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New tagged *naplephos* ligands for asymmetric allylic substitutions under traditional and unconventional conditions

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ABSTRACT

This paper demonstrates the versatility of the class of chiral ligands *naplephos*, which has been further refined by preparing new 'tagged' versions for selective use in polar media (e.g., ionic liquids). These modified types, along with the best performing original varieties, have been examined in two Pd-catalysed asymmetric processes involving C–C and C–N bond formation. High ees have been achieved in traditional solvents, while the experiments performed in ionic liquids confirm the difficulty of predicting the outcome of a reaction in these media and the general decrease in the catalytic performance.

1. Introduction

Homogeneous enantioselective catalysis is a fundamental technology for the production of fine chemicals.[1] Within this field, innovative metal catalysts can be rationally prepared by selecting building blocks for the ligands from the chiral pool. A first benefit of this approach is the wide choice of natural molecules, which allows selecting multi-functional building blocks with the same accurate three-dimensional motifs of the outstanding 'privileged' chiral ligands.[2] A further advantage is the possibility of creating rich libraries of modular ligands, which present precise differences in the stereochemistry of coordination, in the backbone of the ligand or in both.

In addition, the multi-functional natural scaffold provides additional sites for tagging[3] the ligand and defining the physical properties of the catalyst according to the conditions to be used.

Finally, the same multi-functional structure offers hemilabile coordination sites, which can recognise or attract a substrate, thus making the catalyst more active and/or selective.[4] Within this framework, we recently prepared the class of ligands *naplephos* (Fig. 1).[5,6]

The structure of this library, which shows glucose as the natural building block, has been optimised for combining synthetic viability and high performance in catalysis.

More precisely, in position 2 there is a rigid diphenylphosphinoamide arm, essential coordination motif of Trost's privileged ligands based on *trans*-cyclohexanediamine.[7] Position 1 shows a α-benzyl (R′=CH_2Ph), of immediate and selective introduction. Positions 4 and 6, so far protected with a benzylidene ring, are potentially useful for phase-tagging the ligands and, hence, for defining the physical properties of the catalyst. Position 3 is instead useful for introducing tailored steric hindrance next to the metal centre.

Within previous studies, the *naplephos* structure has already been successfully adapted to three different enantioselective

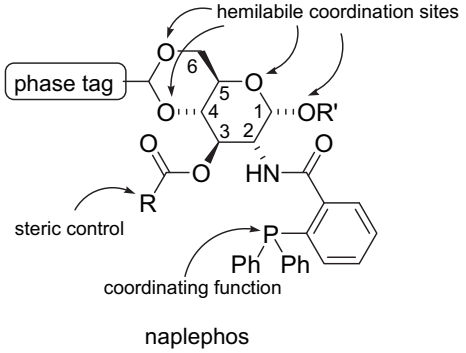

Fig. 1. General formula of *naplephos* ligands.

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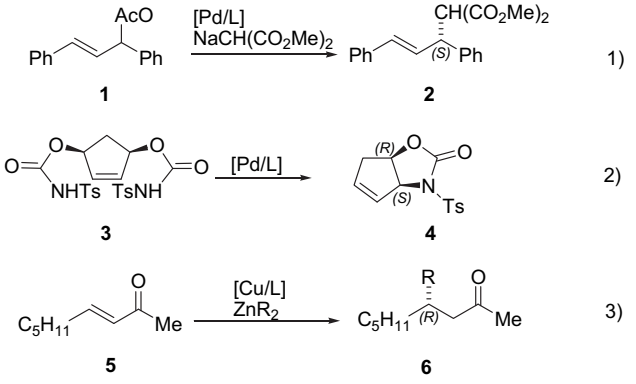
processes (Scheme 1), carried out in traditional conditions, thus giving proof of its versatility.



Scheme 1. Pd-catalysed desymmetrization of *meso*-diols (a), Cu-catalysed addition of dialkylzinc to enones (b), allylic alkylation of (*rac*)-(*E*)-1,3-diphenyl-2-propenyl acetate with dimethylmalonate.

When R is an alkyl group of suitable steric hindrance (i.e., *naplephos-h*, Fig. 2), the ligands can be used in the asymmetric allylic alkylation of (*rac*)-(*E*)-1,3-diphenylpropenyl acetate (**1**) with sodium malonate catalysed by Pd (ee 96%).[5] Instead, if R is a diphenylphosphinoester function (i.e., *naplephos-a*, Fig. 2), the ligands are active in the desymmetrization of cyclic diols (**3**) catalysed by Pd (ee 98%)[8] and in the addition of diethylzinc to enones (**5**) promoted by Cu (ee 95%).[4]

Aiming to demonstrate the versatility of the *naplephos* structure, we have further refined the ligands by preparing new 'tagged' versions (Fig. 3) for selective use in ionic liquids. These modified types, along with the best performing original varieties, have been examined in reactions 1 and 2 of Scheme 1 under traditional and unconventional conditions.

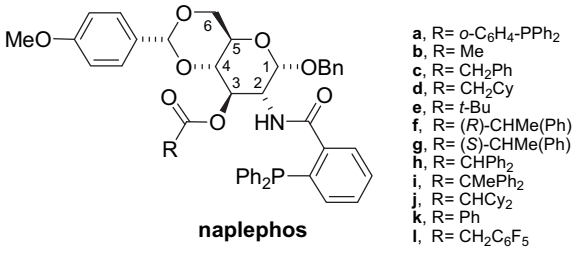


Fig. 2. The library of ligands *naplephos*.

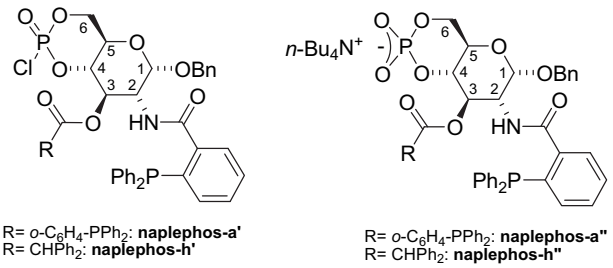


Fig. 3. Structures of *naplephos-a*′, *naplephos-a*″, *naplephos-h*′ and *naplephos-h*″.

2. Results and discussion

2.1. Synthesis of *naplephos-a*′, *naplephos-a*″, *naplephos-h*′ and *naplephos-h*″

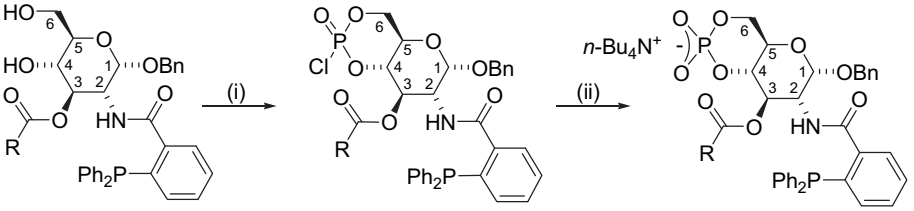
Ionic liquids are among the most promising green solvents.[9] Although their use does not require specific tagging of the catalysts, on several occasions[10] their affinity for the ionic liquid has been shown to improve with the polarity of the ligands. This also inhibits leaching of the catalyst in the organic product phase and increases the possibility of further catalyst re-cycles.

This approach has been pursued during this work, by providing selected *naplephos* ligands of appropriate tags (Fig. 3), whose choice has been dictated by at least three important considerations. First, the tag must be polar or ionic, for securing solubility in the ionic solvent. Then, its structure must preserve the conformational rigidity of the glucose chair, as the benzylidene ring is able to do. Furthermore, the synthesis must be straightforward and easy to carry out.

We devised an approach, which combines these benefits by introducing a 4,6-phosphate moiety within the sugar ring, as depicted in Scheme 2.

By reacting the 4,6-deprotected precursors **7** and **8** with $POCl_3$ in dry dichloromethane, the corresponding 4,6-oxychlorophosphate compounds *naplephos-a*′ and *naplephos-h*′ were isolated in high yield. Subsequent controlled hydrolysis of the P–Cl bond in a water/dioxane mixture afforded the ionic products *naplephos-a*″ and *naplephos-h*″ as their tetra-*n*-butylammonium salts. The choice of this hydrophobic cation was dictated by the aim of facilitating the synthetic work-up, which involves separation of the ligand from a water phase.

The ligands were characterised through elemental analysis and NMR spectroscopy. As anticipated, the 4,6-phosphate ring assumes a chair conformation,[11] which is clearly revealed by the coupling constants within the sugar protons.



(i) $POCl_3$, Et_3N, dichloromethane, 298 K; (ii) *n*-Bu_4NOH, water/dioxane, 298 K

Scheme 2. Synthesis of *naplephos-a*′, *naplephos-a*″, *naplephos-h*′ and *naplephos-h*″.