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SETTING P-DONOR LIGANDS INTO CONTEXT: AN APPLICATION OF THE LIGAND KNOWLEDGE BASE (LKB) APPROACH

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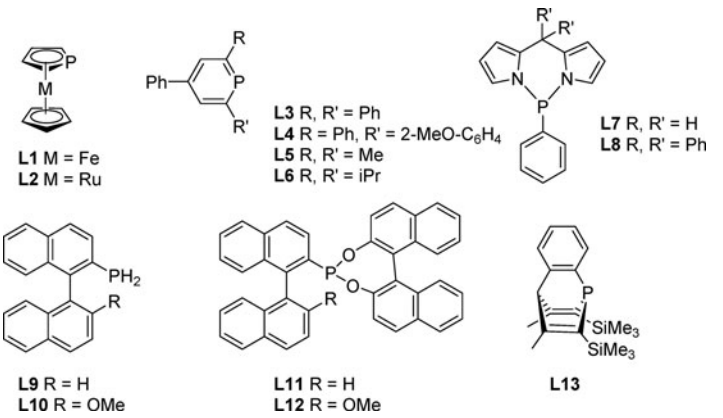
GRAPHICAL ABSTRACT



Abstract *The properties of 13 monodentate P-donor ligands not previously characterized in the Ligand Knowledge Base (LKB) approach have been determined computationally, allowing*

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their addition to the LKB-P map of ligand space.[1] Consideration of ligand positions and close neighbors in ligand space can help to establish a chemical context and hence guide their application to organometallic catalysis. Here we demonstrate this potential application of the LKB-P map and discuss known and likely applications of these ligands.

Keywords P-donor ligands; structure-property relationships; computational chemistry; organometallic chemistry; homogeneous catalysis

INTRODUCTION

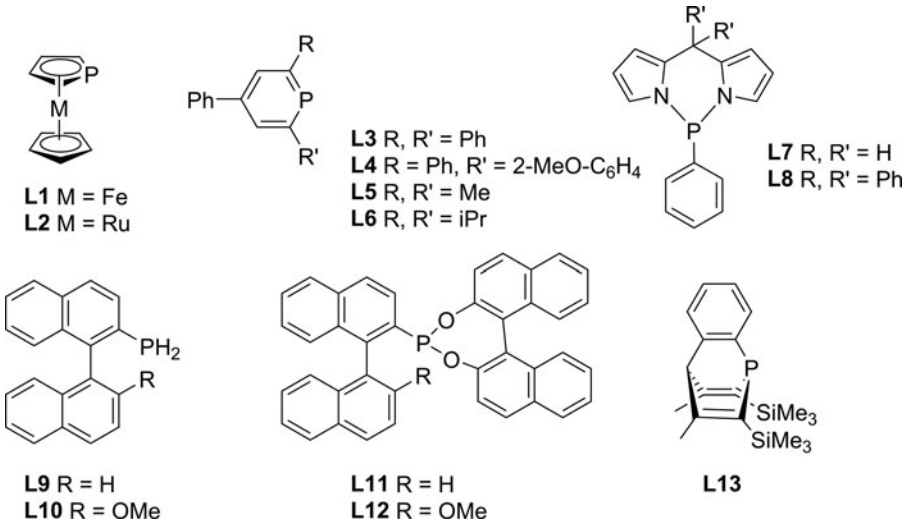
The development of novel catalytic routes in homogeneous organometallic chemistry is often closely linked to the discovery or design of novel ligands, which provide a convenient way of modifying and fine tuning the properties of catalytically active metal centres.[2] In this context, it can be helpful to have access to quantitative measures of ligand properties and such ligand parameters, capturing their steric and electronic properties, have a well-established tradition in this area.[3] With computational chemistry increasingly becoming an integral part of many experimental studies, computational ligand parameters have been developed, ranging from calculated versions of the Tolman steric and electronic parameters[4] to more multivariate approaches.[3,5]

The Ligand Knowledge Bases (LKBs) developed at the University of Bristol represent a large collection of such ligand parameters (the term descriptors will be used interchangeably here), capturing the properties of monodentate P-[1,6] and C-donor[7] as well as bidentate P,P- and P,N-donor[8] ligands in a number of coordination environments. Descriptors for more than 1000 ligands, calculated with standard density functional theory (DFT), have been published to date, with further data held in house. A range of possible applications for these ligand parameters can be envisaged, such as the interpretation of experimental data in the context of ligand effects, the design of experimental screening, the prediction of ligand effects on various measures of catalyst performance and other experimental data,[1,6a,9] as well as the analysis and contextualization of novel ligand designs by comparison with other ligands.[6b] The present contribution will focus on illustrating this last aspect and has arisen from presentations and discussions at the 20th International Conference on Phosphorus Chemistry (ICPC), held in Dublin, Ireland, from 28th June–2nd July 2014.

RESULTS AND DISCUSSION

The knowledge base for monodentate P-donor ligands, LKB-P, has been described extensively in previous work.[1,6,9] For convenience, the descriptors and ligands published to date have been included in the supporting information (Tables S1 and S2). In brief, each ligand is optimized with a standard DFT approach (see computational details below) in a number of different coordination environments, considering not just the free (pro-)ligand, but also its protonated form($[HL]^+$), the borane adduct (BH_3.L), three representative metal complexes ([ClAuL], $[Cl_3PdL]^-$ and $[(H_3P)_3PtL]$), and the interaction between the ligand and a ring of 8 helium atoms (He_8.L), positioned to simulate the steric hindrance encountered in an octahedral coordination environment. From these calculations, 28 parameters can be extracted which include the energies of frontier molecular orbitals of the free ligand, ligand proton affinities, adduct binding energies, structural changes of both ligand and adduct fragments on coordination, metal fragment charges and two measures of steric bulk (Table S1). While analysis of individual descriptors is possible, e.g., seeking

correlations with experimental data,[1,6a] a multivariate approach is often more powerful and can involve either regression models for the interpretation and prediction of suitable data (experimental or calculated) or the processing of data with statistical projection techniques to aid visualisation.[1,6a,9] Principal component analysis (PCA) can reduce the dimensionality of datasets if descriptors are correlated, giving fewer, orthogonal variables (principal components, PCs), which are linear combinations of the original descriptors designed to capture most of the variation in the dataset in as few dimensions as possible. This approach has been used with LKB-P descriptors to generate so-called maps of ligand space, with 353 ligands published so far.[1,6] The present work adds 13 new ligand structures (shown in Scheme 1). These include ligands where the P-donor is part of an (aromatic) ring (including phosphametallocenes **L1**, **L2**[10] and phosphinines **L3**-**L6**[11]), a group of ligands not previously considered, as well as primary phosphines **L9**, **L10,** phosphonites **L11**, **L12**,[12] and the phosphabarrellene **L13**.[13]



Scheme 1 Ligands added to LKB-P.

Figure 1 shows the map of ligand space resulting from PCA of the correlation matrix for the 28 ligand descriptors (Table S1 Supplemental Materials) calculated for 366 ligands, i.e., all previously published data and those for the ligands shown in Scheme 1. A larger version of this map, with all ligands identified, can be found in the supporting information (Figure S1 Supplemental Materials), along with descriptor loadings (Table S3), principal component scores for all ligands (Table S4) and the full descriptor set for **L1**-**L13** (Table S5).

Although PCA is not statistically robust[9] and could respond strongly to the addition of a new class of ligands, in the present case the map has changed little from previous versions,[1,6b] suggesting that ligand space has been mapped well and that the new group of ligands, where the P-donor is part of an sp^2-hybridised ring, are not extreme outliers, in line with their reported role in catalysis, which is similar to other P-donor ligands.[10–11,14] Most of the new ligands occur near the western equator of ligand space (in line with calling it a map, geographical directions will be used to discuss the spatial arrangement of ligands), while **L6**, **L10,** and **L13** are further removed from this main cluster.

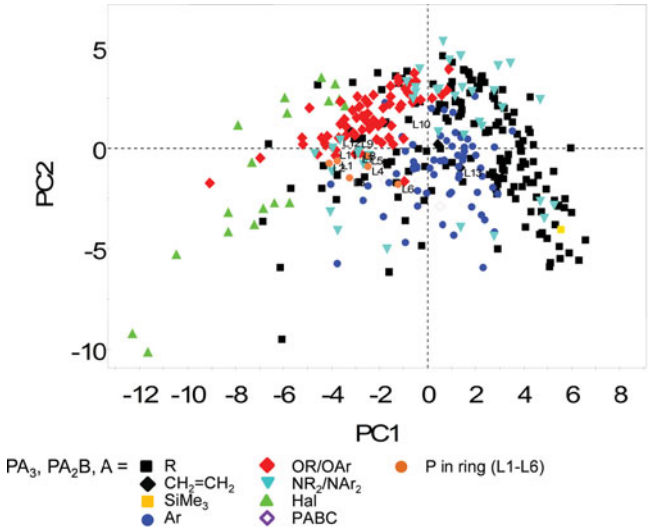


Figure 1 Ligand map generated by principal component analysis of 28 ligand parameters capturing the structures and energies of 366 P-donor ligands through DFT-calculated parameters, collected in LKB-P. The principal components are linear combinations of the original parameters derived to capture most of the variation in fewer uncorrelated parameters (62% in this case). Each symbol corresponds to a ligand, and shape and color are determined by substituents as shown in the legend. (See Figures 2 and 3 below for detailed maps.)

PCA can be used to optimally represent distances between data, so ligands that lie close in ligand space generally have more similar properties compared to those that lie further away. However, it is worth bearing in mind that ligand space has additional dimensions and that at least PC3 and perhaps also PC4 may need to be considered as well, as these capture a further 11% and 6% of the variation in the data set respectively (see supporting information for details (Table S4) and plots (Figure S2)). The discussion here will focus on the first two PCs only, although we note that PC3 at least might warrant further consideration, as it shows a clearer separation of the phosphametallocenes (**L1**, **L2**), phosphinines (**L3**-**L6**), and primary phosphines (**L9**, **L10**, near to PH_3 (**1**)) from other ligands (Figure S 2).

Figure 2 focuses on the area around **L1**-**L12** and identifies ligands lying nearby by their numbers (see supporting information Table S2 for details). The parent phosphametallocenes **L1** and **L2**[10,11e,11f,15] lie close to the MOP phosphonites (**L11**, **L12**) reported by Higham et al.,[12,16] and also reasonably close to the phosphinines[11,14,17] **L3**-**L5**, with the slightly bulkier and more electron-rich **L6** further removed. In addition, phosphametallocenes **L1**, **L2** and MOP-phosphonites **L11**, **L12** lie close to phosphite and phosphonite ligands such as $P(OPh_3)_3$, **229**, and related bridged structures **288**, **289** (red diamonds, see Scheme 2 for structures, Table S2 for ligand numbers) and pyrrolyl-substituted aminophosphines, such as $P(pyrr)_3$, **294**, and the related structures **305**, **307** (turquoise inverted triangles). Interestingly, the tethered *N*-pyrrolyl phosphines **L7** and **L8**, described by Papadouli and Pringle (*presentation at ICPC2012, Dublin)*, appear slightly further away from ligand **294**. They are, however, similar to the untethered $PPh(pyrr)_2$, **306** which has the same substitution pattern, as well as appearing near the bulky phosphites **237** and **239**. Ligands with P-N bonds have been reported in catalytic hydroformylation reactions[18] and are generally considered to have π-acceptor capacity comparable to phosphites. The primary phosphine

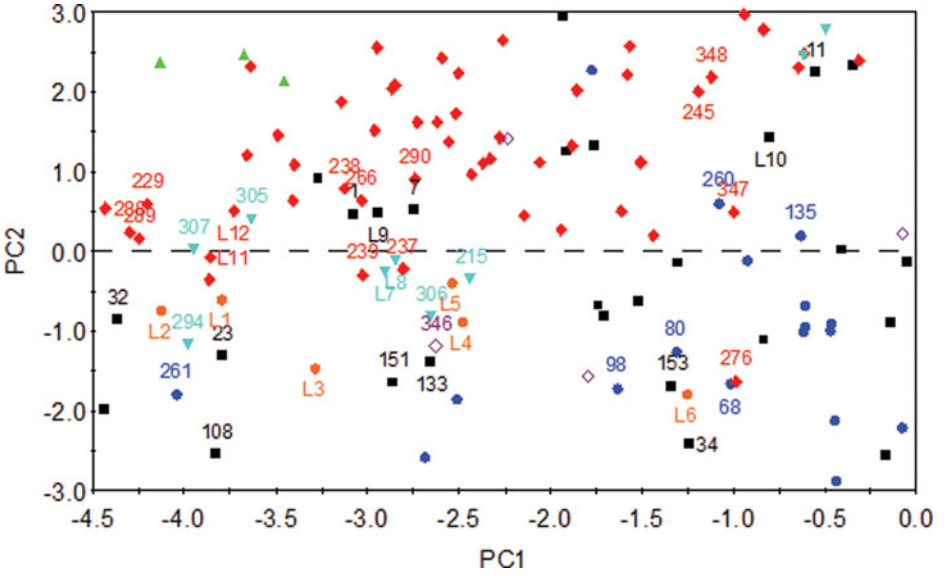


Figure 2 Ligand map zooming in on **L1**-**L12**. (See Table S2 for ligand numbers.)

L9 also appears in this area, lying near to PH_3 (**1**) and $P(CH_2CF_3)_3$ (**7**), while the OMe substituted version **L10** lies further away, perhaps due to a combination of conformational and electronic effects due to the presence of the heteroatom.

Late transition metal complexes of phosphite/phosphonite and pyrrolphosphine ligands can give rise to good catalysts for hydroformylation, hydrocyanation, hydrosilylation, and hydrogenation, and their proximity to these ligands suggests that **L1**, **L2**, **L7**-**L9**, **L11,**

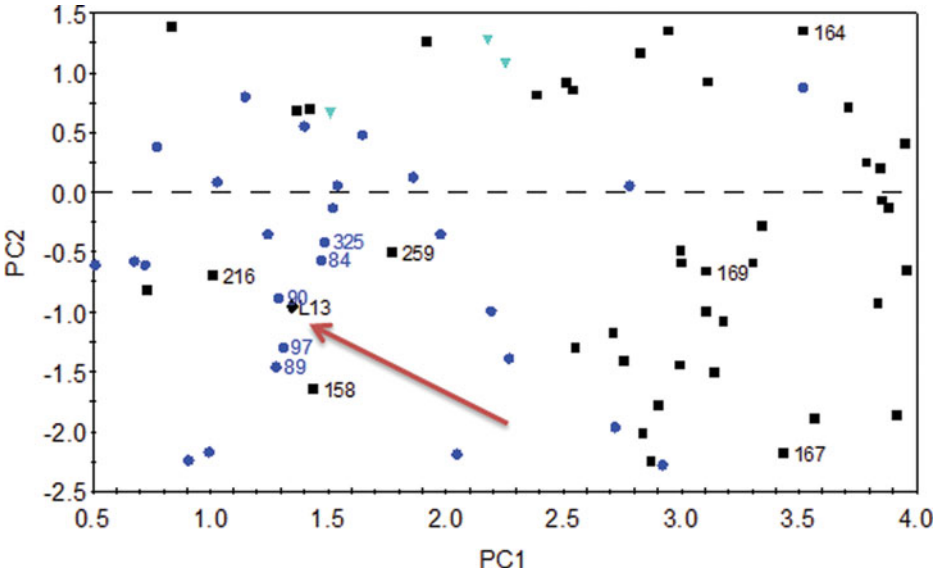
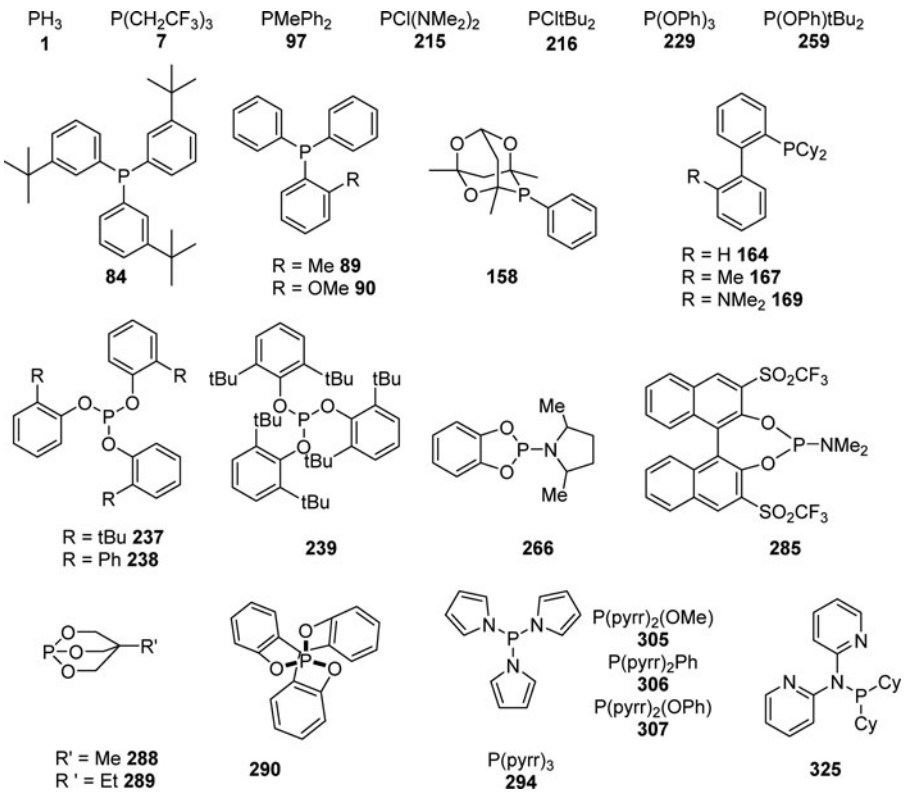


Figure 3 Ligand map zooming in on **L13** and showing a range of further ligands for context.



Scheme 2 Additional ligands discussed in the text and highlighted in Figures 2 and 3.

and **L12** could be useful in similar reactions. This has been confirmed experimentally for Rh-catalyzed enamide hydrogenations using ligands related to **L1** and **L2**, where phospharuthenocene ligands related to **L2** gave the better catalysts,[10d,15a] as well as for **L7** and **L8** (*results presented at ICPC2012, Dublin*), which showed promising *iso* selectivity in rhodium catalyzed hydroformylation, and **L11** and **L12**, which give active hydrosilylation catalysts.[12a] Some of the aryl-derived phosphinines **L3**-**L6** have also been tested in catalysis, here bulkier aryl-substituted phosphinines, such as 2,6-bis-(2,4-dimethylphenyl)-4-phenylphosphinine lead to improved activity in hydroformylation,[11f] as might be suggested by its proximity to ligands **237** and **239**.

The phosphabarrellene ligand **L13** lies further away from the main cluster (Figure 3) and related ligands have shown some activity in hydroformylation,[13b] but also in palladium-catalyzed Negishi and Suzuki cross-coupling reactions,[13a,13c] albeit requiring a different activation route (using $[Pd_2Cl_2(allyl)_2]$)) compared to ligands **164**, **167,** and **169** (which used $Pd(OAc)_2$ as the metal source), which were also screened. This ligand lies close to a number of relatively electron-rich aryl phosphines of medium size (**84**, **89**, **90**, **97**), as well as the cage phosphine (**158**) developed by Pringle et al.,[19] and it might be interesting to explore whether a different activation route could lead to cross-coupling activity for these other ligands as well; especially when bulky substrates are used, smaller, and perhaps slightly more electron-poor ligands may be of use for such reactions.

CONCLUSION

The Bristol Ligand Knowledge Base for monodentate P-donor ligands, LKB-P,[1,6] has been expanded by 13 new ligands and their proximity to other ligands on the resulting map of ligand space has been combined with available experimental data on their catalytic utility to illustrate how this map can help to provide a chemical context for less familiar and perhaps even exotic ligands. Where detailed ligand screening data is available, ensuring that the only variable is the ligand, more quantitative data modeling could be attempted,[1,9] but even this very basic approach to mapping structure-property relationships should be of use for the evaluation of novel ligand designs.[6b]

COMPUTATIONAL DETAILS

All calculations used the Jaguar package[20] and the standard Becke-Perdew (BP86)[21] density functional. The Jaguar triple-ζ form of the standard Los Alamos ECP basis set (LACV3P) was used on the transition metal atoms, employing the 6-31G* basis for all other atoms. "Loose" convergence (five times larger than default criteria) was used for all geometry optimizations. Test calculations using the more stringent default convergence criteria did not lead to significant changes in energies, bond lengths, or angles, but were much more time consuming. Calculations were performed on isolated molecules, and NBO atomic charges[22] were calculated. Vibrational frequencies were not computed, and so the energetic data do not include a correction for zero-point energy, although we would expect this to be quite small. In the absence of frequency calculations, stationary points have not been verified as minima. However, most ligands and complexes are large and optimization to transition states seems unlikely for these carefully built low-symmetry starting geometries. PCA was performed in SIMCA-P+.[23]

SUPPORTING INFORMATION

Ligand lists showing all structures and their numbering, tables of principal component scores for all ligands, principal component loadings, full descriptor data for **L1**-**L13**, ligand maps identifying all ligands, discussion of PC3 and accompanying plots.

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