			100
5	Lb		72 (R)		100
6	Lb			56 (R)	100
7	L_c	95 (S)			100
8	L_c		76 (R)		100
9	L_c			61 (R)	100
10	L_d	91 (S)			100
11	Ld		65 (R)		100
12	L_d			64(R)	100
13	Le	94 (S)			56
14	Le		98 (R)		100
15	L _e			94 (R)	49
16	L_{f}	91 (S)			47
17	L_{f}		72 (R)		35
18	L_{f}			93 (R)	20
19	L_{g}	62 (R)			100
20	$\tilde{L_g}$		57 (S)		100
21	$\tilde{L_g}$			46(S)	99
22	$\tilde{L_h}$	97 (R)			100
23	L _h		90(S)		100
24	L_h			85(S)	39
25	Li	92 (R)			100
26	Li		96 (S)		100
27	Li			85(S)	22
28	Lj	99 (R)			100
29	Ĺ		98 (S)		100
30	Ľ			99 (S)	26

Asymmetric hydrogenation catalysis

Table 1





Fig. 2 Graph of the enantioselectivities obtained with each of the catalysts.

from crystal structures and so crystals of the [Rh(cod)(Li)]BF4 (3j) were grown and its crystal structure determined, which has two molecules in the asymmetric unit (Fig. 3). Attempts to grow crystals suitable for X-ray crystallography of Rh-complexes of the binol-derived ligands (La-d) have so far been unsuccessful, although crystals of the chelate $[PtCl_2(L_d)]$ (4d) have been obtained and its structure is shown in Fig. 4. In both structures (3j and 4d), the acute P-M-P angles of 72.84(3)° in 3j and 73.74(3)° in 4d indicate the degree of strain present in the 4-membered chelates; these values are very similar to the 72.55(6)° that was



Fig. 3 (a) Crystal structure of **3j**. Thermal ellipsoids are plotted at 50% probability. Hydrogen atoms and the BF₄ counterion have been omitted for clarity. The two molecules in the asymmetric unit have the same orientation hence only one is shown for clarity. Selected bond lengths (Å) and angles (°): Rh1–P1 2.2839(7), Rh1–P2 2.3198(7), P1–C1 1.841(3), P2–C1 1.846(3), P1–Rh1–P2 72.84(3), P1–C1–P2 95.68(13). (b) Quandrant diagram of **3j**, where shaded area represents a blocked guadrant.



Fig. 4 (a) Crystal structure of 4d. Thermal ellipsoids are plotted at 50% probability. Hydrogen atoms have been omitted for clarity. Selected bond lengths (Å) and angles (°): Pt–Cl1 2.3572(8), Pt–Cl2 2.3657(8), Pt–P1 2.1620(9), Pt–P2 2.2596(8), P1–C11.798(3), P2–C11.866(3), P1–Pt–P2 73.74(3), P1–C1–P2 92.83(15), O1–P1–O2 104.26(13). (b) Quandrant diagram of 4d, where shaded area represents a blocked quadrant.

determined in an analogous complex of Trichickenfootphos (F in Fig. 1).⁸ The mean planes through M–P–P–C have rms deviations of 0.035/0.049 Å in **3j** and 0.003 Å in **4d** showing that the chelates are almost planar (see Fig. 3 and 4). It is evident from Fig. 4 that the upper left quadrant is blocked in the L_d complex (and presumably the same would be the case for all the ligands L_{a-f}) while Fig. 3 shows lower left quadrant is blocked in the in L_j complex (and presumably the same would be the case for all the ligands L_{g-j}). Therefore, the absolute configurations of the products of asymmetric hydrogenation (Table 1) conform to the quadrant rule.

The remarkable efficiency of the ligand synthesis (Scheme 1) coupled with the ready removal of the volatile chlorosilane by-product suggested that a one-pot procedure may be feasible. This was carried out according to Scheme 2 for L_j and the product tested for asymmetric hydrogenation of MAA. The 97% ee that was obtained compares favourably with the 98% ee recorded with the isolated complex (Table 1).

The simplicity and generality of the chlorosilane elimination route shown in Scheme 1 to C_1 -symmetric, C_1 -backboned, optically pure diphos ligands has been demonstrated by varying the nature of the two P-reagents. The success of the one-pot procedure (Scheme 2), coupled with the fact that the number of



Scheme 2 One pot synthesis of [Rh(nbd)(Li)]

potential ligands increases geometrically with each new chlorophos or silylmethylphosphine component, opens up the possibility of applying HTE methods to diphosphine synthesis and catalyst screening in a way that previously, have only been applied to monophos ligands. This is currently under investigation as is the mechanism of the ligand formation reaction.

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