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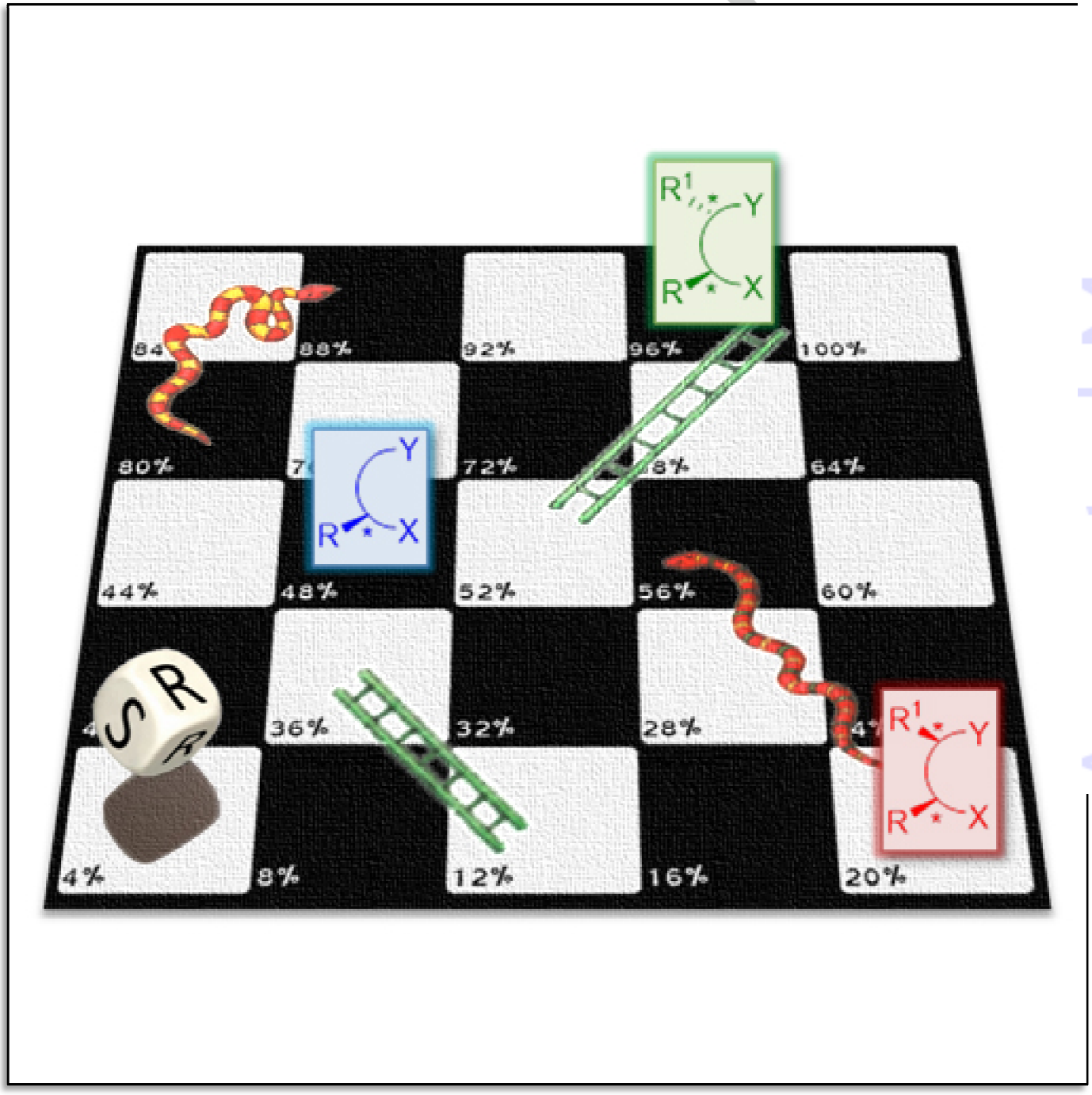
Catalyst optimisation for asymmetric synthesis by ligand chirality element addition – a perspective on stereochemical cooperativity

Christopher J. Richards* and Ross A. Arthurs

Dedication ((optional))



Abstract: The concept of matched and mismatched stereochemical pairings has been utilised extensively in organic synthesis, with the cooperativity resulting from the former enabling many reactions to proceed with high stereoselectivity. This approach was first developed to improve the diastereoselectivity of a reaction by matching the configuration of an enantiopure reagent or catalyst with the configuration of an enantiopure substrate. It has been extended to the asymmetric transformation of prochiral substrates controlled by reagents and catalysts containing two or more stereogenic centres. Matched and mismatched pairings may again be identified, with the former resulting in higher product enantioselectivity. This Minireview examines stereochemical pairings within catalysts generated from the combination of a metal with an enantiopure ligand; specifically examples where the ligand diastereoisomers examined for cooperativity are formally the result of the addition of a chiral element to an existing enantiopure ligand. Comparison of all three ligands in each of the fifty-six examples examined reveals that in the majority of cases the added element of chirality increases and decreases the enantioselectivity with respect to the parent ligand. The iterative application of this effect offers a potentially powerful method for catalyst optimisation for use in asymmetric synthesis.

1. Introduction

The creation of molecular complexity frequently involves reactions generating one or more elements of chirality. Optimising the stereoselectivity of a reaction remains one of the most significant challenges facing the synthetic chemist, despite enormous progress in this area over recent decades.[1] To this end one approach that has been employed frequently is stereochemical cooperativity, *i.e.* the identification of the configuration of two or more elements of chirality that result in the highest reaction stereoselectivity.

Studies in this area began with the reaction of an enantiopure substrate with an enantiopure reagent or catalyst,[2] a type of reaction first described as double asymmetric synthesis in 1977 (Figure 1, A).[3] A detailed review of this approach by Masamune in 1985 introduced the terms matched and mismatched to describe the two possible stereochemical pairings that result in higher and lower diastereoselectivity respectively.[4,5] Underpinning this concept were studies determining the diastereoselectivity of the two corresponding single asymmetric syntheses. For these latter reactions the corresponding values $\Delta\Delta G_1^{\ddagger}$ and $\Delta\Delta G_2^{\ddagger}$ may be summed or subtracted, the results predicting approximately the diastereoselectivities observed in the matched and mismatched double asymmetric syntheses (equations 1 and 2, Figure 2). Additional $\Delta G_{12}^{\ddagger}$ and $\Delta G'_{12}^{\ddagger}$ perturbation terms account for conformational differences in the transition states of the double asymmetric reactions compared to the corresponding single asymmetric reactions. These terms are generally relatively small.

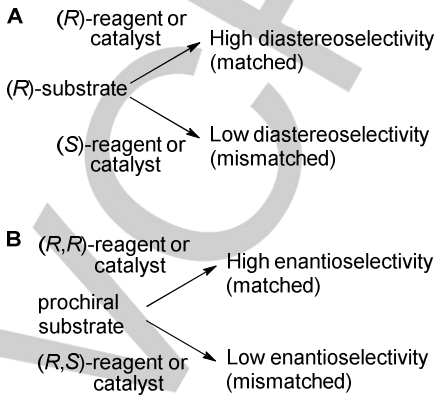


Figure 1. Representative scenarios for stereochemically cooperative reactions: **A** = diastereoselective and **B** = enantioselective.

The concept of matched and mismatched stereochemistry has been extended to numerous catalysed reactions of a prochiral substrate (typically), where the catalyst contains two or more elements of chirality (Figure 1, B).[6,7] Although well established, there appears to have been little comment on the outcome of adding an element of chirality to an existing enantiopure catalyst, *i.e.* are the consequences of this for the two resulting diastereoisomers both additive and subtractive with respect to product enantioselectivity?

$$\Delta\Delta G^{\ddagger}\,(\text{matched}) = \Delta\Delta G_1^{\ddagger} + \Delta\Delta G_2^{\ddagger} + \Delta G_{12}^{\ddagger} \qquad (1)$$

$$\Delta\Delta G^{\ddagger}\,(\text{mismatched}) = \Delta\Delta G_1^{\ddagger} - \Delta\Delta G_2^{\ddagger} + \Delta G'^{\ddagger}_{12} \qquad (2)$$

Figure 2. Free energy differences ($\Delta\Delta G^{\ddagger}$) for matched and mismatched diastereoselective reactions approximate to the sum and the subtraction of the individual free energy differences of the two single asymmetric reactions.

In this Minireview we examine this specific aspect of chiral cooperativity in ligands applied to metal catalysed enantioselective reactions. As summarised in Figure 3, we review examples where a ligand with an existing element of chirality is comparable to modified ligands containing an additional element of chirality. For inclusion, enantioselectivities need to have been reported for a metal catalysed reaction for *both* possible ligand diastereoisomers following chirality addition, in addition to the precursor ligand. Ideally all the reactions studied were run under identical or very similar conditions. By analogy with diastereoselective chiral cooperativity, a matched stereochemical pairing is anticipated to have resulted in an increase in product enantioselectivity, and a mismatched pairing in a reduction in enantioselectivity.

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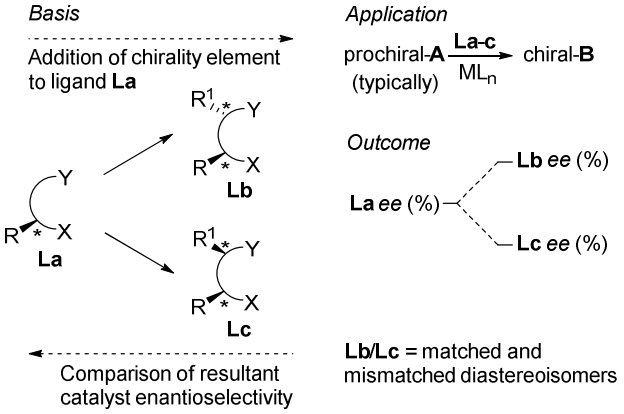


Figure 3. Chirality addition for a generalised ligand system and identification of chiral cooperativity in a metal-catalysed asymmetric reaction.

2. Chirality addition in planar chiral ferrocene-based ligands

Many examples that fulfill the requirements outlined above are found in ferrocene chemistry. The majority of ferrocene-based ligands employed in metal catalysed asymmetric reactions contain two elements of chirality: the planar chirality of a differentially 1,2-disubstituted cyclopentadienyl ring, and the central chirality of an appended stereogenic centre. This is illustrated with the ligand (S,R_p)-PPFA **L1b** (Figure 4).[8,9] In addition to its application in asymmetric catalysis, it has also been used as a precursor for the synthesis of many other ligands due to the stereospecificity of α–substitution reactions.[10]

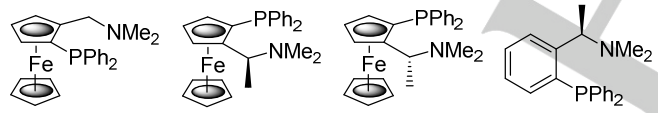
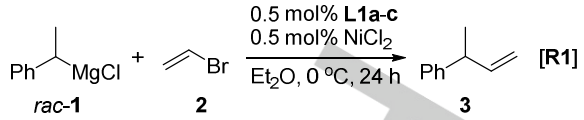
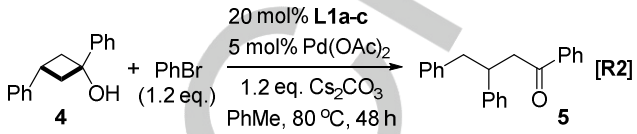


Figure 4. Ligands **L1a**-**d**.

Questions asked about this ligand type were the relative importance of the two elements of chirality, and by extension the effectiveness of diastereomeric (R,R_p)-**L1c**. The former was addressed by the synthesis[11] of (S_p)-**L1a** which gave an essentially identical result (excepting the swap in the configuration of the product) to that of (S,R_p)-**L1b** on application to nickel catalysed asymmetric Grignard cross-coupling of 1-phenylethylmagnesium chloride **1** with vinylbromide **2** (Scheme 1, Table 1, entries 1 and 2).[12] The importance of the planar chirality in controlling the stereochemical outcome was also revealed by the slightly lower enantioselectivity obtained with (R,R_p)-**L1c**, this being the mismatched diastereoisomer (entry 3).



Scheme 1. Nickel catalysed Grignard cross-coupling with ligands **L1**.



Scheme 2. Palladium catalysed *tert*-cyclobutanol arylation with ligands **L1**.

Table 1. Comparative outcomes with ligand series **L1** for the nickel catalysed formation of **3** [R1] and the palladium catalysed formation of **5** [R2].

Entry	Ligand	Product	Yield (%)	*ee* (%)
1[a]	(S_p)-**L1a**	(S)-**3**	>95	65[c]
2[a]	(S,R_p)-**L1b**	(R)-**3**	>95	63[c]
3[b]	(R,R_p)-**L1c**	(R)-**3**	>95	54[c]
4	(S_p)-**L1a**	(S)-**5**	86	13
5	(R,S_p)-**L1b**	(S)-**5**	70	58
6	(R,R_p)-**L1c**	(R)-**5**	37	25
7	(R)-**L1d**	(S)-**5**	22	5

[a] 4:1 ratio of Grignard reagent/vinylbromide [b] 2:1 ratio of Grignard reagent/vinylbromide. [c] Determined by optical rotation.

Ligands **L1a-c** have also been applied to palladium catalysed arylation of *tert*-cyclobutanol **4**, a reaction involving enantioselective C-C bond cleavage (Scheme 2, Table 1, entries 4-6).[13] Utilisation of **L1a**-**c** under identical conditions revealed that the configuration of planar chirality dictates the product configuration, with **L1b** again being the matched diastereoisomer. In this instance (S_p)-**L1a** displaying only planar chirality was poorly selective, as was (R)-**L1d**, a benzene derived substitute for a five-membered aromatic ring based ligand displaying only central chirality (entry 7). This suggests that cooperativity is required for significant selectivity, and it is of note that the ligand displaying highest enantioselectivity in this reaction (91% *ee* for the synthesis of **5**) is a derivative of **L1b** in which the NMe_2 group is replaced by NMe(1-adamantyl). Coordination of this amine functionality to palladium creates an additional stereogenic centre.

A bidentate phosphine/aminophosphine ligand derived from PPFA that has been applied frequently in asymmetric hydrogenation reactions is **L2a**, also known as the BoPhoz

ligand (Figure 5).[14] Chen *et al.* developed methodology for the highly diastereoselective synthesis of P-stereogenic derivatives of **L2a** such that both diastereoisomers (R,S_p,S_{phos})-**L2b** and (R,S_p,R_{phos})-**L2c** became available.[15] Application of this set of ligands to rhodium-catalysed hydrogenation of prochiral α-dehydroamino acid derivatives **6a**/**b** revealed (R,S_p,S_{phos})-**L2b** and (R,S_p,R_{phos})-**L2c** to be more and less enantioselective, respectively, than BoPhoz (Scheme 3, Table 2). A similar set of results to those given in entries 1-3 was obtained by the use of methanol as solvent. Although the influence of the P-stereogenic centre is relatively small in terms of *ee* (BoPhoz having already been identified as a successful ligand for this type of reaction), replacing a phenyl of the phosphine moiety with a larger 1-naphthyl substitutent is clearly beneficial in one of the resulting diastereoisomers. It is noted that epimerisation of the P-stereogenic centre can occur on heating, but under the room temperature conditions of the hydrogenation reactions described, the ligands are configurationally stable.

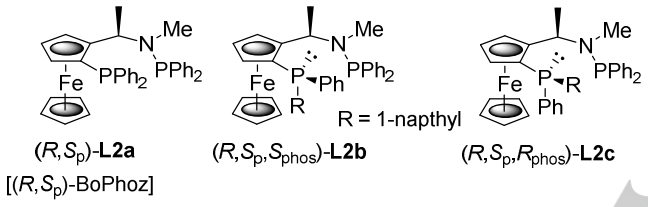
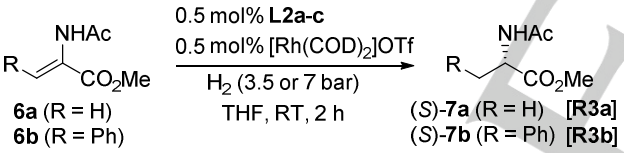


Figure 5. Ligands **L2a**-**c**.



Scheme 3. Rhodium catalysed hydrogenation of **6a**/**b** with ligands **L2**.

Table 2. Comparative outcomes with ligand series **L2** for the rhodium catalysed hydrogenation of **6a** [R3a] and **6b** [R3b].[a]

Entry	Ligand	Product	Pressure (bar)	*ee* (%)
1	(R,S_p)-**L2a**	(*S*)-**7a**	3.5	94.5
2	(R,S_p,S_{phos})-**L2b**	(*S*)-**7a**	3.5	98.3
3	(R,S_p,R_{phos})-**L2c**	(*S*)-**7a**	3.5	92.3
4	(R,S_p)-**L2a**	(*S*)-**7b**	7	95.7
5	(R,S_p,S_{phos})-**L2b**	(*S*)-**7b**	7	97
6	(R,S_p,R_{phos})-**L2c**	(*S*)-**7b**	7	92.4

[a] All reactions to ≥99% conversion.

An alternative approach to BoPhoz related ligands containing an additional element of chirality was investigated with the phosphine-phosphoramidites **L3a**-**d** (Figure 6).[16] Replacement of the aminophosphine component with a phosphoramidite allows the use of either an (S_a) or (R_a)-BINOL derived component to give diastereoisomers (S,R_p,S_a)-**L3b** and (S,R_p,R_a)-**L3c**. Comparison to a directly equivalent ligand without the BINOL element of chirality is not possible. For example, incorporation in its stead of 2,2'-biphenol (an example described[16]) will result in an induced element of axial chirality invalidating direct comparison. Thus catachol derived **L3a** is the only option available of the ligands reported that may be compared in the context of this review, in addition to **L2a**, for the rhodium catalysed hydrogenation of *N*-acetyl enamide **8** (Scheme 4, Table 3). The relatively modest enantioselectivity obtained with **L2a** (BoPhoz) was improved a little with phosphoramidite **L3a**, and significantly higher and lower enantioselectivities resulted with ligands **L3b** and **L3c**, respectively, containing the additional element of axial chirality.

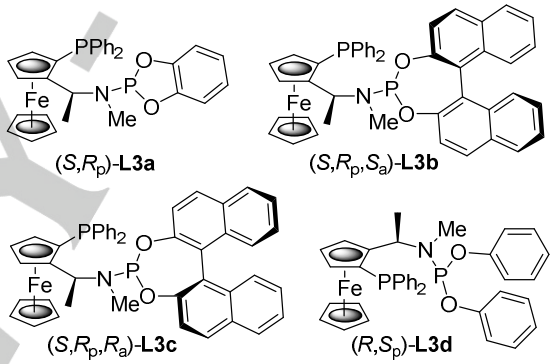
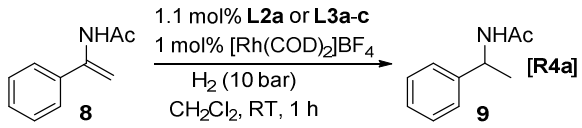


Figure 6. Ligands **L3a**-**d**.



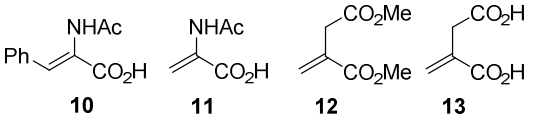
Scheme 4. Rhodium catalysed hydrogenation with **L2a** and ligand series **L3**.

Table 3. Comparative outcomes with **L2a** and ligand series **L3** for the rhodium catalysed hydrogenation of **8** [R4a].[a]

Entry	Ligand	Product	*ee* (%)
1	(S,R_p)-**L2a**	(*R*)-**9**	61.8
2	(S,R_p)-**L3a**	(*R*)-**9**	78.1
3	(S,R_p,S_a)-**L3b**	(*R*)-**9**	99.6
4	(S,R_p,R_a)-**L3c**	(*S*)-**9**	10.6

[a] Full conversion reported.

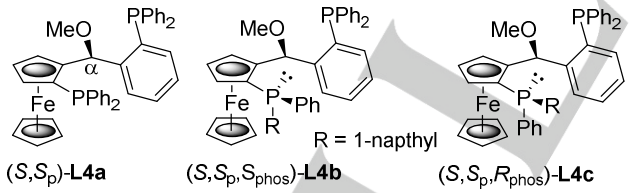
Diastereoisomers **L3b** and **L3c** (as the enantiomeric series) were also reported by Boaz *et al.*, and the outcome of catalysis with these ligands may be compared in this study to (*R*,S_p)-**L3d**.[17] This ligand contains an electronically similar, albeit non-cyclic diol portion of the phosphoramidite moiety. Prochiral substrates hydrogenated by **L3b**-**d** on combination with [Rh(COD)$_2$]OTf were **6b** and **10**-**13** (Figure 7). The results of this work are not tabulated here as the absolute configuration and yield of the products obtained are not stated. However, an examination of the *ee* values given reveals that for all of the substrates a higher enantioselectivity was achieved with at least one of the BINOL derived isomers compared to 'precursor' ligand **L3d** (and both for **11** and **13**). Ligand (*R*,S_p,R_a)-**L3b** was again identified as the matched diastereoisomer for four of the five examples (**11** being the exception), and with three substrates excellent enantioselectivities were observed (**6b** = 99.1% *ee*, **10** = 99.9% *ee*, **13** = 95.7% *ee*).



10 **11** **12** **13**

Figure 7. Substrates for asymmetric hydrogenation employing **L3b**-**d**.

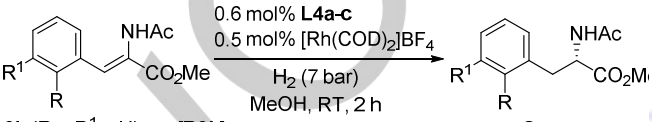
In addition to BINOL, two other compounds used to synthesise cyclic phosphoramidites were the enantiomers of hydrobenzoin and diethyl tartrate.[17] Although the specific results obtained with these ligands are not given, they are quoted as being "consistently poor" revealing that not just any chiral entity will result in higher enantioselectivity for at least one of the resulting diastereoisomers. That BINOL derived phosphoamidites are established as excellent ligands for a range on transition metal catalysed reactions is clearly of significance (*vide infra*).



(*S*,S_p)-**L4a** (*S*,S_p,S_{phos})-**L4b** (*S*,S_p,R_{phos})-**L4c**

Figure 8. Ligands **L4a**-**c**.

Bisphosphine ligand **L4a** was developed by Knochel *et al.* in a study investigating the effectiveness in catalysis of both epimers with respect to the configuration of the α–stereogenic centre (Figure 8).[18] In a range of rhodium catalysed hydrogenation reactions the *S*,S_p ligand was found to be more selective than the corresponding *R*,S_p diastereoisomer. This in turn led Chen *et al.* to synthesise P-stereogenic diastereoisomers of **L4a** for which a comparative set of catalysis results are available for (*S*,S_p,S_{phos})-**L4b** and (*S*,S_p,R_{phos})-**L4c** (Scheme 5, Table 4).[19] For the three α–dehydroamino acid substrates investigated, the matched *S*,S_p,S_{phos} ligand gave higher enantioselectivity and the mismatched *S*,S_p,R_{phos} ligand gave lower enantioselectivity, than (*S*,S_p)-**L4a** containing only two elements of chirality. As this simpler ligand was itself identified by Knochel as the matched diastereoisomer for substrate **6b**,[20] taken together these two papers represent a sequential optimisation of three elements of chirality, resulting in the identification of (*S*,S_p,S_{phos})-**L4b** as an excellent ligand for this specific rhodium-catalysed reaction.[21]



6b (R = R^1 = H) **[R3b]**
6c (R = Br, R^1 = H) **[R3c]**
6d (R = H, R^1 = Br) **[R3d]**

(*S*)-**7b-d**

Scheme 5. Rhodium catalysed hydrogenation of **6b**-**d** with ligands **L4**.

Table 4. Comparative outcomes with ligand series **L4** for the rhodium catalysed hydrogenation of **6b**-**d** [R3b], [R3c] and [R3d].[a]

Entry	Ligand	Product	*ee* (%)
1	(*S*,S_p)-**L4a**	(*S*)-**7b**	90.5
2	(*S*,S_p,S_{phos})-**L4b**	(*S*)-**7b**	99.6
3	(*S*,S_p,R_{phos})-**L4c**	(*S*)-**7b**	69.3
4	(*S*,S_p)-**L4a**	(*S*)-**7c**	91.4
5	(*S*,S_p,S_{phos})-**L4b**	(*S*)-**7c**	>99.9
6	(*S*,S_p,R_{phos})-**L4c**	(*S*)-**7c**	52.4
7	(*S*,S_p)-**L4a**	(*S*)-**7d**	97.3
8	(*S*,S_p,S_{phos})-**L4b**	(*S*)-**7d**	>99.9
9	(*S*,S_p,R_{phos})-**L4c**	(*S*)-**7d**	17.1

[a] All reactions went to completion under the conditions used.

A class of P-N ligands that have been employed widely in asymmetric catalysis are phosphinoferrocenyloxazolines **L5** (Figure 9). The vast majority of the literature in this area describes the use of (*S*,S_p)-**L5b** (or its enantiomer) as these ligands are obtained readily by highly diastereoselective lithiation of a precursor ferrocenyloxazoline followed by addition of PPh_2Cl.[22] Curiosity about the effectiveness of diastereoisomer (*S*,R_p)-**L5c** in asymmetric catalysis led Hou, Dai and co-workers to investigate a comparison of **L5a**-**c** (R = *t*Bu) in palladium catalysed allylic alkylation (Scheme 6, Table 5).[23] Ligand (S_p)-**L5a** displaying only planar chirality resulted in moderate selectivity for (*S*)-**15**, with the configuration of this product reversed and higher enantioselectivity obtained with

(*S*,S_p)-**L5b**. Thus the oxazoline-based element of central chirality dominates the control of enantioselectivity, which is in agreement with the previous application of benzene-derived PHOX ligand (*S*)-**L5d**.[24] On the basis that the influence of the two chirality elements are additive, (*S*,R_p)-**L5c** should be more selective for (*R*)-**15**, as is indeed the case with this being the matched diastereoisomer.

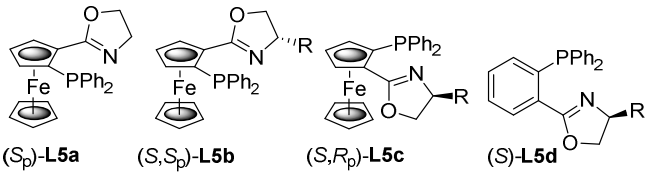
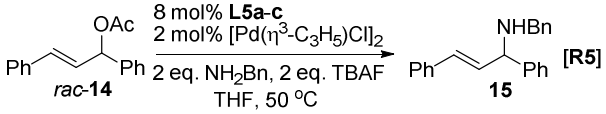


Figure 9. Ligands **L5a**-**d**.

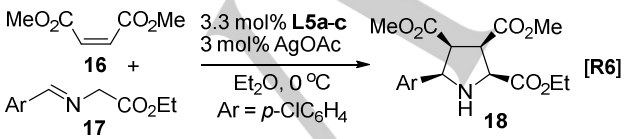


Scheme 6. Palladium catalysed allylic amination of **14** with ligands **L5**.

Table 5. Comparative outcomes with ligand series **L5** for the palladium catalysed allylic amination of **14** [R5] and silver catalysed formation of **18** [R6].

Entry	Ligand	Product	Yield (%)	*ee* (%)
1[a]	(S_p)-**L5a**	(*S*)-**15**	96	73.7
2[a]	(*S*,S_p)-**L5b** (R = *t*Bu)	(*R*)-**15**	83	91.3
3[a]	(*S*,R_p)-**L5c** (R = *t*Bu)	(*R*)-**15**	96	97.2
4[b]	(S_p)-**L5a**	**18**[c]	98	81
5[b]	(*S*,S_p)-**L5b** (R = Bn)	**18**[c]	93	88
6[b]	(*S*,R_p)-**L5c** (R = Bn)	*ent*-**18**	96	78

[a] Reaction run to completion (TLC). [b] Reaction time not stated. [c] (1*S*,2*R*,3*R*,4*R*)-**18**.



Scheme 7. Silver catalysed [3 + 2] cycloaddition to give **18** with ligands **L5**.

In contrast, application of **L5a**-**c** (R = Bn) to the silver catalysed formal [3 + 2] cycloaddition between dimethyl maleate **16** and an azomethine ylide derived from **17** gave **18**, with the configuration and selectivity of the product being controlled primarily by the element of planar chirality (Scheme 7, Table 5).[25] The diastereoisomers **L5b** and **L5c** resulted, respectively, in slightly higher and lower enantioselectivity compared to **L5a**.

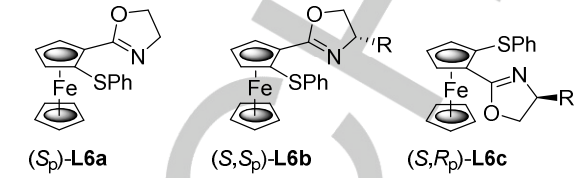
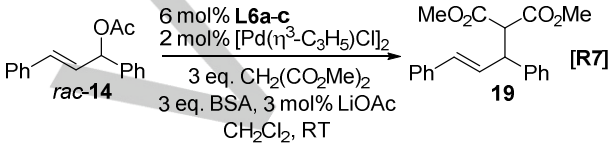


Figure 10. Ligands **L6a**-**c**.



Scheme 8. Palladium catalysed allylic alkylation of **14** with ligands **L6**.

A related class of bidentate ferrocenyloxazoline derived ligands which meet the criteria for inclusion in this review are thioether derivatives **L6a**-**c** (Figure 10).[23] Two sets of diastereisomers **L6b**-**c** (R = *i*Pr and *t*Bu) were applied to palladium catalysed allylic alkylation, in addition to precursor planar chiral ligand **L6a** (Scheme 8, Table 6). As for the phosphine containing ligands **L5**, applied to the related allylic amination reaction, the oxazoline-based element of central chirality dominates enantiocontrol. Ligand **L6a** displayed very low enantioselectivity, with the only clearly matched example in this instance being (*S*,S_p)-**L6b** (R = *t*Bu). A feature of these sulfur-containing ligands is the creation of an additional stereogenic centre on palladium ligation.

Table 6. Comparative outcomes with ligand series **L6** for the palladium catalysed allylic alkylation of **14** [R7].

Entry	Ligand	Product	Time (h)	Yield (%)	*ee* (%)
1	(S_p)-**L6a**	(*R*)-**19**	48	90	8.3
2	(*S*,S_p)-**L6b** (R = *i*Pr)	(*S*)-**19**	3	98	89.4
3	(*S*,R_p)-**L6c** (R = *i*Pr)	(*S*)-**19**	3	98	90.4
4	(*S*,S_p)-**L6b** (R = *t*Bu)	(*S*)-**19**	10	98	98
5	(*S*,R_p)-**L6c** (R = *t*Bu)	(*S*)-**19**	1	98	89.8

When examining the influence of an additional element of chirality to create a pair of diastereoisomers it is of course possible to do this in two ways (start with R and add R^1, or start with R^1 and add R, Figure 3). However, for planar chiral 1,2-

disubstituted ferrocene-based ligands containing a carbon-based stereogenic centre it is not possible to have a non-planar chiral equivalent with which to determine the outcome of adding FeCp to one diastereotopic face or the other. The closest comparison is with benzene derivatives such as **L1d** and **L5d**.[26]

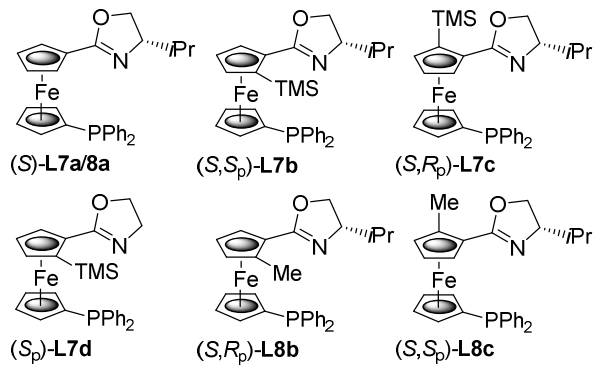
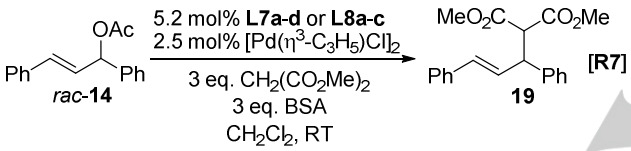


Figure 11. Ligands **L7a**-**d** and **L8a**-**c**.



Scheme 9. Palladium catalysed allylic alkylation of **14** with ligands **L7** and **L8**.

Table 7. Comparative outcomes with ligand series **L7** and **L8** for the palladium catalysed allylic alkylation of **14** [R7].[a]

Entry	Ligand	Product	Yield (%)	*ee* (%)
1	(*S*)-**L7a** [(*S*)-**L8a**]	(*S*)-**19**	98	92.8
2	(*S*,S_p)-**L7b**	(*R*)-**19**	99	64.0
3	(*S*,R_p)-**L7c**	(*S*)-**19**	99	98.6
4[b]	(S_p)-**L7d**	(*R*)-**19**	98	79.4
5	(*S*,R_p)-**L8b**	(*R*)-**19**	98	34.2
6	(*S*,S_p)-**L8c**	(*S*)-**19**	99	98.5

[a] Reactions run to completion (TLC). [b] With 5 mol% KOAc.

In contrast, ferrocenyloxazolines **L7a**-**d** (Figure 11) reported by Hou, Dai and co-workers, contain metal ligating groups on both cyclopentadienyl rings such that the outcome of adding both central *and* planar chirality may be determined.[27] In this series (*S*)-**L7a**, which contains only the oxazoline-based stereogenic centre, displayed good enantioselectivity for the synthesis of (*S*)-**19**, the product of a palladium catalysed allylic alkylation reaction (Scheme 9, Table 7). Planar chiral (S_p)-**L7d** displayed lower selectivity for the *R* enantiomer of the product. Adding planar chirality to (*S*)-**L7a** resulted in higher and lower enantioselectivity with (*S*,R_p)-**L7c** being the matched diastereoisomer. Alternatively, adding central chirality to (S_p)-**L7d** (and invoking enantiomeric entry 3, *i.e.* (*R*,S_p)-**L7c**) also resulted in higher and lower enantioselectivity (Figure 12). That both approaches increase and decrease the selectivity is a consequence of the similar influence on enantioselectivity of both elements of chirality, influences that are clearly additive or subtractive. A similar outcome was observed when a methyl group rather than a TMS group was employed to generate planar chirality by formal addition to the parent ligand **L8a** to give **L8b**/**c** (this also changes the R_p/S_p configurational assignment).

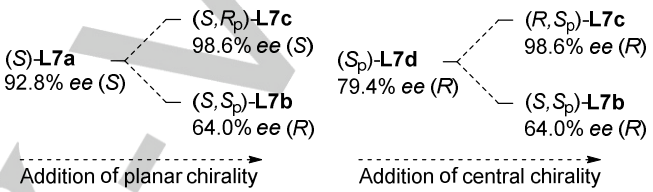


Figure 12. The outcome of both possible chirality addition pathways with **L7a**-**d** as applied to the palladium catalysed allylic alkylation reaction [R7].

In a related study Hou *et al.* described 1,1'-N,O-ferrocenyl ligands **L9** (Figure 13) and applied these to the reaction between benzaldehyde **20** and diethylzinc (Scheme 10, Table 8).[28] For both series (R = *i*Pr and *t*Bu) ligands (*S*,R_p)-**9Lb** resulted in higher enantioselectivity than the corresponding parent ligand (*S*)-**L9a**. Ligands (*S*,S_p)-**9Lc** resulted in significantly different outcomes. The *iso*-propyl derivative gave the product **21** in reduced *ee* compared to **L9a** (R = *i*Pr) and with a swap in configuration. In contrast the *tert*-butyl derivative resulted in product displaying the same configuration with a higher *ee* compared to **L9a** (R = *t*Bu).

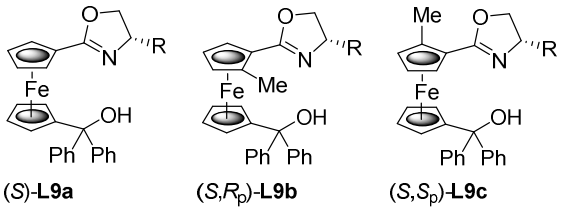
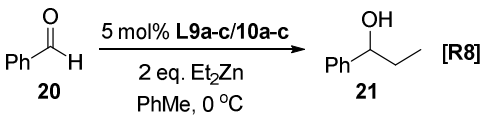


Figure 13. Ligands **L9a**-**c**.



Scheme 10. The reaction of benzaldehyde **20** with diethylzinc using ligands **L9** and **L10**.

Table 8. Comparative outcomes with ligand series **L9** for the reaction of benzaldehyde **20** with diethylzinc [R8].[a]

Entry	Ligand	Product	Yield (%)	*ee* (%)
1	(*S*)-**L9a** (R = *i*Pr)	(*R*)-**21**	[b]	80.9
2	(*S*,R_p)-**L9b** (R = *i*Pr)	(*R*)-**21**	96	83.2
3	(*S*,S_p)-**L9c** (R = *i*Pr)	(*S*)-**21**	94	37.0
4	(*S*)-**L9a** (R = *t*Bu)	(*R*)-**21**	[b]	88.6
5	(*S*,R_p)-**L9b** (R = *t*Bu)	(*R*)-**21**	93	94.9
6	(*S*,S_p)-**L9c** (R = *t*Bu)	(*R*)-**21**	95	92.2

[a] Reaction time not stated. [b] Yield not given.

Also applied to the reaction of benzaldehyde **20** with diethylzinc were 1,2-N,O-ferrocenyl ligands **L10** reported by Bolm *et al.* (Figure 14).[29] In the context of this review the planar chiral parent precursor to diastereoisomers **L10b**/**c** does not contain substituents at position 4 of the oxazoline, but in this work comparison was made to the gem-dimethyl derivative **L10a**. This notwithstanding, the results obtained (Scheme 10, Table 9) revealed matched and mismatched configurations for **L10b** and **L10c**, respectively, with the pseudo-parent ligand **L10a** resulting in an intermediate value of *ee*.

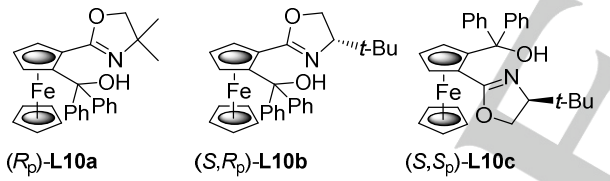


Figure 14. Ligands **L10a**-**c**.

Table 9. Comparative outcomes with ligand series **L10** for reaction of benzaldehyde **20** with diethylzinc [R8].

Entry	Ligand	Product	Time (h)	Yield (%)	*ee* (%) (config.)
1	(R_p)-**L10a**	(*R*)-**21**	20	97	51
2	(*S*,R_p)-**L10b**	(*R*)-**21**	6	83	93
3	(*S*,S_p)-**L10c**	(*R*)-**21**	59	55	35

The success of chiral ferrocene-based ligands containing a 1-substituted ethyl group[10] (*i.e.* those derived from Ugi's amine[30]) has resulted in the incorporation of the 1-(diphenylphosphino)ethyl moiety as a substituent in a series of 1,2-disubstituted ferrocenyloxazoline ligands (Figure 15).[31] In these reports three of the four possible diastereoisomers containing three elements of chirality are described, specifically **L11b**-**c** (R = *i*Pr, Ph) and **L11d** (R = *i*Pr). This work also describes the synthesis of ligand **L11a**, which in the context of this review is the stereochemical precursor to **L11b**/**c** by formal addition of the oxazoline substituent. Also described is **L11e**, the precursor to **L11b**/**d** by formal introduction of an α–methyl substituent. All of these ligands were used for the synthesis of ruthenium complexes $RuCl_2(PPh_3)$(**L11a**-**e**) employed as catalysts for the transfer hydrogenation of acetophenone **22** (Scheme 11, Table 10, Figure 16).[31b]

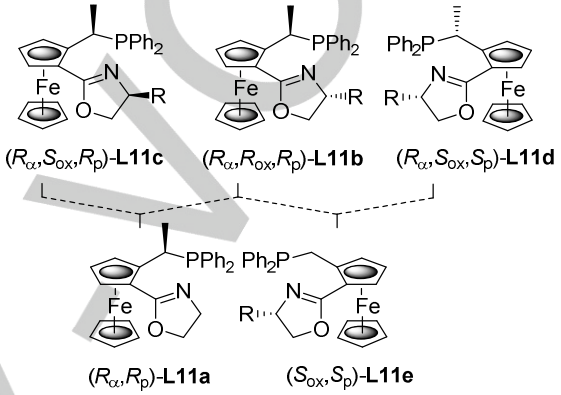
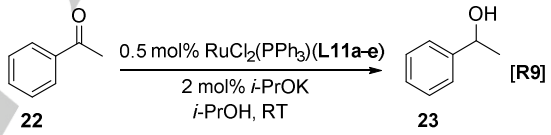


Figure 15. Ligands **L11a**-**e**.



Scheme 11. Ruthenium catalysed transfer hydrogenation of **22** with ligands **L11**.

Table 10. Comparative outcomes with ligand series **L11** for the ruthenium catalysed transfer hydrogenation of **22** [R9].

Entry	Ligand[a]	Product	Time	Con. (%)	*ee*
1	(R_α,R_p)-**L11a**	(*S*)-**23**	20 min	98	9
2	(R_α,R_{ox},R_p)-**L11b** (R = *i*Pr)	(*S*)-**23**	10 min	99	9
3	(R_α,S_{ox},R_p)-**L11c** (R = *i*Pr)	(*R*)-**23**	5 h	18	6
4	(R_α,R_{ox},R_p)-**L11b** (R = Ph)	(*S*)-**23**	15 min	>99	9
5	(R_α,S_{ox},R_p)-**L11c** (R = Ph)	(*R*)-**23**	6 h	90	73
6	(R_α,S_{ox},S_p)-**L11d** (R = *i*Pr)	(*R*)-**23**	1h	80	41
7	(S_{ox},S_p)-**L11e** (R = *i*Pr)	(*R*)-**23**	30 min	96	93

[a]In complex $RuCl_2(PPh_3)$(**L11a**-**e**).

The complex containing (R,R_p)-**L11a** is an effective catalyst for this reduction reaction (entry 1), but addition of an isopropyl group (entries 2 and 3), or a phenyl group (entries 4 and 5) increased and decreased the enantioselectivity, such that the complex configured as (R_α,R_{ox},R_p)-**L11b** is the matched diastereoisomer which resulted in excellent enantioselectivity with either an *i*Pr or Ph substituent. Alternatively, starting from the complex containing (S,S_p)-**L11e** (entry 7), for which the only example reported has an isopropyl oxazoline substituent, the enantioselectivity of reduction was again both raised and lowered on addition of an α–methyl substituent (entries 2 and 6). Unlike many of the reactions reported in this review which are run for a set period, or others for which the reaction time is not reported, the times given in Table 6 are significant as it is stated that these transfer hydrogenations were monitored periodically. It is thus of note that there is an inverse correlation between reaction time/conversion and enantioselectivity.

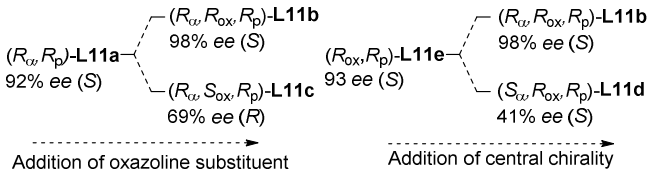
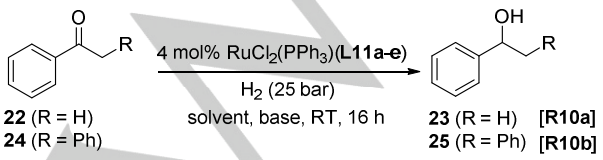


Figure 16. The outcomes of ruthenium catalysed transfer hydrogenation of **22** with ligands with ligands **L11a**-**e** (R = *i*Pr) [R9].

The ruthenium complexes $RuCl_2(PPh_3)$(**L11a**-**c**) have also been applied as catalysts for the hydrogenation of alkyl aryl ketones (Scheme 12, Table 11, Figure 17).[31a] The outcomes from the reduction of acetophenone **22** mirror those of transfer hydrogenation with the same substrate (entries 1-3), where the complex containing **L11b** (R = *i*Pr) again resulted in excellent enantioselectivity. The use of the more challenging substrate **24** is instructive as the relatively modest *ee* obtained with the complex containing **L11a** (entry 4) was improved to 99% *ee* when replaced by **L11b** (R = *i*Pr). With both of these substrates the ruthenium complex containing the mismatched diastereoisomer **L11c** (R = *i*Pr) resulted in the formation of the opposite enantiomer of the product in significantly lower *ee*. These are two representative examples of a total of 16 sets of results with ligands **L11a**-**c** which explored varying the base, solvent and oxazoline substituent (R = *i*Pr, Ph), and also included as substrate 4-methylacetophenone. In all cases the reaction outcomes closely follow the pattern revealed in Table 11.



Scheme 12. Ruthenium catalysed hydrogenation of **22** and **24** with ligands **L11**.

Table 11. Comparative outcomes with ligand series **L11** for the ruthenium catalysed hydrogenation of **22** [R10a] and **24** [R10b].[a]

Entry	Ligand[a]	Product	Solvent	*ee* (%)
1[b]	(R_α,R_p)-**L11a**	(*S*)-**23**	PhMe/H_2O[c]	95
2[b]	(R_α,R_{ox},R_p)-**L11b** (R = *i*Pr)	(*S*)-**23**	PhMe/H_2O[c]	99
3[b]	(R_α,S_{ox},R_p)-**L11c** (R = *i*Pr)	(*R*)-**23**	PhMe/H_2O[c]	44
4[d]	(R_α,R_p)-**L11a**	(*S*)-**25**	*i*-PrOH	74
5[d]	(R_α,R_{ox},R_p)-**L11b** (R = *i*Pr)	(*S*)-**25**	*i*-PrOH	99
6[d]	(R_α,S_{ox},R_p)-**L11c** (R = *i*Pr)	(*R*)-**25**	*i*-PrOH	38

[a] All reactions to ≥99% conversion. [b] Base = K_2CO_3. [c] 9:1 PhMe/H_2O. [d] Base = KO*t*Bu.

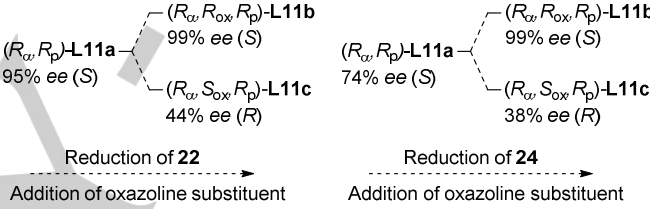


Figure 17. The outcomes of ruthenium catalysed hydrogenation of **22** [R10a] and **24** [R10b] with ligands **L11a**-**c**.

3. Chirality addition on axially chiral ligands

Ligands that display axial chirality have proven to be extremely effective in asymmetric catalysis.[32] For the most part these are biaryl-based compounds containing substituents which prevent rotation about the Ar-Ar single bond. An analysis of matching and mismatching effects was performed by Zhang and co-workers using ligands **L12b** and **L12c** containing two atropisomeric biaryl units (Figure 18).[33] These are related to the TunePhos series of ligands introduced by the same group,[34] and for this study ligand **L12a** was synthesised for comparison. All three ligands were applied to the asymmetric hydrogenation of β and α-ketoesters **26** and **28** following the synthesis of ruthenium catalysts $RuCl_2(dmf)_n$(**L12a**-**c**) (Scheme 13, Table 12) The results display the same trend for both substrates such that the enantioselectivity is improved and reduced by introduction of the second element of axial chirality, with (S_a,S_a)-**L12b** proving to be the matched diastereoisomer. Thus, even a remote chirality element can have an influence on enantioselectivity, both adding to and subtracting from the enantioselectivity observed with the parent ligand.

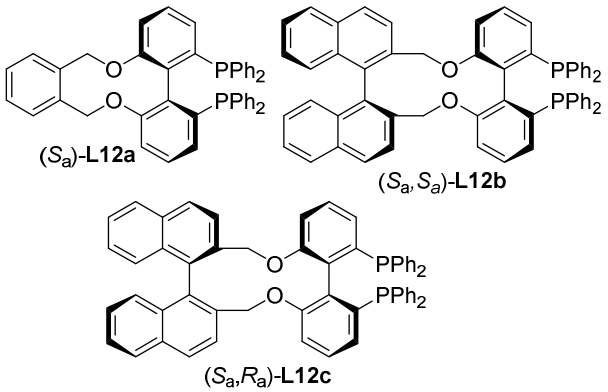
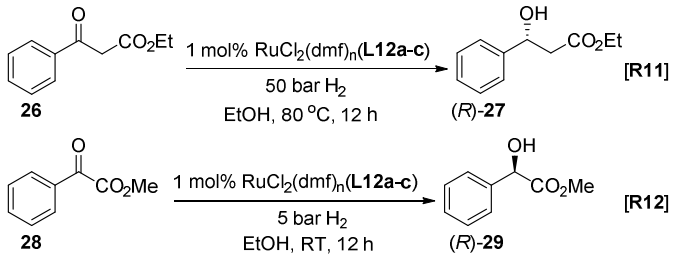


Figure 18. Ligands **L12a**-**c**.



Scheme 13. Ruthenium catalysed hydrogenation of **26** and **28**.

Table 12. Comparative outcomes with ligand series **L12** for the ruthenium catalysed hydrogenation of **26** [R11] and **28** [R12].[a]

Entry	Ligand	Product	Temp. (°C)	*ee* (%)
1	(S_a)-**L12a**	(*R*)-**27**	80	83
2	(S_a,S_a)-**L12b**	(*R*)-**27**	80	89
3	(S_a,R_a)-**L12c**	(*R*)-**27**	80	78
4[b]	(S_a)-**L12a**]	(*R*)-**29**	RT	90
5	(S_a,S_a)-**L12b**	(*R*)-**29**	RT	95
6	(S_a,R_a)-**L12c**	(*R*)-**29**	RT	85

[a] All reactions gave 100% conversion unless otherwise stated. [b] 90% conversion.

Another pair of diastereoisomers studied that are also related to TunePhos ligands are **L13b**/**c** which contain, compared to C_3-TunePhos **L13d**, additional elements of chirality in the three-carbon alkyl linker (Figure 19).[35] In this study comparison was not made with **L13d**, but instead with (S_a)-BINAP **L13a**. This is somewhat sterically and electronically different, but the results for the ruthenium catalysed hydrogenation of **30** to give naproxen **31** are similar, where **L13b** resulted in slightly higher enantioselectivity than BINAP, and **L13c** in slightly lower enantioselectivity (Scheme 14, Table 13). The incomplete conversions obtained with **L13b**/**c** point to higher activity with the BINAP derived complex. When these reactions were run at 0 °C for 24 hours very similar enantioselectivities were observed with complete conversion in each case. These results were mirrored further in several other comparative reactions with substrate **30** at different pressures of H_2, temperatures and reaction times.

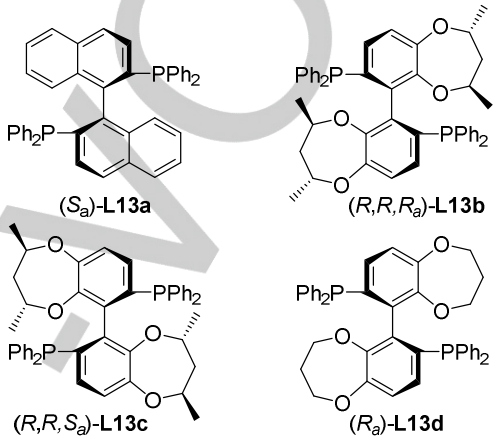
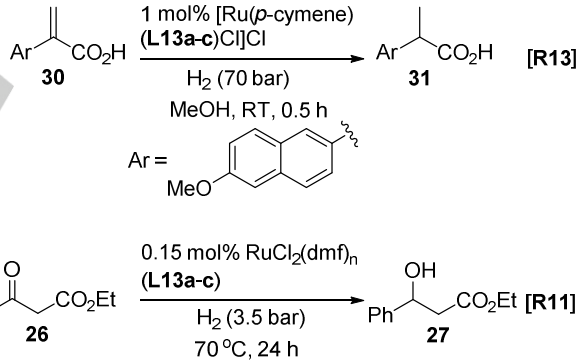


Figure 19. Ligands **L13a**-**d**.



Scheme 14. Ruthenium catalysed hydrogenation of **26** and **30** with ligands **L13**.

Table 13. Comparative outcomes with ligand series **L13** for the [Ru(*p*-cymene)(**L13a**-**c**)Cl]Cl catalysed hydrogenation of **30** [**R13**].

Entry	Ligand	Product	Conversion (%)	*ee* (%)
1	(S_a)-**L13a**	(*S*)-**31**	90	90
2	(R,R,R_a)-**L13b**	(*R*)-**31**	36	94
3	(R,R,S_a)-**L13c**	(*S*)-**31**	46	87

Ligands **L13a-c** were also used for the synthesis of $RuCl_2(dmf)_n$(**L13a-c**) and the resulting complexes applied to the hydrogenation of ethyl 4-chloroacetoacetate and related acetoacetate β–keto esters. In all cases high enantioselectivity resulted (94.2-99.4% *ee*) such that there was essentially no difference in outcome. In contrast, hydrogenation of β–keto ester **26** gave higher and lower enantioselectivity with **L13c** and **L13b**, respectively, compared to BINAP **L13a** (Scheme 14, Table 14).[35,36] Ligand (R_a)-**L13d** has been applied to this substrate in a separate study, albeit under different conditions (52 bar, 60 °C) and with a catalyst generated *in situ* from $[Ru(benzene)Cl_2]_2$.[34] That (*S*)-**27** was formed in 72% *ee* highlights the superiority of **L13c** with this substrate.

Table 14. Comparative outcomes with ligand series **L13** for the $RuCl_2(dmf)_n$(**L13a-c**) catalysed hydrogenation of **26** [R11].[a,b]

Entry	Ligand	Product	Time (h)	*ee* (%)
1	(S_a)-**L13a**	(*R*)-**27**	24	89.3
2	(*R*,*R*,R_a)-**L13b**	(*S*)-**27**	24	82.4
3	(*R*,*R*,S_a)-**L13c**	(*R*)-**27**	24	97.7

[a] All reactions gave complete conversion. [b] MeOH or EtOH and 1.25% (v/v) CH_2Cl_2 as solvent.

In contrast to the rather remote nature of the chirality element(s) added to axially chiral ligands **L12a** and **L13a**, P-N ligand **L14a** was modified to give diastereoisomers **L14b/c** in which the added methoxy substituents of the C_2-symmetric pyrrolidine moiety are only three bonds removed from a metal on coordination (Figure 20).[37] The metal in this instance is palladium and the resulting complexes were applied to the asymmetric allylic alkylation of **14** to give **19** (Scheme 15, Table 15). The added groups did influence the outcome, either adding or subtracting from the selectivity of the reaction.

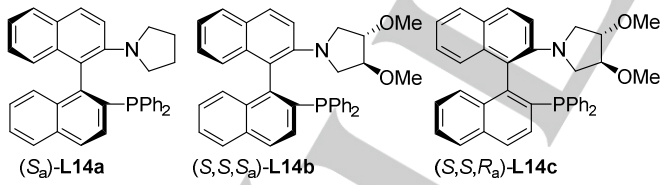
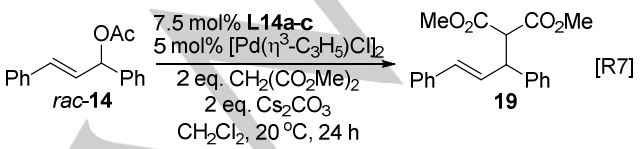


Figure 20. Ligands **L14a-c**.



Scheme 15. Palladium catalysed allylic alkylation of **14** with ligands **L14**.

Table 15. Comparative outcomes with ligand series **L14** for the palladium catalysed allylic alkylation of **14** [R7].

Entry	Ligand	Product	Yield (%)	*ee* (%)
1	(S_a)-**L14a**	(*R*)-**19**	81	55
2	(*S*,*S*,S_a)-**L14b**	(*R*)-**19**	97	83
3	(*S*,*S*,R_a)-**L14c**	(*S*)-**19**	98	26.9

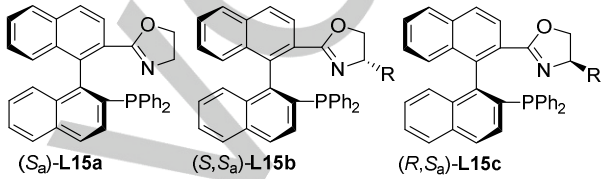
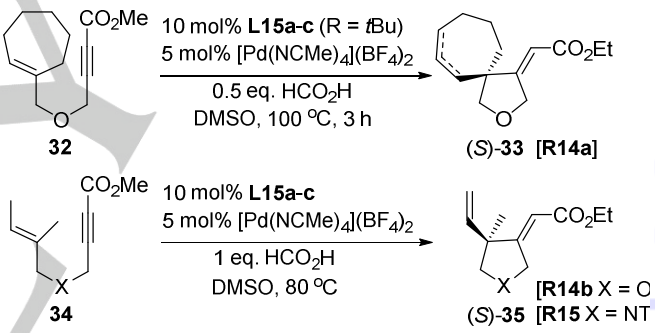


Figure 21. Ligands **L15a-c**.



Scheme 16 Palladium catalysed ene-type spirocyclisation of **32** and the related cyclisation of **34** with ligands **L15**.

A related class of PN-ligands **L15a-c** contain oxazoline and diphenylphosphine substituents attached to a 1,1'-binaphthyl framework (Figure 21). Cationic palladium complexes derived from these ligands were applied to a variety of ene-type cyclisation reactions (Scheme 16, Table 16).[38] In comparison to the parent ligand **L15a**, use of epimers **L15b** and **L15c** containing the additional oxazoline-based stereogenic centre resulted in higher enantioselectivity, and in the product having the same absolute configuration. Notwithstanding that methyl substituted oxazoline (*R*,S_a)-**L15c** is somewhat more matched than (*S*,S_a)-**L15b** (entries 10 and 11), the configuration resulting from introduction of an oxazoline substituent is generally of little importance. Instead it is stated that the introduced substituent improves enantioselectivity by acting as a steric block, an outcome rationalised by a quadrant model based on X-ray crystal structures of $PdCl_2$ complexes derived from **L15b/c** (R = *t*Bu).[38b] This led to the synthesis of the 4,4-dimethyloxazoline derivative of ligand (S_a)-**L15a** with which high enantioselectivities

were also obtained in these ene-type cyclisation reactions (*e.g.* (*S*)-**35** (X = NTs) in 93% *ee*, >99% yield).

Table 16. Comparative outcomes with ligand series **L15** for the palladium catalysed ene-type spirocyclisation of **32** [R14a] and **34** [R14b and R15].

Entry	Ligand	Product	Time (h)	Yield (%)	*ee* (%)
1	(S_a)-**L15a**	(*S*)-**33**	3	81[a]	51[b]
2	(*S*,S_a)-**L15b** (R = *t*Bu)	(*S*)-**33**	3	97[a]	80[b]
3	(*R*,S_a)-**L15c** (R = *t*Bu)	(*S*)-**33**	3	99[a]	82[b]
4	(S_a)-**L15a**	(*S*)-**35** X = O	18	89	41
5	(*S*,S_a)-**L15b** (R = *t*Bu)	(*S*)-**35** X = O	24	92	87
6	(*R*,S_a)-**L15c** (R = *t*Bu)	(*S*)-**35** X = O	12	>99	78
7[c]	(S_a)-**L15a**	(*S*)-**35** X = NTs	3	>99	35
8[c]	(*S*,S_a)-**L15b** (R = *t*Bu)	(*S*)-**35** X = NTs	3	>99	92
9[c]	(*R*,S_a)-**L15c** (R = *t*Bu)	(*S*)-**35** X = NTs	3	>99	93
10	(*S*,S_a)-**L15b** (R = Me)	(*S*)-**35** X = NTs	3	>99	52
11	(*R*,S_a)-**L15c** (R = Me)	(*S*)-**35** X = NTs	3	>99	89

[a] Combined yield for two double bond isomers. [b] Total *ee* value for two double bond isomers. [c] A similar series of results were also obtained with use of diethyl [4-(dimethylamino)-4-oxobut-2-yn-1-yl][(2*E*)-2-methylbut-2-en-1-yl]propanedioate as substrate.

The penultimate types of ligand examined in this section of the review are spirocycles **L16** (Figure 22) and **L17** (Figure 23) derived from SPINOL.[39] In contrast to 1,1'-biaryl ligands **L12**-**L15**, these axially chiral ligands are based on a rigid framework as conformational change requires the distortion of several bonds rather than just C-C bond rotation.

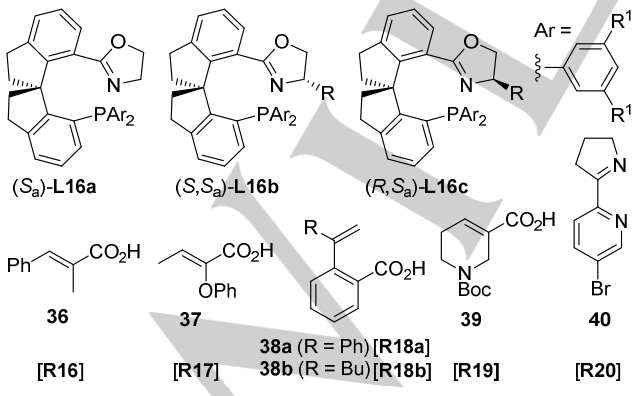


Figure 22. Ligands **L16a**-**c** and substrates employed in iridium catalysed hydrogenation with ligands **L16**.

Table 17. Comparative outcomes with ligand series **L16** for the iridium catalysed hydrogenation of substrates **36**-**40** [R16-R20].[a]

Entry	Ligand	Ligand R/R^1	Substrate(S/C)	H_2 (bar)/temp (°C)/time (h)	Conn. (%)	*ee* (%) (config.)
1[b]	(S_a)-**L16a**	-/*t*Bu	**36** (400)	6/RT/8	100	>99 (*S*)
2[b]	(*S*,S_a)-**L16b**	Bn/*t*Bu	**36** (400)	6/RT/0.5	100	>99 (*S*)
3	(*S*,R_a)-**L16c**	Bn/H	**36** (400)	6/RT/24	0	-
4[c]	(S_a)-**L16a**	-/*t*Bu	**37** (200)	6/RT/24	75	95 (*S*)
5[c]	(*S*,S_a)-**L16b**	Bn/*t*Bu	**37** (200)	6/RT/24	95	98 (*S*)
6[c]	(*S*,R_a)-**L16c**	Bn/H	**37** (200)	6/RT/24	0	-
7[d]	(S_a)-**L16a**	-/Me	**38a** (200)	50/45/4	100	98 (*R*)
8[d]	(*S*,S_a)-**L16b**	Bn/Me	**38a** (200)	6/45/4	100	95 (*R*)
9[d]	(*R*,S_a)-**L16c**	Bn/Me	**38a** (200)	6/45/20	71	91 (*R*)
10[d]	(S_a)-**L16a**	-/*t*Bu	**38b** (400)	6/45/3.5	100	99 (*R*)
11[d]	(*S*,S_a)-**L16b**	Bn/*t*Bu	**38b** (400)	6/45/24	24	89 (*R*)
12[d]	(*R*,S_a)-**L16c**	Bn/*t*Bu	**38b** (400)	6/45/24	28	79 (*R*)
13[c]	(S_a)-**L16a**	-/*t*Bu	**39** (100)	6/60/12	100	97 (*R*)
14[c]	(*S*,S_a)-**L16b**	Bn/*t*Bu	**39** (100)	6/60/12	100	96 (*R*)
15[c]	(*R*,S_a)-**L16c**	Bn/*t*Bu	**39** (100)	6/60/12	64	91 (*R*)
16[e]	(S_a)-**L16a**	-/*t*Bu	**40** (100)	50/RT/24	100	29 (*S*)
17[e]	(*S*,S_a)-**L16b**	Bn/*t*Bu	**40** (100)	50/RT/24	100	96 (*S*)
18[e]	(*R*,S_a)-**L16c**	Bn/*t*Bu	**40** (100)	50/RT/24	0	-

[a] All reactions run in MeOH unless otherwise stated. [b] With 0.5 eq. NEt_3. [c] With 0.5 eq. Cs_2CO_3. [d] With 1 eq. NEt_3. [e] In THF with 10 mol% I_2.

P-N ligands **L16** have been applied by Zhou *et al.* to the iridium catalysed hydrogenation of a number of substrates, principally carboxylic acid derivatives (Figure 22, Table 17). With **36**[40,41] and **37**[42] high *ee* was achieved with the parent ligand **L16a** and the (*S*,S_a) diastereoisomer **L16b** under conditions where a related (*S*,R_a)-**L16c** ligand resulted in no hydrogenation. A similar outcome was observed with the 2-vinylbenzoic acid derivative **38a**[43] excepting that, under conditions that allowed direct comparison of **L16b** with **L16c**, the latter did result in hydrogenation, albeit with a longer reaction time and lower enantioselectivity. With the related butyl rather than phenyl-substituted substrate **38b**[44] high enantioselectivity was achieved with the parent ligand **L16a**. In this instance both diastereoisomers **L16b**/**c**, with a longer reaction time, resulted in

lower conversion and enantioselectivity. This is the opposite of the outcome observed with **L15b**/**c** in the palladium catalysed ene-type cyclisation of **34** (Scheme 16), *i.e.* the configuration of the additional stereogenic centre is relatively unimportant as both diastereoisomers reduce enantioselectivity. The outcomes from the use as substrate of **39**[45] were similar to that of the other α,β-unsaturated acids. Finally, the hydrogenation of cyclic imine **40**[46] resulted in much higher enantioselectivity with **L16b** than with parent **L16a**, and **L16c** gave no reduction under the conditions used. Thus in summary for these substrates, high enantioselectivity resulted from either the parent ligand or the matched (*S*,*S*$_a$)-diastereoisomer, and for α,β-unsaturated acids there is little difference between them. The difference observed with other substrates is more marked, with cyclic imine **40** highlighting the significant increase in enantioselectivity that results from the correctly configured additional stereogenic centre.

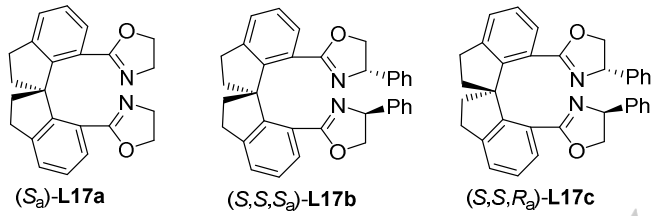
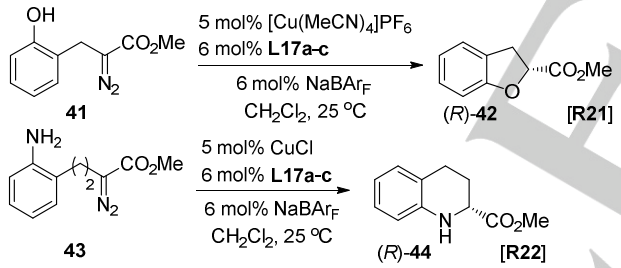


Figure 23. Ligands **L17a**-**c**.



Scheme 17. Copper catalysed O-H and N-H insertive cyclisation reactions with ligands **L17**.

Bisoxazoline ligands **L17** based on the same rigid spirocyclic framework have also been synthesised and applied to copper-catalysed intramolecular phenolic O-H bond insertion (Scheme 17, Table 18).[47] With substrate **41** the parent ligand (*S*$_a$)-**L17a** resulted in almost the same outcome as diastereoisomer (*S*,*S*,*S*$_a$)-**L17b**, and both ligands were employed in further exemplification of this reaction. In contrast diastereoisomer (*S*,*S*,*R*$_a$)-**L17c** resulted in a significant reduction in enantioselectivity. On extension of this chemistry to the synthesis of dihydrobenzopyrans, ligand **L17b** resulted in significantly higher selectivity than observed with **L17a** (96% *ee vs.* 45-48% *ee*).[47] A similar outcome was observed on extension of this reaction to intramolecular N-H bond insertion with aniline derivative **43**, where ligand **L17b** gave significantly higher selectivity than was observed with **L17a**.[48] For this reaction diastereoisomer **L17c** resulted in racemic product.

Table 18. Comparative outcomes with ligand series **L17** for the copper catalysed reactions of **41** [R21] and **43** [R22].

Entry	Ligand	Product	Time (min.)	Yield (%)	*ee* (%)
1	(*S*$_a$)-**L17a**	(*R*)-**42**	5	98	98
2	(*S*,*S*,*S*$_a$)-**L17b**	(*R*)-**42**	5	84	97
3	(*S*,*S*,*R*$_a$)-**L17c**	**42**[a]	30	94	49
4	(*S*$_a$)-**L17a**	(*R*)-**44**	120	82	43
5	(*S*,*S*,*S*$_a$)-**L17b**	(*R*)-**44**	15	74	85
6	(*S*,*S*,*R*$_a$)-**L17c**	*rac*-**44**	10	73	0

[a] Absolute configuration not stated but assumed to be *S*.

BINOL-derived phosphoramidites have already been discussed for ligand series **L3** where this ligand component was incorporated into a planar chiral ferrocene-based structure. More typically, such BINOL-derived ligands incorporate a simpler secondary amine component which may or may not include additional carbon-based stereogenic centres.[49] The ligands in series **L18** meet the criteria for inclusion in this review where the dibenzylamine component of **L18a** was replaced by either bis[(*R*)-1-phenylethyl]amine or its (*S*,*S*)-enantiomer (Figure 24).

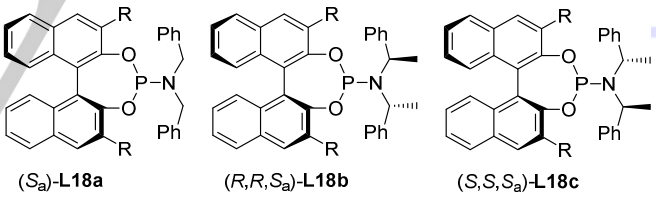
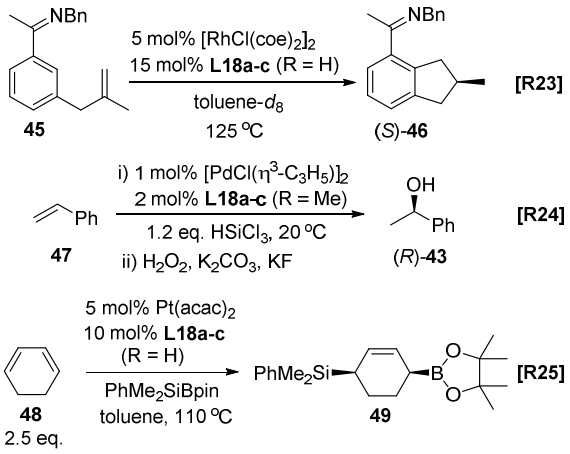


Figure 24. Ligands **L18a**-**c**.

Ligands **L18** (R = H) have been applied to rhodium catalysed intramolecular alkene hydroarylation with substrate **45** containing an *ortho*-directing imine functionality (Scheme 18, Table 19).[50] The moderate selectivity achieved with **L18a** was improved somewhat with diastereoisomers **L18b**/**c**, where both resulted in product of the same absolute configuration formed in essentially identical *ee*. This reveals that the configuration is controlled by the axial chirality of the binaphthyl moiety, and suggests that the higher enantioselectivity achieved with **L18b**/**c** is due a steric effect from the additional methyl groups which is independent of the configuration of the new stereogenic centres. This conclusion is supported by this same study reporting an *ee* of 83% for (*S*)-**46** generated under the same conditions with the phosphoramidite ligand derived from diisopropylamine.



Scheme 18. Application of phosphoramidite ligands **L18** to rhodium catalysed hydroarylation, palladium catalysed hydrosilylation, and platinum catalysed silaboration.

Table 19. Comparative outcomes with ligand series **L18** for the rhodium catalysed hydroarylation of **45** [R23], the palladium catalysed hydrosilylation of **47** [R24] and the platinum catalysed silaboration of **48** [R25].

Entry	Ligand	Product	Time (h)	Yield (%)	*ee* (%)
1	(S_a)-**L18a** (R = H)	(*S*)-**46**	2.5	52	58
2	(*R*,*R*,S_a)-**L18b** (R = H)	(*S*)-**46**	<2	100	88
3	(*S*,*S*,S_a)-**L18c** (R = H)	(*S*)-**46**	<2	99	87
4	(S_a)-**L18a** (R = Me)	(*R*)-**23**	20	99	4
5	(*R*,*R*,S_a)-**L18b** (R = Me)	(*R*)-**23**	20	96	54
6	(*S*,*S*,S_a)-**L18c** (R = Me)	(*R*)-**23**	20	94	20
7[a]	(S_a)-**L18a** (R = H)	(1*R*,4*S*)[b]-**49**	24	84	77
8	(*R*,*R*,S_a)-**L18b** (R = H)	(1*R*,4*S*)[b]-**49**	30	40	28
9	(*S*,*S*,S_a)-**L18c** (R = H)	(1*R*,4*S*)[b]-**49**	48	58	69

[a] $Pt(acac)_2$ reduced to Pt(0) with DIBAL-H. [b] Tentative assignment.

A similar trend was, in part, observed on application of **L18** (R = Me) to the palladium catalysed hydrosilylation of **47** followed by stereospecific oxidation (Scheme 18, Table 19 entries 4-6).[51] In this instance the parent ligand **L18a** gave essentially no enantioselectivity, this being improved to a modest 54% *ee* with **L18b**. Diastereoisomer **L18c** gave product of the same configuration as **L18b** but with a lower selectivity. In this instance the corresponding phosphoamidite ligand derived from diisopropylamine resulted in product of opposite configuration (48% *ee*).

Finally, ligand series **L18** (R = H) was also applied to the platinum catalysed 1,4-silaboration of cyclohexadiene **48** to give *cis*-product **49** (Scheme 18, Table 19 entries 7-9).[52] Notwithstanding that the platinum complex formed with parent ligand **L18a** was pre-reduced with DIBAL-H to a Pt(0) species, this gave the highest yield and enantioselectivity for the formation of **49**. Diastereoisomers **L18b**/**c**, with which the corresponding platinum complexes were not pre-reduced, resulted in lower yields and enantioselectivites, with the matched diastereoisomer for this reaction, **L18c**, proving to be a little inferior with respect to enantioselectivity than parent ligand **L18a**. Again all three ligands resulted in product of the same absolute configuration.

4. Chirality addition on ligands containing carbon-based stereogenic centres

Although many of the bidentate ligands applied successfully in asymmetric catalysis are based on frameworks displaying planar or axial chirality, a number of ligands are known containing only carbon-based stereogenic centres. A notable example is Kagan's DIOP ligand (**L19a**), the first bisphosphine ligand applied to asymmetric catalysis (Figure 25).[53] A limitation noted by Kagan with this ligand are the remote stereogenic centres relative to the coordinating phosphines. This led to the synthesis of **L19c**, a C_2-symmetric (*S*,*S*)-DIOP derivative containing two additional methyl substituents to give *S* configured stereogenic centres. Application of **L19c** to the rhodium catalysed asymmetric hydrogenation of dehydroamino acids and enamides resulted in lower enantioselectivity compared to the corresponding Rh-DIOP species.[54]

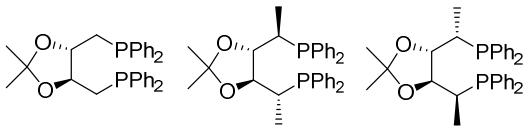
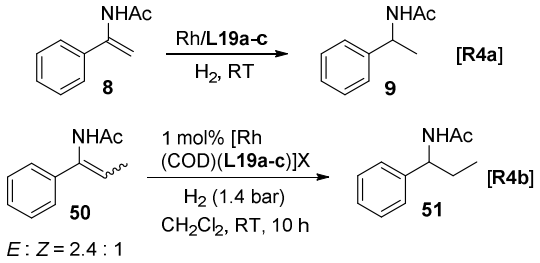


Figure 25. Ligands **L19a**-**c**.

Following the synthesis of the diastereoisomer **L19b**,[55] Zhang and RajanBabu, in separate studies, performed a comparison of **L19a**-**c** in the rhodium catalysed hydrogenation of enamide **8** (Scheme 19, Table 20).[56,57] Although the two studies employed different solvents, catalyst loadings and hydrogen pressures, essentially identical results were obtained. Ligands **L19b** and **L19c** resulted, respectively, in higher and lower enantioselectivity than that achieved with DIOP **L19a**. Further work by RajanBabu gave a similar set of results with *para*-substituted (F, Me) derivatives of enamide **8**, and these ligands were also applied to enamide **50** as a mixture of *E*/*Z* isomers (Scheme 19, Table 21). In this instance the parent ligand DIOP **L19a** gave good enantioselectivity, with this being improved by

use of matched isomer **L19b**, and eroded with mismatched **L19c**.[57]



Scheme 19. Rhodium catalysed hydrogenation of **8** and **50** with ligands **L19**.

Table 20. Comparative outcomes with ligand series **L19** for the rhodium catalysed hydrogenation of **8** to give **9** [R4a].[a]

Entry	Ligand	Prod.	Solvent	H_2 (bar)	Time (h)	*ee* (%)
1[b]	(*S*,*S*)-**L19a**	(*R*)-**9**	MeOH	1.1	24	51.6
2[b]	(*R*,*S*,*S*,*R*)-**L19b**	(*R*)-**9**	MeOH	10	60	98.3
3[b]	(*S*,*S*,*S*,*S*)-**L19c**	(*S*)-**9**	MeOH	10	60	17.3
4[c][d]	(*R*,*R*)-**L19a**	(*S*)-**9**	CH_2Cl_2	1.4	10	53
5[c]	(*R*,*S*,*S*,*R*)-**L19b**	(*R*)-**9**	CH_2Cl_2	1.4	10	98
6[c]	(*S*,*S*,*S*,*S*)-**L19c**	(*S*)-**9**	CH_2Cl_2	1.4	10	20

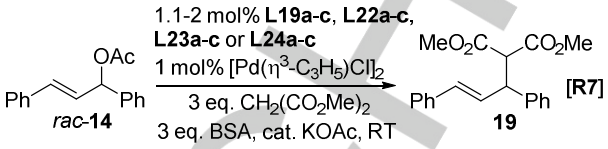
[a] All reactions went with >99% conversion. [b] 2 mol% $[Rh(COD)_2]SbF_6$ + 2.2 mol% **L19**. [c] 1 mol% [Rh(COD)(**L19**)]SbF_6 [d] Corresponding BF_4 complex.

Table 21. Comparative outcomes with ligand series **L19** for the rhodium catalysed hydrogenation of **50** [R4b].[a]

Entry	Ligand	Product	X	*ee* (%)
1	(*R*,*R*)-**L19a**	(*S*)-**51**	BF_4	92
2	(*R*,*S*,*S*,*R*)-**L19b**	(*R*)-**51**	SbF_6	96
3	(*S*,*S*,*S*,*S*)-**L19c**	(*R*)-**51**	BF_4	6

[a] All reactions went with >99% conversion.

Ligands **L19a**-**c** have also been applied to palladium catalysed allylic alkylation of *rac*-**14** to give **19** (Scheme 20, Table 22).[58] Parent ligand DIOP **L19a** has been demonstrated to result in essentially no product enantioselectivity,[59] and this was also the case with **L19b**. In contrast **L19c** did result in modest enantioselectivity demonstrating that, when compared to the outcome of asymmetric hydrogenation, the identity of matched and mismatched diastereoisomers can be reaction dependent.



Scheme 20. Palladium catalysed allylic alkylation of **14** with ligands **L19** and **L22**-**L24**.

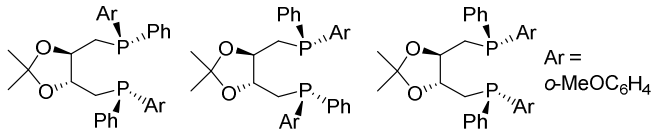
Table 22. Comparative outcomes with ligand series **L19** and **L22**-**L24** for the palladium catalysed allylic alkylation of **14** [R7].[a]

Entry	Ligand	Product	Ligand (mol%)	Solvent	*ee* (%)
1	(*S*,*S*)-**L19a**	**19**	1.3	CH_2Cl_2	~0
2	(*R*,*S*,*S*,*S*)-**L19b**	**19**	2	CH_2Cl_2	~0
3	(*S*,*S*,*S*,*S*)-**L19c**	(*S*)-**19**	2	CH_2Cl_2	63
4	(*R*,*R*)-**L22a**	(*S*)-**19**	2	THF	97
5	(*S*,*S*,*S*,*S*)-**L22b**	(*R*)-**19**	1.6	THF	>99
6	(*R*,*S*,*S*,*R*)-**L22c**	(*S*)-**19**	1.6	THF	94
7	(*R*,*R*)-**L23a**	(*S*)-**19**	1.1	CH_2Cl_2	31
8	(*S*,*S*,*S*,*S*)-**L23b**	(*R*)-**19**	1.1	CH_2Cl_2	60
9	(*R*,*S*,*S*,*R*)-**L23c**	(*S*)-**19**	1.1	CH_2Cl_2	44
10	(*R*,*R*)-**L24a**	(*R*)-**19**	2	toluene	37
11[b]	(*S*,*S*,*S*,*S*)-**L24b**	(*S*)-**19**	2	toluene	93
12[b]	(*R*,*S*,*S*,*R*)-**L24c**	(*R*)-**19**	2	toluene	94

[a] Reaction run to completion (TLC) and products were obtained in 92-99% yield. [b] Reaction at -15 °C for 18 h.

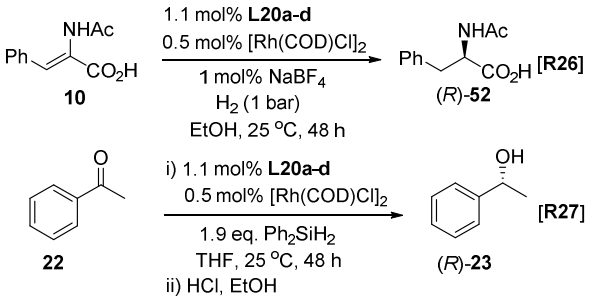
Another investigation into the modification of Kagan's DIOP ligand **L19a**/**20a** involved the synthesis of derivatives **L20b**-**d** containing phosphorus-based stereogenic centres (Figure 26).[60] Application of these to the rhodium catalysed hydrogenation of *N*-acetyl-dehydroamino acid **10** resulted in a similar outcome with ligands **L20a** (DIOP) and **L20b** (Scheme 21, Table 23). Diastereoisomer **L20c** is mismatched, and the C_1-symmetric variant **L20d** resulted in an intermediate value of *ee*. Modest enantioselectivities were obtained on application of these ligands to the rhodium catalysed hydrosilylation of acetophenone, where **L20b** again proved to be the most

selective of the diastereomeric variants. In this instance it also proved to be more selective than DIOP **L20a**.



(*R*,*R*,S_{phos},S_{phos}) **-L20b** (*R*,*R*,R_{phos},R_{phos}) **-L20c** (*R*,*R*,R_{phos},S_{phos}) **-L20d**

Figure 26. Ligands **L20b-d**.



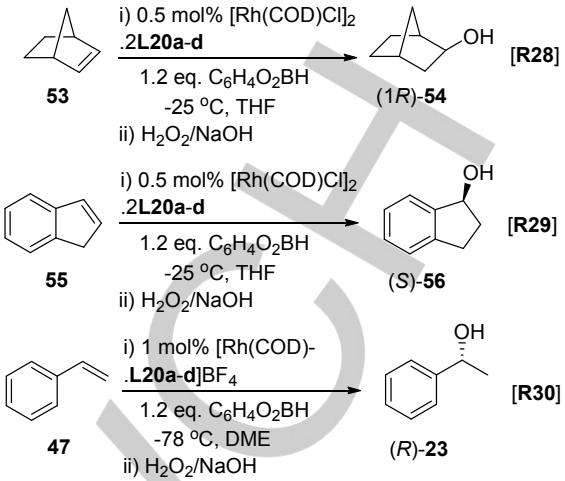
Scheme 21. Rhodium catalysed hydrogenation of **10** and hydrosilylation of **22** with ligands **L20**.

Table 23. Comparative outcomes with ligand series **L20** for the rhodium catalysed hydrogenation of **10** [R26], and rhodium catalysed hydrosilylation of **22** [R27].[a]

Entry	Ligand	**52** *ee* (%) (config.)	**23** *ee* (%) (config.)
1	(*R*,*R*)-**L20a**	72 (*R*)	28 (*R*)
2	(*R*,*R*,S_{phos},S_{phos})-**L20b**	70 (*R*)	43 (*R*)
3	(*R*,*R*,R_{phos},R_{phos})-**L20c**	20 (*R*)	13 (*R*)
4	(*R*,*R*,R_{phos},S_{phos})-**L20d**	54 (*R*)	10 (*R*)

[a] The conversions/yields are not stated.

This series of ligands was also applied to the rhodium catalysed hydroboration of alkenes **53**, **55** and **47** (Scheme 22, Table 24).[60,61] Although no trend resulted with these contrasting substrates, in two of the three cases a P-stereogenic diastereomeric ligand gave a higher *ee* than that obtained from DIOP **L20a**. The example where this is not the case is characterised by poor enantioselection.



Scheme 22. Rhodium catalysed hydroboration of **53**, **55** and **47** with ligands **L20**.

Table 24. Comparative outcomes with ligand series **L20** for the rhodium catalysed hydroboration reaction of **53**, **55** and **47** [R28-R30].[a]

Entry	Ligand	**54** *ee* (%) (config.)	**56** *ee* (%) (config.)	**23** *ee* (%) (config.)
1	(*R*,*R*)-**L20a**	60 (1*R*)	74 (*S*)	48 (*R*)
2	(*R*,*R*,S_{phos},S_{phos})-**L20b**	84 (1*R*)	49 (*S*)	13 (*R*)
3	(*R*,*R*,R_{phos},R_{phos})-**L20c**	60 (1*R*)	54 (*S*)	~0
4	(*R*,*R*,R_{phos},S_{phos})-**L20d**	80 (1*R*)	77 (*S*)	19 (*R*)

[a] The conversions/yields are not stated.

Another series of ligands in which carbon-based stereogenic centres were combined with phosphorus-based stereogenic centres are pyrrolidine-based diastereoisomers **L21b-d** (Figure 27).[62] In common with the parent ligand **L21a** (pyrphos) two of the P-stereogenic variants are also C_2-symmetric (**L21b**/**c**). As also reported in the preceding ligand series (**L20d**), a third asymmetric diastereoisomer **L21d** was also synthesised. Following formation of the corresponding cationic rhodium(COD) complexes, these were applied to the hydrogenation of *Z*-α-acetamidocinnamic acid **10** in methanol. Unusually the enantioselectivity, and also in this case turnover frequency (TOF) values, were determined over a range of hydrogen pressures, and at both 25 °C and 50 °C. The results were reported graphically and are not tabulated here, but clear trends emerged. Under the range of hydrogen pressures investigated (up to 75 bar) **L21b** and **L21c** gave the highest and lowest TOF values respectively, with **L21a** and **L21d** resulting in similar intermediate levels of reactivity. At low hydrogen pressures **L21b** also resulted in the highest enantioselectivity,

and under all the conditions tested **L21c** gave the lowest enantioselectivity. At higher hydrogen pressures it was found that the enantioselectivity that resulted from the use of **L21b** and **L21d** (which gave similar values to **L21b**) decreased. In contrast, the *ee* values obtained from the use of **L21a** were found to be essentially independent of pressure, such that this ligand gave the highest values of *ee* at >25 bar (25 °C) and >35 bar (50 °C).

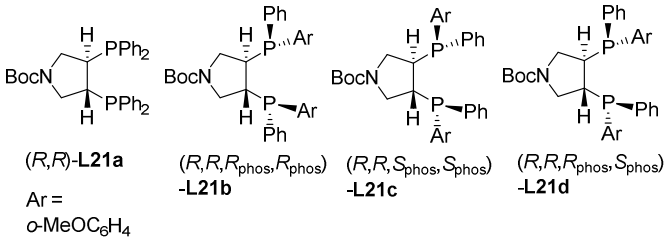


Figure 27. Ligands **L21a**-**d**.

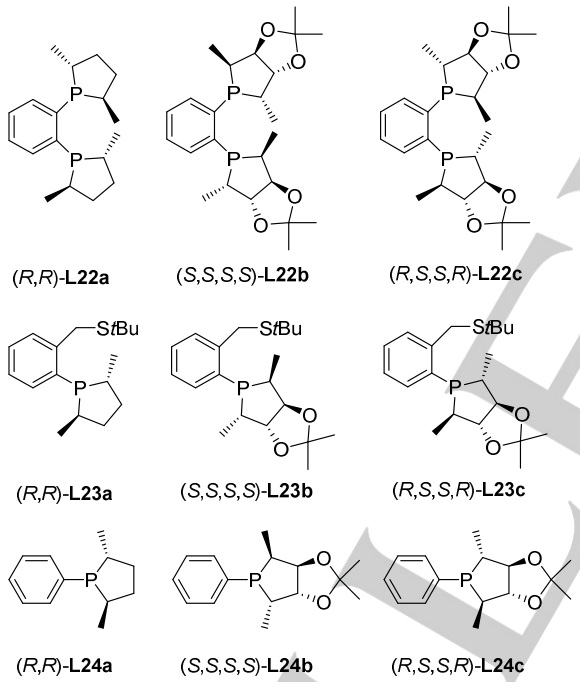


Figure 28. Ligands **L22a**-**c**, **L23a**-**c** and **L24a**-**c**.

Ligands **L19b**/**c** were both derived from D-mannitol, and a series of phospholane ligands **L22**-**L24** (Figure 28) have also been synthesised from this same starting material[55] and applied to palladium catalysed allylic alkylation (Scheme 20, Table 22).[58] The ligand series **L22** has as its parent Me-Duphos (**L22a**) which is a competent ligand for this reaction. Enantioselectivity was improved and slightly eroded with diastereoisomers **L22b** and **L22c** respectively (entries 4-6).[63] The related C_1-symmetric thiophosphine ligands **L23** were less selective, and both diastereoisomers resulted in higher enantioselectivity compared to the outcome with the parent ligand **L23a** (entries 7-9). Again the *S*,*S*,*S*,*S* configured ligand is the matched isomer. Finally monodentate ligand series **L24** gave the opposite sense of enantioselectivity compared to bidentate phospholanes **L22**/**L23**. The diastereoisomers **L24b**/**c** gave essentially the same outcome, with the stereogenic centres containing a phosphorus substituent (*i.e.* positions 2 and 5) adjacent to phosphorus dictating the configuration of the product. The configuration of positions 3 and 4 is not important. This is again similar to ligand series **L15** where the presence of an additional substituent, and not the resulting configuration, is the factor leading to higher enantioselectivity.

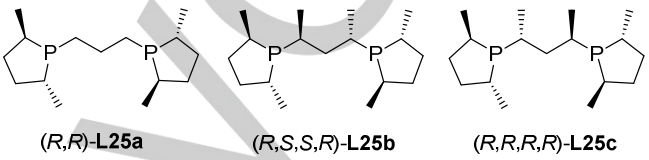
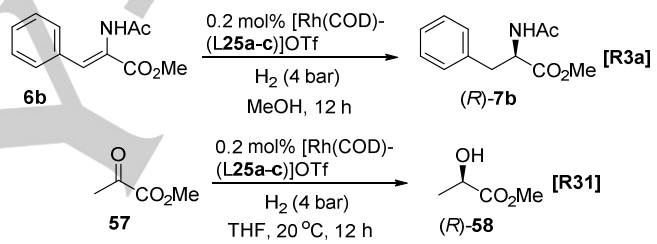


Figure 29. Ligands **L25a**-**c**.



Scheme 23. Rhodium catalysed hydrogenation of **6b** and **57** with ligands **L25**

Table 25. Comparative outcomes with ligand series **L25** for the rhodium catalysed hydrogenation of **6b** [R3a] and **57** [R31].[a]

Entry	Ligand	Product	*ee* (%)
1	(*R*,*R*)-**L25a**	(*R*)-**7b**	60
2	(*R*,*S*,*S*,*R*)-**L25b**	(*R*)-**7b**	82
3	(*R*,*R*,*R*,*R*)-**L25c**	(*R*)-**7b**	71
4	(*R*,*R*)-**L25a**	(*R*)-**58**	5
5	(*R*,*S*,*S*,*R*)-**L25b**	(*R*)-**58**	75
6	(*R*,*R*,*R*,*R*)-**L25c**	(*R*)-**58**	43

[a] All reactions went with >99% conversion.

Finally, bisphospholane **L25a** (Figure 29) containing a flexible three carbon linker was developed for the rhodium catalysed hydrogenation of carbonyl groups, but this ligand

resulted in only moderate enantioselection.[64] This led to the synthesis of diastereoisomers **L25b**/**c** in the hope that greater conformational control of the backbone unit would both retain the efficiency and improve the enantioselectivity of rhodium catalysed hydrogenation.[65] Initial screening of this ligand series for the reduction of α–dehydroamino acid derivative **6b** revealed that both diastereoisomers **L25b**/**c** resulted in an improvement in *ee*, with the product **7b** obtained using all three ligands having the same configuration (Scheme 23. Table 25, entries 1-3). The matched isomer **L25b** also resulted in the highest *ee* on extension to the reduction of α-ketoester **57**. Again all three ligands resulted in the generation of **58** with the same configuration (entries 4-6), but with this substrate the improvement in enantioselectivity on changing from **L25a** to **L25b** was more marked.

5. Discussion

Given the very extensive literature on metal-catalysed asymmetric reactions, no claim is made that this review covers all known examples that fulfill the criteria for inclusion. However, twenty-five ligand groups are discussed in the sections above, and these include a wide variety of structural types. Most ligands are bidentate, and in these cases the resulting chelated metal catalysts may reduce the conformational impact of an added element of chirality relative to that a non-cyclic counterpart. All of the ligands in a given group have been applied to a metal-catalysed asymmetric transformation under at least very similar reaction conditions. In a small number of cases no catalysis results are known for the parent ligand, or alternatively these can not be used due to the parent ligand displaying induced chirality.[66] In these instances the outcome from an otherwise very similar ligand are used for comparison. In all fifty-six examples are described which to address the changes in product enantioselectivity that results from chirality element addition to an existing enantiopure ligand.[67] A number of these examples are representative of a set of very similar outcomes with the same ligand and reaction.

To better address the results given above the data were reconfigured, where needed, such that the parent ligand in each case ($\mathbf{L_a}$ = **Lxa** where **x** is the ligand number) is that which gives rise to the *R* enantiomer of the product (see supporting information). The *ee* value resulting from the more enantioselective diastereoisomer ($\mathbf{L_{max}}$, typically **Lxb**) with the same configuration as $\mathbf{L_a}$ is then positive if the product is *R*, and negative if *S*. This was repeated in the same way for the less selective diastereoisomer ($\mathbf{L_{min}}$, typically **Lxc**). Given the non-linear relationship between *ee* and $\Delta\Delta G^{\ddagger}$ a clearer picture of the outcomes of chirality element addition results from a comparison of enantiomeric ratios,[68] and thus the fifty-six sets of results were used to determine the following (where *er* = enantiomeric ratio and, for example, *er*-$\mathbf{L_a}$ is the enantiomeric ratio that resulted from application of ligand $\mathbf{L_a}$).

a) ln(*er*-$\mathbf{L_a}$)
b) ln(*er*-$\mathbf{L_{max}}$/*er*-$\mathbf{L_a}$)
c) ln(*er*-$\mathbf{L_{min}}$/*er*-$\mathbf{L_a}$)

Equations 1 and 2 (Figure 2) require ln(*er*-$\mathbf{L_{max}}$/*er*-$\mathbf{L_a}$) to be positive and ln(*er*-$\mathbf{L_{min}}$/*er*-$\mathbf{L_a}$) to be negative, and in an ideal case where the contributions of $\Delta G_{12}^{\ddagger}$ and $\Delta G'_{12}{}^{\ddagger}$ are zero then ln(*er*-$\mathbf{L_{max}}$/*er*-$\mathbf{L_a}$) = -ln(*er*-$\mathbf{L_{min}}$/*er*-$\mathbf{L_a}$) [*i.e.* b) = -c)].[69] The outcomes a), b) and c) are plotted as bar graphs for each of the fifty-six ligand/reaction combinations (Figure 30) and the reactions are assigned to one of the following three catagories.[70]

(i) The *ee* value obtained with the parent ligand increased and decreased for the diastereoisomers resulting from chirality element addition (in thirty six examples – green in Figure 30). In all but two of these examples the pattern of outcomes a)-c) is as outlined in the paragraph above, *i.e.* the configuration of the product from the parent ligand is unchanged in the product resulting from the matched ligand diastereoisomer. In two cases [L6/R7 (R = *t*Bu) and L24/R7] the configuration inverts, and both are where the *ee* resulting from the parent ligand is relatively low such that the introduced element of chirality dominates the selectivity. All of these results are compatible with equations 1 and 2 where the addition and subtraction of the terms $\Delta\Delta G_1^{\ddagger}$ and $\Delta\Delta G_2^{\ddagger}$ primarily dictates the enantioselectivity of the reaction. The correlation between the values given by b) and –c) is low, a consequence of the terms $\Delta G_{12}^{\ddagger}$ and $\Delta G'_{12}{}^{\ddagger}$, assuming that all other things are equal.[71] However it is significant that the majority of the examples fit the matched/mismatched model, and this is especially the case for reactions employing planar chiral ferrocene ligands.[72] This may be a consequence of the partial rigidity of the chelate resulting from metal coordination in which four atoms (1,2-cyclopentadienyl carbons and respective substituents) have little conformational freedom. Then each chirality element can influence the environment about the metal relatively independently, and not be masked by significant conformational change. In addition, all of the ten examples of the most abundant reaction type [R7 – palladium catalysed allylic alkylation] are in category i). There is insufficient data to compare this observation with other reaction types (there being only three examples of the next most abundant), but there is at least the possibility of certain reaction types fitting well the matched/mismatched model due to catalyst structure and mechanistic invariance.

(ii) The *ee* value obtained with the parent ligand increased for both diastereoisomers resulting from chirality element addition, and the same product enantiomer is formed from all three ligands in a given set (in ten examples – blue in Figure 30).

(iii) The *ee* value obtained with the parent ligand decreased for both diastereoisomers resulting from chirality element addition, and the same product enantiomer is formed from all three ligands in a given set (in nine examples – red in Figure 30).

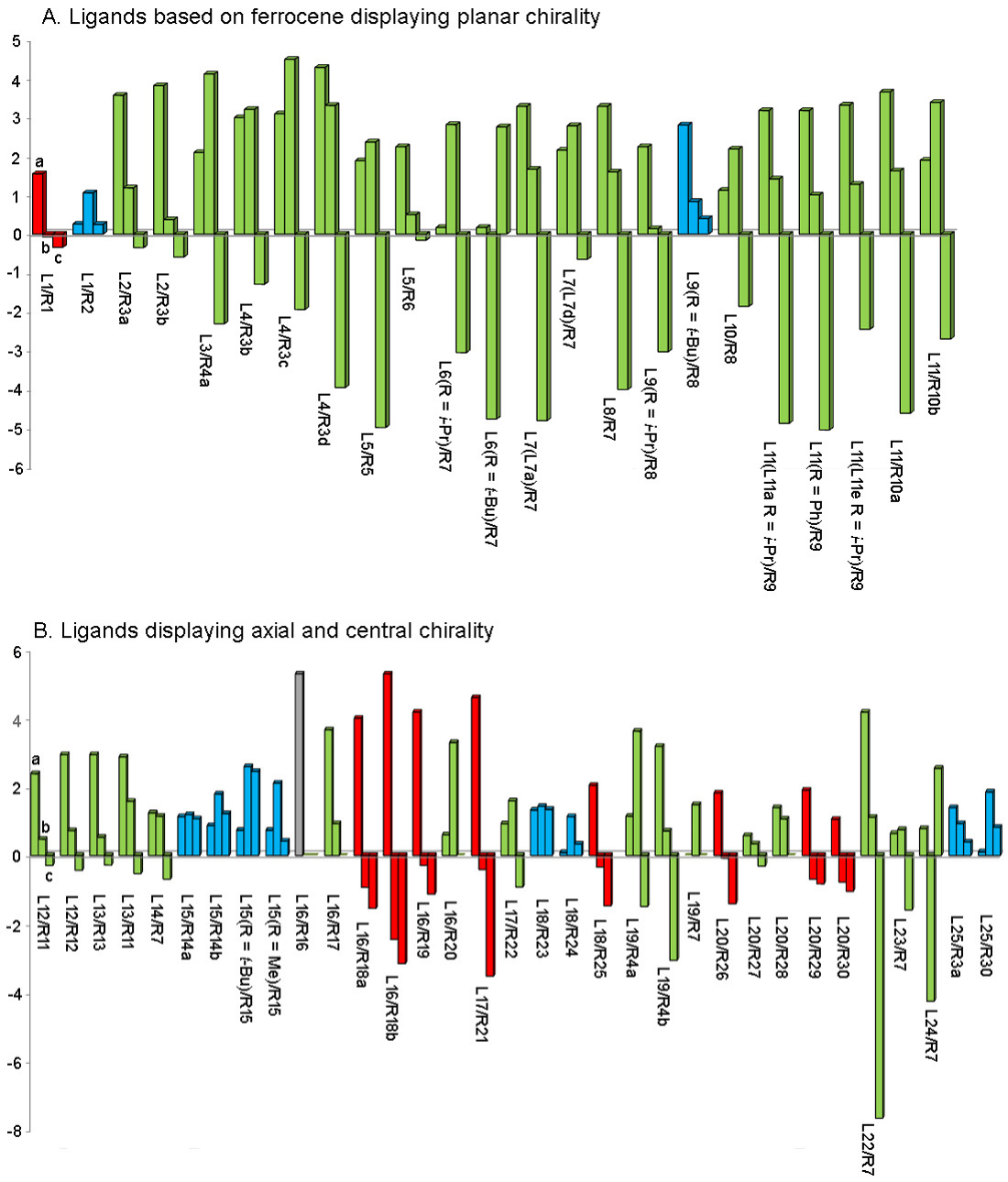


Figure 30. Ligand/reaction outcomes where for each set a) = ln(*er*-$\mathbf{L_a}$), b) = ln(*er*-$\mathbf{L_{max}}$/*er*-$\mathbf{L_a}$) and c) ln(*er*-$\mathbf{L_{min}}$/*er*-$\mathbf{L_a}$). Catagory i) = green, catagory ii) = blue, catagory iii) = red and unclassified = grey.

Four of the examples assigned to category (ii) (**L15**, Table 16) have already been discussed in terms of the added stereogenic centre acting as a stereochemical block, where both ligand diastereoisomers resulted in an increase in product *ee*. A similar argument could apply to the other examples in this category. Alternatively, the non-adherence to the model could be due to conformational changes being of greater significance, *e.g.* where the perturbation term $\Delta G'_{12}{}^{\ddagger}$ is greater than $\Delta\Delta G_2{}^{\ddagger}$ (equation 2). Either way such effects can similarly result in a reduction in product *ee* for both diastereoisomers resulting from chirality element addition, as observed for the nine examples in category (iii). For five of these examples one of the

diastereoisomers has an *ee* difference of ≤3% with respect to the parent ligand. It is of note that almost all examples in categories (ii) and (iii) use as ligands **L1**, **L15**, **L16** (**L17**), **L18**, **L20** and **L25**. Thus there may be specific features of these systems that result in non-ideal outcomes, for example, the rigidity/chelate size of complexes formed with of **L16**/**L17**, the monodentate nature of **L18** (and in catalysis hemilabile **L1**[73]), and the alkyl backbone of bisphosphines **L20** and **L25**.

Finally, taking all three categories (i)-(iii) as a whole, in four of every five cases chirality element addition gave an increase in product *ee* for one, and sometimes for both, of the resulting diastereoisomers. In only one of every fourteen cases does chirality element addition result in a significant (>3%) decrease in product *ee* for both resulting diastereoisomers.

6. Conclusion

Twenty-five ligand groups were identified for which a parent enantiopure ligand, and the two diastereoisomers resulting from chirality element addition, were applied to a metal-catalysed asymmetric transformation under identical or very similar conditions. For a catalyst formed from the combination of an enantiopure ligand and a metal complex, addition of a further element of chirality to the ligand will result in an increase in the enantioselectivity of the product of catalysis for one of the resulting ligand diastereoisomers, provided the following conditions are met. a) The new and existing elements of chirality influence largely independently the selectivity of the resulting catalyst, and that conformational changes resulting from the new element of chirality have relatively little influence on catalyst selectivity. b) That the transition state structures for which the free energy difference between determines the enantioselectivity of the reaction are the same in all cases, excepting the further element of chirality in the additional ligand diastereoisomers.

Of the fifty-six examples listed in this review the majority (~60%) gave rise to results that are compatible with these conditions. In particular, the results obtained from planar chiral ferrocene-based ligands fit this ideal scenario very well. As a consequence there is the possibility of applying chirality addition sequentially for *ee* optimisation in a given metal-catalysed reaction, and one example of this approach is identified from existing literature results.

Of the examples for which the results do not fit this ideal outcome there is a roughly equal split between both ligand diastereoisomers resulting in an increase in *ee*, and both ligand diastereoisomers resulting in a decrease in *ee*. Certain ligands give the majority of the examples in these categories, and with further exemplification it may be possible to better identify the types of ligand for which chirality element addition is and isn't suited. Taking as a whole the examples given in this review, chirality element addition resulted in an increase in *ee* for at least one of the diastereoisomers in about four out of five examples. This approach has the potential to be applied more widely in metal-catalysed asymmetric synthesis, and possibly in other areas of asymmetric catalysis.[74]

Acknowledgements

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Keywords: Asymmetric catalysis • Ligand design • Chelates • Matched and mismatched • Stereochemical cooperativity

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[67] This figure is from all of the tabulated results excepting that just one set of data from Table 20 is used (MeOH as solvent).
[68] For an ideal system for which the conformational terms $\Delta G_{12}^{\ddagger}$ and $\Delta G'_{12}{}^{\ddagger}$ do not contribute (*er*-$\mathbf{L_{max}}$)/(*er*-$\mathbf{L_a}$) = (*er*-$\mathbf{L_a}$/*er*-$\mathbf{L_{min}}$), and (*er*-$\mathbf{L_a}$) is equal to (*er*-$\mathbf{L_{max}}$) divided by the square route of (*er*-$\mathbf{L_{max}}$)/(*er*-$\mathbf{L_{min}}$).
[69] Values are expressed as natural logarithms partly for convenience, and also as the value of $\Delta\Delta G^{\ddagger}_{S\text{-}R}$ (kJ mol^{-1}) for the parent ligand is given by ln(*er*-**La**) x 8.314 x *T* (K)/1000 (similarly for *er*-$\mathbf{L_{max}}$ and *er*-$\mathbf{L_{min}}$).
[70] Not every example falls neatly into one of these categories. For the complete list of reactions and the basis of the assignments see the supporting information.
[71] A comparison of values b) and c) requires that for each reaction in a ligand set the enantiomers are formed *via* two diastereomeric transition states, and that these transition states are the same for a comparative set of ligands with respect to mechanism and metal ligation.
[72] The random probability of a reaction/ligand series giving 36 category (i) outcomes [vs. (ii) or (iii)] from 55 examples is 0.015, and giving 20 category (i) outcomes from from 23 examples (the ferrocene ligands) is 0.00024.
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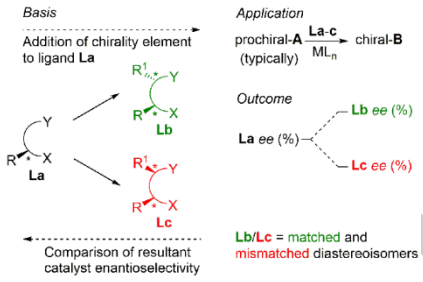

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