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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

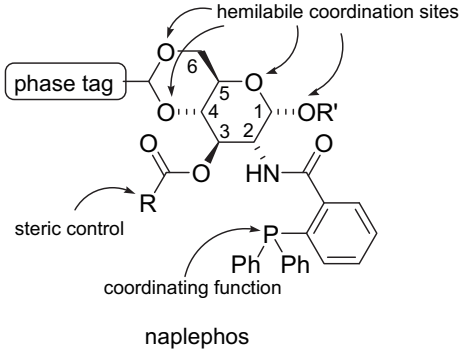

Fig. 1. General formula of *naplephos* ligands.

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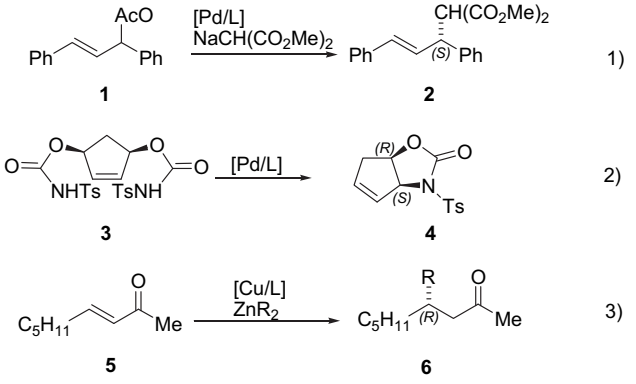
processes (Scheme 1), carried out in traditional conditions, thus giving proof of its versatility.



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.

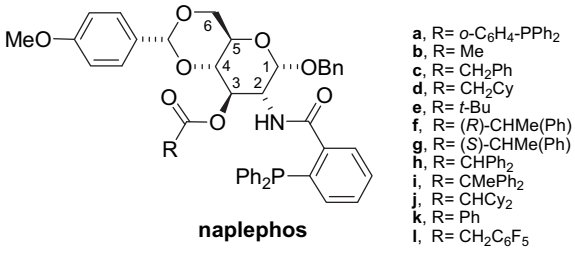


Fig. 2. The library of ligands *naplephos*.

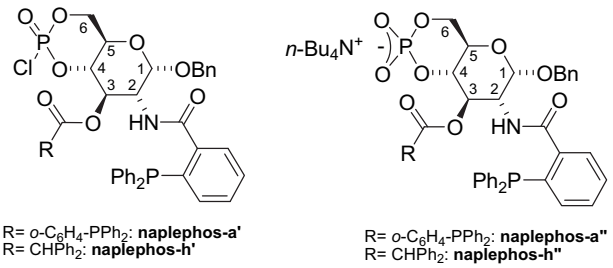


Fig. 3. Structures of *naplephos-a*′, *naplephos-a*″, *naplephos-h*′ and *naplephos-h*″.

2. Results and discussion

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

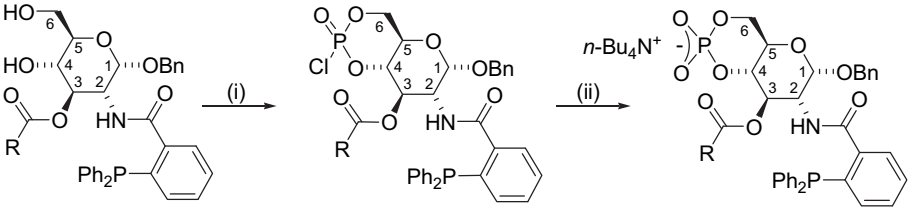
Ionic liquids are among the most promising green solvents.[9] Although their use does not require specific tagging of the catalysts, on several occasions[10] their affinity for the ionic liquid has been shown to improve with the polarity of the ligands. This also inhibits leaching of the catalyst in 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*″.

In *naplephos-a′* and *naplephos-h′* the phosphorous atom of the phosphate ring is stereogenic, and two diastereomers can be in principle observed in solution. Notably, even though not completely unexpectedly,[12] the NMR spectra reveal that both ligands exist as a unique diastereomer.

In the ^{31}P NMR spectra the signal typical of a monophosphate diester group appeared in the range [−2.5, −3.5] ppm. In the case of *naplephos-a″* its location was achieved by analysis of ^{31}P–^{1}H HSQC spectrum (Fig. S1 of Supplementary data). The ^{31}P–^{1}H HSQC showed three groups of cross peaks, two at ^{31}P NMR values of −7.07 and −5.15 ppm correlated with proton signals in the aromatic region and were attributed to the phenylphosphine groups. The third phosphate group at −2.49 ppm was linked at O-4 and O-6 of the substituted α-GlcN, as testified by the cross peak between this ^{31}P signal at −2.49 ppm and H-4 and H6$_{eq/ax}$ resonating, respectively, at 4.51 ppm and 3.92/4.28 ppm. Furthermore, correlations of the phosphodiester group with H5 and H3 were also visible. The low-field shifts of H4 and H6 were a further confirmation of the location of the cyclic phosphate.

As predicted, both neutral and cationic phosphate ligands display high solubility in the ionic liquid [BMIM]BF$_4$, as well as in common organic solvents (THF, dichloromethane, chloroform or toluene).

2.2. Asymmetric allylic alkylation of (*rac*)-(*E*)-1,3-diphenylpropenyl acetate

As mentioned in the Introduction section, *naplephos* ligands have already been investigated in the asymmetric allylic alkylation of (*rac*)-(*E*)-1,3-diphenylpropenyl acetate with dimethylmalonate.[5] In a recent paper,[5] we described how both the steric hindrance in 3 and the ligand/Pd ratio were decisive for the enantioselectivity of the reaction. In fact, *naplephos-h* produced the (*S*)-product in ees up to 96% by increasing the ligand/Pd ratio up to 4:1 with dry THF as solvent, and by using Na(CHCO$_2$Me)$_2$ as the nucleophile (Table 1).

Although in these conditions the reaction is fast and selective, we were strongly motivated to assess the performance of the ligands in other conditions, aiming to (i) use lower and more convenient ligand/Pd ratios, (ii) reduce the impact of the process, (iii) save precious chemicals, (iv) confirm the versatility of the ligands, (v) recycle the metal catalyst. The first conditions can be in principle satisfied by using dichloromethane as solvent, since the reactions can be performed in milder conditions by generating the nucleophile with BSA.

As for the catalyst recycle, a proven alternative is the use of an unconventional solvent, such as an inexpensive ionic liquid, capable of selectively dissolving the metal catalyst.

On this basis, the allylic alkylation of (*rac*)-(*E*)-1,3-diphenylpropenyl acetate with dimethylmalonate was first performed in dry dichloromethane by setting the *naplephos*/Pd ratio to 1:1, and by generating the nucleophile in the presence of BSA and catalytic lithium acetate.

A comparison of the results (Table 1) with those obtained in THF discloses two important trends. First, analogous steric effects hold true in the two solvents, in that the higher ee is achieved with the newly described *naplephos-h′* ligand (97% ee), while more or less crowded ligands produce a less enantioriched product.

Furthermore, the effect of the ligand/Pd ratio is reversed. When ligand/Pd ratios higher than 1:1 were used in dichloromethane, both conversion and enantioselectivity decreased. This effect is reproducible, although its origin is not yet clearly explained.[13]

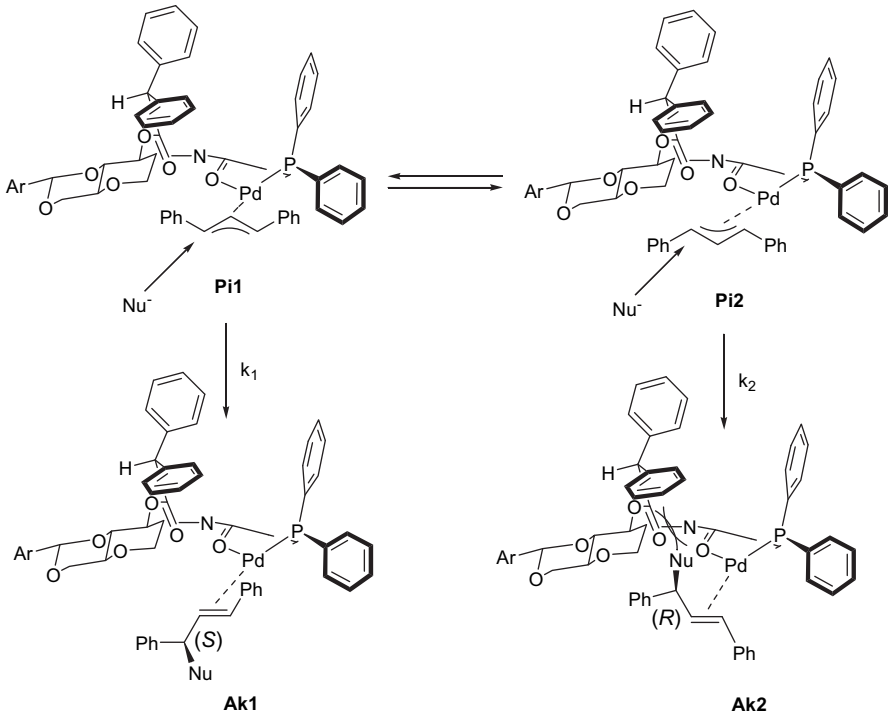
The steric effect can be reasonably elucidated on the grounds of both literature results[14] and molecular models. It is likely[5,13,15] that the ligands coordinate Pd through the phosphorous atom and the amido carbonyl oxygen in position 2, and, hence, the expected oxidative addition of the acetate affords the two diastereomeric π-allyl intermediates **Pi1** and **Pi2** (as shown for *naplephos-h* in Scheme 3).

On the grounds of the acknowledged mechanism,[14] nucleophilic attack of malonate takes place preferentially at the allyl carbon termini located trans to P, with formation of the corresponding alkene products **Ak1** and **Ak2**. Enantioselectivity ensues from the diverse rates of nucleophilic attack. By assuming that the geometry of the transition state of the attack is close to that of **Ak1** and **Ak2**, it is reasonable that $k_1 > k_2$, because **Ak2** is selectively hindered by the ester substituent in position 3. Thus, a bulky R group (i.e., R=CHPh$_2$) helps the enantioselectivity, although undue hindrance (e.g., R=CHCy$_2$ of *naplephos-j*) reduces the catalyst's performance,

Table 1
Asymmetric allylic alkylation of (*rac*)-(*E*)-1,3-diphenyl-2-propenyl acetate with *naplephos* ligands

no.	Ligand	Cone angle[a] (°) (Charton parameter)[a]	Solvent and conditions	Conversion[c] (%)	Time (h)	ee(*S*)[b] %	Refs.
1	*Naplephos-c*	106 (0.70)	THF[c]	99	5	85	5
2	*Naplephos-c*	106 (0.70)	CH_2Cl_2[d]	99	18	88	This work
3	*Naplephos-f*	121 (1.18)	THF[c]	99	2	91	5
4	*Naplephos-f*	121 (1.18)	CH_2Cl_2[d]	50	18	95	This work
5	*Naplephos-g*	121 (1.18)	THF[c]	99	2	86	5
6	*Naplephos-g*	121 (1.18)	CH_2Cl_2[d]	40	18	90	This work
7	*Naplephos-h*	126 (1.25)	THF[c]	99	2	91	5
8	*Naplephos-h*	126 (1.25)	CH_2Cl_2[d]	99	18	96	This work
9	*Naplephos-h′*	126 (1.25)	CH_2Cl_2[d]	99	18	97	This work
10	*Naplephos-h″*	126 (1.25)	CH_2Cl_2[d]	—	18	—	This work
11	*naplephos-h′*	126 (1.25)	$BMIMBF_4$[e]	99	18	0	This work
12	*Naplephos-h″*	126 (1.25)	$BMIMBF_4$[e]	30	18	67	This work
13	*naplephos-h″*	126 (1.25)	1° recycle	30	18	55	This work
14	*Naplephos-i*	136	THF[c]	99	18	80	5
15	*Naplephos-i*	136	CH_2Cl_2[d]	99	18	96	This work
16	*Naplephos-j*	144	THF[c]	50	18	80	5
17	*Naplephos-j*	144	CH_2Cl_2[d]	99	18	76	This work

[a] Relative to the R substituent in the carbonyl α position. Respectively taken from Refs. 19 and 20.
[b] Evaluated by NMR spectroscopy of the crude reaction mixture.
[c] Reaction conditions: rt, THF, 0.50 mmol of substrate, 1.5 mmol of dimethylmalonate, 1.5 mmol of NaH, 0.010 mmol of [Pd(μ-Cl)(μ^3-C$_3$H$_5$)]$_2$, 0.040 mmol of *naplephos*.
[d] Reaction conditions: rt, dichloromethane, 0.50 mmol of substrate, 1.5 mmol of dimethylmalonate, 1.5 mmol of BSA, 0.010 mmol of [Pd(μ-Cl)(μ^3-C$_3$H$_5$)]$_2$, LiOAc, 0.020 mmol of *naplephos*.
[e] Reaction conditions: rt, [BMIM]BF$_4$, 0.50 mmol of substrate, 2.5 mmol of dimethylmalonate, 2.5 mmol of BSA, 0.010 mmol of [Pd(μ-Cl)(μ^3-C$_3$H$_5$)]$_2$, LiOAc, 0.020 mmol of *naplephos*.



Scheme 3. Possible intermediates in the allylic alkylation of (*rac*)-(*E*)-1,3-diphenyl-2-propenyl acetate with dimethylmalonate by using 1 equiv of *naplephos* ligands.

plausibly because it hampers the carbonyl coordination and the steric control moves away from the catalytic centre.

It is interesting to note that the 4,6-oxychlorophosphate *naplephos-h′* induced the highest enantioselectivity (97% ee, entry 9 of Table 1), close to the *untagged* version *naplephos-h* (96% ee, entry 8). This demonstrates that the presence of the phase-tag has no effect on the stereochemistry of the reaction.

Moreover, in dichloromethane *naplephos-h* gave a better performance compared to THF (96 vs 91% ee, entry 8 vs entry 7), thus achieving the target of its use in the more convenient 1:1 Pd/ligand ratio.

Instead, lack of activity was evidenced by using *naplephos-h″*, which *only* shows a negative charge in its backbone with respect to its parent *naplephos-h″*. This failure is plausibly due to the bulky counterion *n*-Bu_4N^+, which in dichloromethane is expected to form a steady ionic couple with the charged complex.

On the other hand, this ligand, as well its parent *naplephos-h′*, could be both used in RTIL due to their high solubility in the ionic medium. It should be noted that very few examples of asymmetric allylic alkylation in ionic liquids have been reported so far,[16–18] and in all cases a marked or even dramatic reduction of both conversion and enantioselectivity was observed.

According to our assumptions, the presence of the polar phase tags resulted in prompt dissolution of both *naplephos-h′* and *naplephos-h″* (and of the corresponding Pd complexes) in [BMIM]BF_4 where the reactions were performed by adding the substrate and the nucleophile to a solution of the catalyst at 298 K. After 18 h the organic product was extracted with diethyl ether and analysed. The catalyst phase was possibly re-cycled for further runs (Table 1).

Naplephos-h″ produced an acceptable ee, 67% of (*S*)-product, in moderate yield (30%), that is, with a certain drop of performance with respect to the traditional condition (entry 12 vs 9). The first recycle gave a reproducible behaviour, although accompanied by a reduction of ee (55%, entry 13).

Remarkably, *naplephos-h′*, which was the most effective ligand in traditional conditions, only afforded a racemic product, even though in complete conversion (entry 11).

2.3. Asymmetric desymmetrization of *meso*-cyclopenten-2-ene-1,4-diol

Ligand *naplephos-a″* was instead investigated in the asymmetric cyclization reaction that leads to the formation of **4** (Scheme 1).

As mentioned in the Introduction section the untagged version *naplephos-a* was already successfully tested under traditional conditions,[8] which allowed to isolate the product in ee up to 98%. On that occasion we described also the only example so far known in RTIL for this reaction, which involved the use of **8** as polar ligand, namely the 4,6-deprotected precursor of *naplephos-a*. Disappointingly, in the ionic solvent [BMIM]BF_4 the ee dropped to 55%.[8]

Even on the basis of literature reports, we attributed[8] this significant reduction to two main factors: (i) the ionic nature of the solvent, which can play a detrimental effect on the enantioselectivity (on the basis of the acknowledged mechanism for this reaction) and (ii) the lack of sufficient rigidity in the sugar chair of **8**, due to the absence of the 4,6-benzylidene fragment.

For this second reason, we were very interested to assess the effect of the cyclic phosphate tag, which combines the due polarity to the desired rigidity. Quite surprisingly, by using *naplephos-a″* the ee of the reaction was nearly the same, and the product (*S*,*S*)-**4** was again isolated in ee of 57%. This result, although not fully appreciated, has the merit of providing clear evidence on the relative importance of the two effects mentioned above. In particular, it can be interpreted by assuming that the ionic nature of the solvent plays the dominant role in determining the enantioselectivity of the reaction.

3. Conclusion

This paper demonstrates the versatility of the *naplephos* structure, which has been adapted to asymmetric catalytic processes involving C–C and C–N bond formation, via Pd promoted allylic substitution. The multi-functional site offered by the sugar scaffold has been used to provide the ligands of a polar and ionic tag, thus making the corresponding catalysts readily soluble in RTIL. In the

ionic solvent the results corroborate the pioneering studies obtained so far for this type of reaction, confirming that the difficulty of predicting the outcome of a reaction is accompanied by a general lowering of the catalytic activity.

4. Experimental

4.1. General considerations

NMR spectra were recorded in $CDCl_3$ ($CHCl_3$ δ 7.26 and $^{13}CDCl_3$ δ 77, as internal standards) with a 200 and 300 MHz (Varian Model Gemini), a 400 MHz (Bruker DRX-400) and a 600 MHz (Bruker 600 DRX equipped with a cryo probe) spectrometers. ^{31}P NMR experiments were carried out using aqueous 85% phosphoric acid as external reference (δ 0). The following abbreviations were used for describing NMR multiplicities: s, singlet; d, doublet; dd, double doublet; t, triplet; dt, double triplet; m, multiplet; app, apparent. Specific optical rotatory powers [α] were measured with a Perkin–Elmer Polarimeter (model 141) at 298 K and 589 nm in chloroform (c=1.0 g/100 mL). *Naplephos-a,-c,-f,-g,-h,-i,-j*[5] and **7**[8] were prepared according to literature methods. THF was distilled from $LiAlH_4$, dichloromethane from CaH_2.

4.2. Preparation of 8

A mixture (10 mL) of TFA/water (1:1 v/v) was added to a solution of *naplephos-h* (0.74 g, 0.85 mmol) in dichloromethane (10 mL). The resulting biphasic system was stirred vigorously for 30 min at rt. After dilution with 10 mL of water and 10 mL of dichloromethane, sodium carbonate (about 4.6 g) was added slowly up to the end of the effervescence. The organic phase was extracted with water (3×10 mL), dried with anhydrous sodium sulfate and concentrated (1 mL) under vacuum. The white solid product was precipitated by adding petroleum ether, washed with petroleum ether and dried under vacuum (0.54 g, 85%). Detailed presentation of physical data for **8**: [Found: C, 73.64; H, 5.55; N, 1.88. $C_{46}H_{42}NO_7P$ requires C, 73.49; H, 5.63; N, 1.86]; [α] −4.23 (c 1.0, $CHCl_3$); δ_H 7.4–6.9 (m, 29H), 6.26 (d, 1H, $^3J_{NH-H2}$=9.6 Hz, N*H*), 5.29 (t, 1H, $^3J_{H3-H2}$=$^3J_{H3-H4}$=8.8 Hz, H3), 5.11 (s, 1H, C*H*Ph$_2$), 4.84 (d, 1H, $^3J_{H1-H2}$=3.2 Hz, H1), 4.63 (d, 1H, $^2J_{gem}$=3.2 Hz, C*H*HPh), 4.42 (d, 1H, CH*H*Ph), 4.38 (dt, 1H, H2), 3.9–3.5 (m, 4H, H4, H5, H6$_{eq}$, H6$_{ax}$); δ_C 183.1, 177.6, 150–135 (aromatics), 106.4, 83.9, 80.8, 79.2, 78.2, 71.0, 66.1, 61.1; δ_P −8.81.

4.3. General procedure for the preparation of the 4,6-oxychlorophosphate ligands (*naplephos-a′,-h′*)

The appropriate precursor (7 or 8) (0.72 mmol) was dissolved in dry dichloromethane (2.5 mL) under stirring at rt. Triethylamine (240 μL, 1.73 mmol) was added, and then phosphorus oxychloride (80 μL, 0.86 mmol). After 1 h, the solution was diluted with 10 mL of dichloromethane, and was extracted with water (3×10 mL). The organic phase was dried with anhydrous sodium sulfate, and the solvent was evaporated under vacuum affording the analytically pure product as a white powder (naplephos-a′: 0.60 g, 90%; naplephos-h′: 0.51 g, 85%). Detailed presentation of physical data for naplephos-a′: [Found: C, 66.49; H, 4.71; N, 1.48. C51H43ClNO8P3 requires C, 66.13; H, 4.68; N, 1.51]; [α] +14.9 (c 1.0, CHCl3); νmax (Nujol): 3428 (NH amide), 1744 (C•O ester), 1663 (C=O amide) cm^{-1}; δ_H 8.10 (m, 1H), 7.5–6.9 (m, 32H), 6.43 (d, 1H, $^3J_{NH-H2}$=9.60 Hz, NH), 5.62 (t, 1H, $^3J_{H3-H2}$=$^3J_{H3-H4}$=9.96 Hz, H3), 4.95 (d, 1H, $^3J_{H1-H2}$=3.44 Hz, H1), 4.51 (s, 2H, CH_2Ph), 4.80 (dt, 1H, H2), 4.34 (t, 1H, $^3J_{H4-H5}$=9.6 Hz, H4), 4.23–4.00 (m, 3H, H5, H6$_{eq}$, H6$_{ax}$); δ_C 168.7, 166.2, 145–125 (aromatics), 98.2, 79.0, 71.9, 69.6, 62.5, 52.7; δ_P −2.35 (d), −5.15, −8.64. Detailed presentation of physical data for *naplephos-h′*: [Found: C, 66.78; H, 4.70; N, 1.75. $C_{46}H_{40}ClNO_8P_2$ requires C, 66.39; H, 4.84; N, 1.68]; [α] −38.7 (c 1.0, CHCl3); νmax (Nujol): 3462 (NH amide), 1740 (C=O ester), 1663 (C=O amide) cm^{-1}; δ_H 7.4–6.9 (29H), 6.27 (d, 1H, $^3J_{NH-H2}$=9.6 Hz, NH), 5.53 (t, 1H, $^3J_{H3-H2}$=$^3J_{H3-H4}$=10.0 Hz, H3), 5.10 (s, 1H, C*H*Ph$_2$), 4.95 (d, 1H, $^3J_{H1-H2}$=3.6 Hz, H1), 4.65(d, 1H, $^2J_{gem}$=3.6 Hz, C*H*HPh), 4.58 (d, 1H, CH*H*Ph), 4.47 (dt, 1H, H2), 4.3–4.1 (m, 4H, H4, H5, H6$_{eq}$, H6$_{ax}$); δ_C 172.89, 168.62, 140–125 (aromatics), 98.25, 79.26, 71.85, 69.94, 69.74, 62.66, 57.17, 52.24; δ_P −2.56 (d), −8.90.

4.4. General procedure for the preparation of the tetra-*n*-butylammonium salts of the phosphate ligands (naplephos-*a″*,-*h″*)

The appropriate 4,6-oxychlorophosphate ligand (*naplephos-a′* or *naplephos-h′*) (0.40 mmol) was dissolved in dioxane (3 mL) under stirring at rt. A 40% (w/w) solution in water of tetra-*n*-butylammonium hydroxide was added (0.52 g, 0.80 mmol), and after 1 h the solution was diluted with 10 mL of water and 10 mL of dichloromethane. The organic phase was extracted with water (5×10 mL) and then dried with anhydrous sodium sulfate. The solvent was evaporated under vacuum affording the pure product as a white powder (*naplephos-a″*: 0.40 g, 88%; *naplephos-h″*: 0.36 g, 86%). Detailed presentation of physical data for *naplephos-a″*: [Found: C, 69.82; H, 6.74; N, 2.35. $C_{67}H_{79}N_2O_9P_3$ requires C, 70.02; H, 6.93; N, 2.44]; [α] +1.54 (c 1.0, $CHCl_3$); ν_{max} (Nujol): 3462 (NH amide), 1712 (C=O ester), 1662 (C=O amide) cm^{-1}; δ_H 8.25 (m, 1H), 7.51 (m, 1H), 7.49 (m, 2H), 7.4–7.1 (m, 27H), 6.98 (m, 2H), 6.42 (d, 1H, $^3J_{NH-H2}$=9.2 Hz, N*H*), 5.45 (t, 1H, $^3J_{H3-H2}$=$^3J_{H3-H4}$=10.0 Hz, H3), 4.88 (d, 1H, $^3J_{H1-H2}$=3.60 Hz, H1), 4.58 (d, 1H, $^2J_{gem}$=11.6 Hz, C*H*HPh), 4.50 (t, 1H, $^3J_{H4-H5}$=9.6 Hz, H4), 4.42 (dt, 1H, H2), 4.40 (d, 1H, CH*H*Ph), 4.26 (t, 1H, $^3J_{H6ax-H5}$=$^3J_{H6ax-H6eq}$=10.0 Hz, H6$_{ax}$) 4.00–3.77 (m, 2H, H5, H6$_{eq}$); δ_C 171.0, 168.9, 141–129 (aromatics), 77.9, 72.8, 68.7, 67.8, 61.3, 55.5, 32.1, 26.5, 22.1, 16.1; δ_P −3.11, −5.81, −8.41. Detailed presentation of physical data for *naplephos-h″*: [Found: C, 70.01; H, 7.39; N, 2.72. $C_{62}H_{76}N_2O_9P_2$ requires C, 70.57; H, 7.26; N, 2.65]; [α] +0.33 (c 1.0, $CHCl_3$); ν_{max} (Nujol): 3432 (NH amide), 1732 (C=O ester), 1656 (C=O amide) cm^{-1}; δ_H 7.82 (m, 1H), 7.66 (m, 2H), 7.6–7.0 (m, 26H), 6.72 (m, 1H), 6.21 (d, 1H, $^3J_{NH-H2}$=9.2 Hz, N*H*), 5.42 (t, 1H, $^3J_{H3-H2}$=$^3J_{H3-H4}$=10.0 Hz, H3), 5.10 (s, 1H, C*H*Ph$_2$), 4.60 (d, 1H, $^2J_{gem}$=11.6 Hz, C*H*HPh), 4.52 (d, 1H, $^3J_{H1-H2}$=3.2 Hz, H1), 4.44 (d, 1H, CH*H*Ph), 4.31 (t, 1H, $^3J_{H4-H5}$=9.6 Hz, H4), 4.21 (t, 1H, $^3J_{H6ax-H5}$=$^3J_{H6ax-H6eq}$=9.2 Hz, H6$_{ax}$), 4.07 (dt, 1H, H2), 3.98–3.89 (m, 2H, H5, H6$_{eq}$); δ_C 173.4, 167.5, 97.6, 75.4, 72.3, 70.3, 66.5, 65.5, 59.0, 56.8, 52.6, 31.6, 24.2, 10.0; δ_P −3.52, −8.55.

4.5. NMR spectroscopy for structural assignments of *naplephos-a″*

ROESY and NOESY experiments were recorded using data sets (t_1×t_2) of 4096×256 points. Double quantum-filtered phase-sensitive COSY experiments were performed using data sets of 4096×256 points. TOCSY experiments were performed with spin-lock times of 100 ms, using data sets (t_1×t_2) of 4096×256 points. In all homonuclear experiments the data matrix was zero-filled in both dimensions to give a matrix of 4K×2K points and was resolution enhanced in both dimensions by a cosine-bell function before Fourier transformation. Coupling constants were determined by 2D phase-sensitive DQF-COSY. HSQC and HMBC experiments were measured in the ^1H-detected mode via single quantum coherence with proton decoupling in the ^{13}C domain, using data sets of 2048×256 points. Experiments were carried out in the phase-sensitive mode. In all heteronuclear experiments the data matrix was extended to 2048×1024 points using forward linear prediction extrapolation.

4.6. Allylic alkylation of (*rac*)-(*E*)-1,3-diphenylpropenyl acetate in dichloromethane

A solution of $[Pd(\mu\text{-}Cl)(\eta^3\text{-}C_3H_5)]_2$ (0.0035 g, 0.010 mmol) and the appropriate *naplephos* (0.022 mmol) in 1.0 mL of dry dichloromethane was stirred under nitrogen for 0.5 h. A solution of (*rac*)-(*E*)-1,3-diphenyl-2-propenyl acetate (0.120 g, 0.50 mmol) in 1.0 mL of the same solvent was then added. After stirring the resulting light yellow solution for additional 0.5 h, a solution of dimethylmalonate (165 μL, 1.50 mmol), BSA (355 μL, 1.50 mmol) and lithium acetate (0.001 g, 0.015 mmol) in 2 mL of dry dichloromethane was added. After the required reaction time, the system was quenched by addition of aqueous ammonium chloride. The organic phase was dried over sodium sulfate, and the product was isolated by column chromatography on silica gel (dichloromethane). The enantiomeric excesses were determined by HPLC on Chiracel OD-H, using 2-propanol/hexane 2:98, 1.0 mL/min, UV, 254 nm: (*R*)-**2** 9.6 min, (*S*)-**2** 10.3 min.

4.7. Allylic alkylation of (*rac*)-(*E*)-1,3-diphenylpropenyl acetate in [BMIM]BF_4

A solution of $[Pd(\mu\text{-}Cl)(\eta^3\text{-}C_3H_5)]_2$ (0.0035 g, 0.010 mmol) and the appropriate *naplephos* (0.022 mmol) in 1.0 mL of [BMIM]BF_4 was vigorously stirred under nitrogen for 0.5 h. (*rac*)-(*E*)-1,3-Diphenylpropenyl acetate (0.120 g, 0.50 mmol) was then added and the resulting light yellow solution was stirred for additional 0.5 h. Dimethylmalonate (285 μL, 2.5 mmol), BSA (625 μL, 2.5 mmol) and lithium acetate (0.001 g, 0.015 mmol) were added. After the required reaction time, the product was extracted with dry diethyl ether (2×2 mL), the residual ether was removed by vacuum, and the recycle was performed in the same condition mentioned above. The reunified organic phases were evaporated, and the product was isolated by column chromatography on silica gel (dichloromethane). The enantiomeric excesses were determined by HPLC on Chiracel OD-H, using 2-propanol/hexane 2:98, 1.0 mL/min, UV, 254 nm: (*R*)-**2** 9.6 min, (*S*)-**2** 10.3 min.

4.8. Desymmetrization of *meso*-2-cyclopenten-1,4-diol-isocyanate in THF

Without NEt_3: Tosyl isocyanate (0.202 g, 1.02 mmol) was added to a solution of *cis*-2,4-cyclopentenediol (0.056 g, 0.5 mmol) in dry THF (0.9 mL). The colourless solution was stirred at rt for 15 min and at 333 K for 30 min. The reaction mixture was allowed to reach the desired catalysis temperature (Table 1) and then added dropwise to an orange solution of $[Pd(dba)_2]$ (0.014 g, 0.025 mmol) and ligand (0.045 mmol) in dry THF (0.9 mL) held at the same temperature. The orange reaction mixture was stirred for 30 min. The solvent was removed under vacuum, and column chromatography on silica gel (1:10 ethyl acetate/hexane) gave the desired product as a white solid in 80–85% yield. The enantiomeric excesses were determined by chiral HPLC, Chiracel OD-H, 1:10 isopropanol/hexane, UV 254 nm, retention times: (3*R*,6*S*)-**4**: 22–24 min; (+)-(3*S*,6*R*)-**4**: 30–32 min. The absolute configuration was obtained by comparison with a sample of known chirality.

With NEt_3: Tosyl isocyanate (0.202 g, 1.02 mmol) was added to a solution of *cis*-2,4-cyclopentenediol (0.056 g, 0.5 mmol) in dry THF (0.9 mL). The colourless solution was stirred at rt for 15 min and at 333 K for 30 min. The reaction mixture was allowed to cool to rt, and triethylamine (0.101 g, 1.00 mmol) was added. The resulting white slurry was allowed to reach the desired catalysis temperature (Table 1) and then added dropwise to an orange solution of $[Pd(dba)_2]$ (0.014 g, 0.025 mmol) and ligand (0.045 mmol) in dry THF (0.9 mL) held at the same temperature. The orange reaction mixture was stirred for 30 min. The solvent was removed under vacuum, and column chromatography on silica gel (1:10 ethyl acetate/hexane) gave the desired product as a white solid in 80–85% yield. The enantiomeric excesses were determined by chiral HPLC, Chiracel OD-H, 1:10 isopropanol/hexane, UV 254 nm, retention times: (3*R*,6*S*)-**4**: 22–24 min; (3*S*,6*R*)-**4**: 30–32 min. The absolute configuration was obtained by comparison with a sample of known chirality.

In [*BMIM*]BF_4: *naplephos-a″* (0.015 mmol) and $[Pd(dba)_2]$ (0.0057 g, 0.010 mmol) were dissolved in [BMIM]BF_4 (1 mL) under vigorous stirring. *meso*-2-Cyclopenten-1,4-diol-isocyanate (0.043 g, 0.10 mmol) and triethylamine (0.010 g, 0.10 mmol) were added to the solution, and after 30 min the product was extracted from the catalytic phase with diethyl ether (3×15 mL) in 70–80% yield and analysed.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tet.2011.05.013.

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