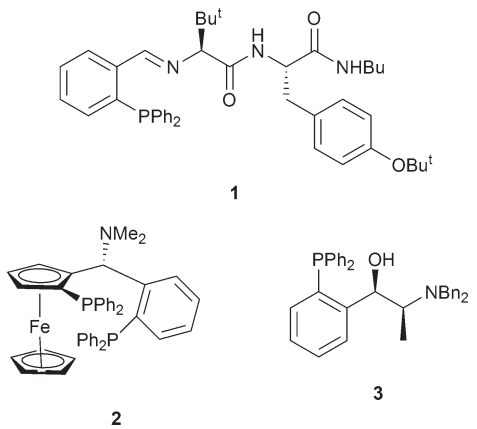
# Amino-sugar modular ligands—useful cores for the formation of asymmetric copper 1,4-addition catalysts†

**Antonella De Roma,[a] Francesco Ruffo[a] and Simon Woodward*[b]**

*Received (in Cambridge, UK) 30th July 2008, Accepted 22nd August 2008*
*First published as an Advance Article on the web 17th September 2008*
**DOI: 10.1039/b813137f**

**Modular phosphine ligands, synthesised rapidly from commercial *N*-acetylglucosamine, are very effective in copper(I)-catalysed 1,4-additions of $ZnR_2$ to linear aliphatic enones (87–95% ee).**

One key requirement in the efficient design of new catalytic asymmetric processes is ready access to a library of chiral ligands showing enough molecular diversity to allow the attainment of synthetically useful stereoselectivities (>90% ee) in initial screening. In the past 10 years significant attention has been turned towards the use of chiral ligands based on natural carbohydrates.[1] Large numbers of 'sugar-cores' have been developed (*e.g.* >30 types leading to *ca.* 200 ligands in ref. 1) that deliver diverse coordination architectures. Highly successful asymmetric hydrogenations (96–>99% ee),[2] allylations (up to 99% ee),[3] aldehyde methylations (up to 94% ee),[4] Heck reactions (up to 99% ee)[5] and other processes have resulted from the use of these ligands.[1] However, recent attempts to apply such ligands to asymmetric conjugate addition (ACA) reactions were not as successful.[6] As a number of the most successful ligands in highly enantioselective ACA reactions include potential nitrogen-based donor sets (**1–3**,[7] Scheme 1) we sought to explore the unprecedented use of amino-sugar[8] based ligands in such ACA transformations.[9]

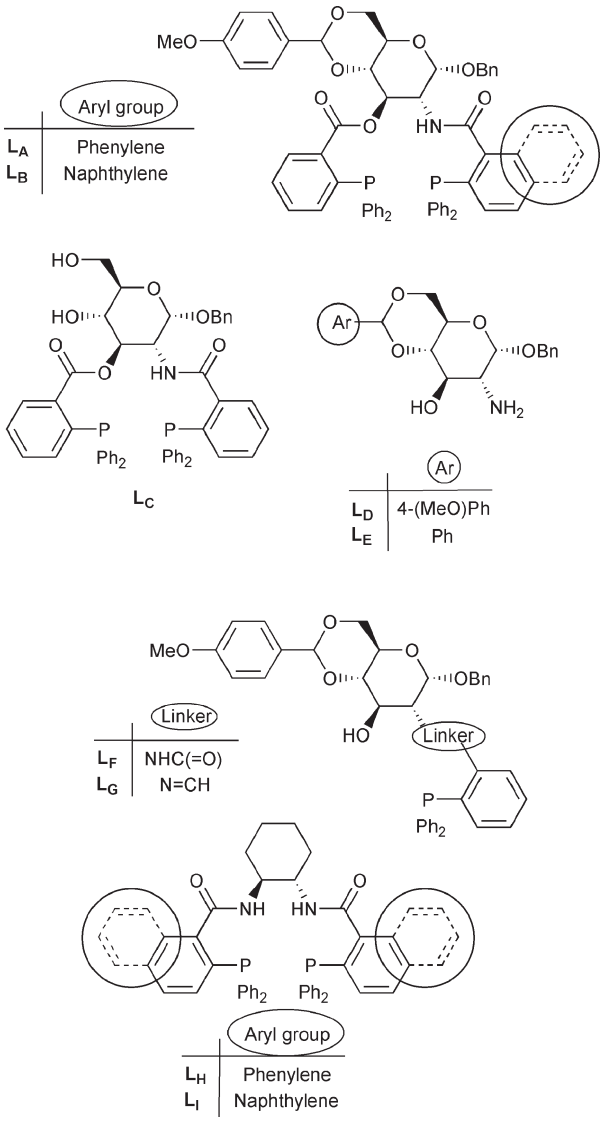



**Scheme 1**

[a] *Dipartimento di Chimica "Paolo Corradini", Università di Napoli "Federico II", Complesso Universitario di Monte S. Angelo, via Cintia, 80126 Napoli, Italy. E-mail: ruffo@unina.it; Fax: +39-081674090*
[b] *School of Chemistry, The University of Nottingham, Nottingham, UK NG7 2RD. E-mail: simon.woodward@nottingham.ac.uk; Fax: +44-(0)115-9513564; Tel: +44-(0)115-9513541*
† Electronic supplementary information (ESI) available: Full experimental, spectroscopic and chiral GC data for all compounds presented. See DOI: 10.1039/b813137f

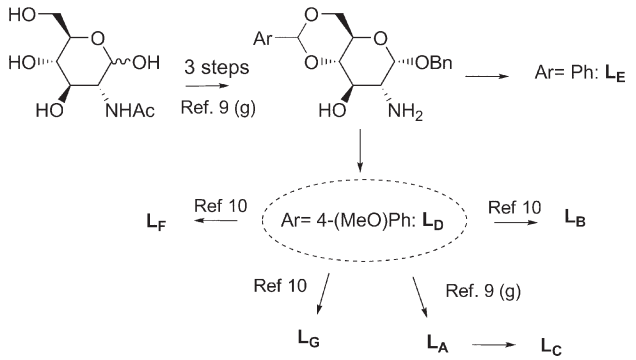
The amino-sugar family $\mathbf{L_{A–C,F,G}}$ was compared against the amino-sugar precursors $\mathbf{L_{D–E}}$ and the nearest commercial analogues of such architectures, the 'Trost ligands' $\mathbf{L_{H–I}}$ (Scheme 2).

Despite the success of systems **1–3** (which provide ee values of 80–98% for a range of enones[7]) there is still a need to identify easily obtained variable architectures: firstly, to circumvent the limitations of single enantiomeric series ligand sets (*e.g.* **1–3**); and secondly, to attain catalysts of increased activity through greater




**Scheme 2**



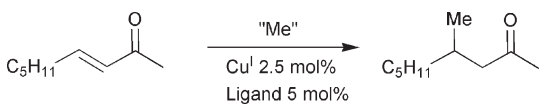

**Scheme 3**

ligand acceleration effects. The amino-sugar ligands of Scheme 2 are highly attractive as they are readily available in only a few simple, high yielding steps from very low cost *N*-acetyl-D-glucosamine ($\sim$0.5 Euro $g^{-1}$) (Scheme 3 and ESI†).‡

The library of Scheme 2 was screened in demanding additions of methyl nucleophiles to (*E*)-nonen-2-one (Table 1).§

No activity was found for 1,4-additions of $AlMe_3$; the behaviour of $\mathbf{L_A}$ and $\mathbf{L_G}$ is representative of all the ligands tried. The situation with $ZnMe_2$ was radically different. In toluene and the presence of the air-stable, non-hygroscopic $Cu^I$ precursor $Cu(OTf)_2$, the amino-sugar library conformed as expected delivering $>24:1$ stereoselectivities with ligands $\mathbf{L_A}$ and $\mathbf{L_G}$. The attainment of such selectivities in all alkyl substrates is rare.[7] The presence of the phosphorus donor ($\mathbf{L_{A,G}}$ *vs.* $\mathbf{L_{D–E}}$) was vital as was the inclusion of an *O*,*N*-linker set as opposed to *N*,*N* versions ($\mathbf{L_A}$ *vs.* the 'Trost' ligands $\mathbf{L_{H–I}}$). Previously, we have proposed that the presence of appropriately placed free hydroxide functions in bimetallic cuprate complexes can be beneficial.[11] Removal of the diphenylphosphinobenzoic ester fragment led to a highly significant reversal in the stereoselectivity: +95 to −61% ee ($\mathbf{L_A}$ *vs.* $\mathbf{L_F}$). However, removal of the 4,6-acetal unit led to a loss in selectivity ($\mathbf{L_A}$ *vs.* $\mathbf{L_C}$).

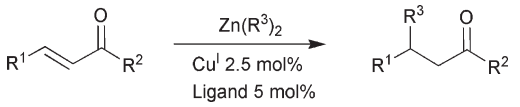
**Table 1** Representative additions of methyl nucleophiles to (*E*)-nonen-2-one[a]




| Ligand | Me source | Conditions | Yield (%) | Ee (%)[b] |
|---|---|---|---|---|
| $\mathbf{L_A}$ | $AlMe_3$ | THF, 22 °C, 12 h | <5 | — |
| $\mathbf{L_G}$ | $AlMe_3$ | THF, 22 °C, 12 h | <5 | — |
| $\mathbf{L_A}$ | $ZnMe_2$ | Toluene, 22 °C, 12 h | 70 | 95 (*R*) |
| $\mathbf{L_B}$ | $ZnMe_2$ | Toluene, 22 °C, 12 h | 10 | 17 (*S*) |
| $\mathbf{L_C}$ | $ZnMe_2$ | Toluene, 22 °C, 12 h | 25 | 53 (*S*) |
| $\mathbf{L_D}$ | $ZnMe_2$ | Toluene, 22 °C, 12 h | <5 | — |
| $\mathbf{L_E}$ | $ZnMe_2$ | Toluene, 22 °C, 12 h | <5 | — |
| $\mathbf{L_F}$ | $ZnMe_2$ | Toluene, 22 °C, 12 h | 78 | 61 (*S*) |
| $\mathbf{L_G}$ | $ZnMe_2$ | Toluene, 22 °C, 12 h | 75 | 92 (*R*) |
| $\mathbf{L_H}$ | $ZnMe_2$ | Toluene, 22 °C, 12 h | <5 | — |
| $\mathbf{L_I}$ | $ZnMe_2$ | Toluene, 22 °C, 12 h | <5 | — |

[a] $ZnMe_2$ (0.24 mmol, 2.0 equiv.), (*E*)-nonen-2-one (0.12 mmol), ligand (7.5 μmol, 5 mol%) and $Cu(OTf)_2$ (3.0 μmol, 5 mol%) in toluene (2 mL). Yields by GC against calibrated internal standard (undecane). All conversions >99%. [b] Stereochemical correlation by direct comparison with an authentic sample of (*R*)-product (ref. 10).

**Table 2** Representative additions of methyl nucleophiles to enones[a]



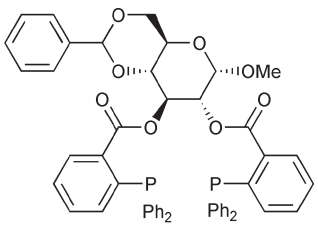

| Run | Ligand | $R^1$ | $R^2$ | $R^3$ | Yield (%) | Ee (%)[b] |
|---|---|---|---|---|---|---|
| 1 | $\mathbf{L_A}$ | $C_5H_{11}$ | Me | Me | 70 | 95 (*R*) |
| 2 | $\mathbf{L_G}$ | $C_5H_{11}$ | Me | Me | 75 | 92 (*R*) |
| 3 | $\mathbf{L_A}$ | $C_5H_{11}$ | Me | Et | 80 | 91 (*R*) |
| 4 | $\mathbf{L_G}$ | $C_5H_{11}$ | Me | Et | 80 | 87 (*R*) |
| 5 | $\mathbf{L_A}$ | $C_6H_{13}$ | Me | Me | 57 | 91 (*R*) |
| 6 | $\mathbf{L_G}$ | $C_6H_{13}$ | Me | Me | 52 | 90 (*R*) |
| 7 | $\mathbf{L_A}$ | $C_6H_{13}$ | Me | Et | 95 | 93 (*R*) |
| 8 | $\mathbf{L_G}$ | $C_6H_{13}$ | Me | Et | 99 | 90 (*R*) |
| 9 | $\mathbf{L_A}$ | $^i$Pr | Me | Me | 47 | 89 (*R*) |
| 10 | $\mathbf{L_G}$ | $^i$Pr | Me | Me | 33 | 94 (*R*) |
| 11 | $\mathbf{L_A}$ | $^i$Pr | Me | Et | 79 | 93 (*R*) |
| 12 | $\mathbf{L_G}$ | $^i$Pr | Me | Et | 66 | 88 (*R*) |
| 13 | $\mathbf{L_G}$ | Me | Et | Et | 78 | 91 (*S*) |

[a] $ZnMe_2$ (0.24 mmol, 2.0 equiv.), enone (0.12 mmol), ligand (7.5 μmol, 5 mol%) and $Cu(OTf)_2$ (3.0 μmol, 5 mol%) in toluene (2 mL). Yields by GC against calibrated internal standard (undecane). All conversions >99% except for runs 6 (84%) and 10 (82%). [b] Stereochemical correlation by direct comparison with authentic samples of (*R*)-product (see ESI).

The generality of the best ligand architectures was further tested against a range of demanding substrates (Table 2).

It was noted that the most successful ligands $\mathbf{L_A}$ and $\mathbf{L_G}$ were effective for the addition of both $ZnMe_2$ and $ZnEt_2$ to a class of enones possessing only aliphatic substituents with minimal steric profiles and that the reactions were technically very simple to carry out—only air stable $Cu(OTf)_2$ is required. In general, for all substrates ligand $\mathbf{L_A}$ gave better yields (up to 95%, run 7) and enantioselectivities (up to 95%, run 1). An exception was $\mathbf{L_G}$ which gave a superior result in $ZnMe_2$ addition to the branched enone $R^1 = {}^i$Pr (run 10). The selectivity was also affected by the presence of a bigger substituent $R^2$. In fact when both $R^2$ and $R^3$ have increased steric profile only ligand $\mathbf{L_G}$ gives good results (run 13; with $\mathbf{L_A}$ we obtained only 67% ee).

An attempt was made to further simplify the ligand structure to $\mathbf{L_J}$ which can be easily prepared in only two steps from the commercial source methyl-α-D-glucoside ($\sim$0.2 Euro $g^{-1}$).[12] High enantioselectivity (up to 94% ee) was attained but in the present protocol the yields were unsatisfactory ($\sim$30%). At present the ligands $\mathbf{L_{A,G}}$ are optimal but further studies with $\mathbf{L_J}$ will be targeted in the future due to its low cost and ready availability.




$\mathbf{L_J}$

In conclusion, we have described for the first time use of amino-sugar phosphine ligands in asymmetric 1,4-additions of diorganozinc species to acyclic enones. Excellent enantioselectivities (up to 95% ee) and yields were obtained with ligands $\mathbf{L_A}$ and $\mathbf{L_G}$ for these demanding substrates.

SW thanks the EPSRC for support through grant EP/F033478/1. ADeR and FR thank MIUR for financial support (Prin 2007). SW acknowledges valuable input from the COST D40 Innovative Catalysis Programme.

## Notes and references

‡ For details of ligand synthesis and spectroscopic data see the ESI.†
§ *General procedure for asymmetric conjugate additions (ACA) to enones*: a solution of the copper-catalyst precursor $Cu(OTf)_2$ (1 mol%, 0.003 mmol) and the corresponding ligand (2.5 equiv., 0.0075 mmol) in 2 mL of dry toluene was stirred for 30 min at room temperature. The alkylating organometallic reagent $ZnR_2$ (2 equiv. 2 M toluene or 1 M hexane solutions, 0.24 mmol) was added dropwise and then the substrate (0.12 mmol). After 12 h the reaction was quenched with 2 M HCl (2 mL). Undecane or dodecane (10 μL) was then added as an internal standard and the organic layer filtered twice through a plug of silica. Yields and enantiomeric excesses were measured by GC using an octakis(6-*O*-methyl-2,3-di-*O*-pentyl)-γ-CD column (method of ref. 10*c*).

1 Reviews: (*a*) M. Diéguez, C. Claver and O. Pàmies, *Eur. J. Org. Chem*., 2007, 4621; (*b*) M. Diéguez, O. Pàmies and C. Claver, *Chem. Rev*., 2004, **104**, 3189; (*c*) M. Diéguez, O. Pàmies, A. Ruiz, Y. Diaz, S. Castillon and C. Claver, *Coord. Chem. Rev*., 2004, **248**, 2165.
2 Selected examples: (*a*) M. T. Reetz and T. Neugebauer, *Angew. Chem., Int. Ed*., 1999, **38**, 179; (*b*) M. Diéguez, A. Ruiz and C. Claver, *J. Org. Chem*., 2002, **67**, 3796; (*c*) H. Huang, X. Liu, H. Chen and Z. Zheng, *Tetrahedron: Asymmetry*, 2005, **16**, 693; (*d*) M. Diéguez, J. Mazuela, O. Pàmies, J. J. Verendel and P. G. Andersson, *J. Am. Chem. Soc*., 2008, **130**, 7208.
3 M. Diéguez, O. Pàmies and C. Claver, *Adv. Synth. Catal*., 2005, **347**, 1257.
4 Y. Mata, M. Diéguez, O. Pàmies and S. Woodward, *J. Org. Chem*., 2006, **71**, 8159.
5 Y. Mata, O. Pàmies and M. Diéguez, *Chem.–Eur. J*., 2007, **13**, 3296.
6 (*a*) Y. Meta, M. Diéguez, O. Pàmies and S. Woodward, *J. Organomet. Chem*., 2007, **692**, 4315; (*b*) Y. Mata, M. Diéguez, O. Pàmies and S. Woodward, *Inorg. Chim. Acta*, 2008, **361**, 1381.
7 Reviews: (*a*) A. Alexakis, J. E. Bäckvall, N. Krause, O. Pámies and M. Diéguez, *Chem. Rev*., 2008, **108**, 2796; (*b*) S. R. Harutyunyan, T. den Hartog, K. Geurts, A. J. Minnaard and B. L. Feringa, *Chem. Rev*., 2008, **108**, 2824. Specific cases: (*c*) H. Mizutani, S. J. Degrado and A. H. Hoveyda, *J. Am. Chem. Soc*., 2002, **124**, 779; (*d*) A. Hajra, N. Yoshikai and E. Nakamura, *Org. Lett*., 2006, **8**, 4153; (*e*) F. López, S. R. Harutyunyan, A. J. Minnaard and B. L. Feringa, *J. Am. Chem. Soc*., 2004, **126**, 12784.
8 For an excellent introduction to amino-sugar chemistry see: *Comprehensive Glycoscience*, ed. J. P. Kamerling, G. J. Boons, Y. C. Lee, A. Suzuki, N. Taniguchi and A. G. J. Voragen, Elsevier, Amsterdam, 2006, vol. 1, ch. 1.01, pp. 1–37, ch. 1.13, pp. 490–540.
9 Use of amino-sugar ligands in other areas has been reported. (*a*) Allylic substitution: K. Glegola, E. Framery, C. Goux-Henry, K. M. Pietrusiewicz and D. Sinou, *Tetrahedron*, 2007, **63**, 7133; (*b*) S. A. Johannesen, K. Glegola, D. Sinou, E. Framery and T. Skrydstrup, *Tetrahedron Lett*., 2007, **48**, 3569, and references therein; (*c*) Suzuki reactions: R. Kolodziuk, A. Penciu, M. Tollabi, E. Framery, C. Goux-Henry, A. Iourtchenko and D. Sinou, *J. Organomet. Chem*., 2003, **687**, 384; (*d*) hydrovinylation reaction: H. Park and T. V. RajanBabu, *J. Am. Chem. Soc*., 2002, **124**, 737; (*e*) oxidation: R. Del Litto, G. Roviello and F. Ruffo, *Catal. Fine Chem. Synth. 2002–2007*, 2007, **5**, 293, and references therein; (*f*) M. E. Cucciolito, R. Del Litto, G. Roviello and F. Ruffo, *J. Mol. Catal. A: Chem*., 2005, **236**, 176; (*g*) V. Benessere, A. De Roma and F. Ruffo, *ChemSusChem*, 2008, **1**, 425.
10 (*a*) H. Mizutani, S. J. Degrado and A. H. Hoveyda, *J. Am. Chem. Soc*., 2002, **124**, 779; (*b*) S. M. W. Bennett, S. M. Brown, A. Cunningham, M. R. Dennis, J. P. Muxworthy, M. A. Oakley and S. Woodward, *Tetrahedron*, 2000, **56**, 2847; (*c*) P. K. Fraser and S. Woodward, *Chem.–Eur. J*., 2003, **9**, 776; (*d*) C. Börner, M. R. Dennis, E. Sinn and S. Woodward, *Eur. J. Org. Chem*., 2001, 2435; (*e*) A. Alexakis, C. Benhaim, M. Humam and S. Rosset, *J. Am. Chem. Soc*., 2002, **124**, 5262; (*f*) A. Alexakis, J. Vastra and P. Mangeney, *Tetrahedron Lett*., 1997, **38**, 7745; (*g*) X. Hu, H. Chen and X. Zhang, *Angew. Chem., Int. Ed*., 1999, **38**, 3518; (*h*) S. M. W. Bennett, S. M. Brown, J. P. Muxworthy and S. Woodward, *Tetrahedron Lett*., 1999, **40**, 1767; (*i*) H. Ahlbrecht, R. Schmidt and U. Beyer, *Eur. J. Org. Chem*., 1998, **7**, 1371.
11 S. Woodward, *Synlett*, 2007, 1490.
12 R. Del Litto, A. De Roma and F. Ruffo, *Inorg. Chem. Commun*., 2007, **10**, 618.