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Naplephos: a modular library of chiral phosphines based on D-glucose for highly enantioselective asymmetric catalysis

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ABSTRACT

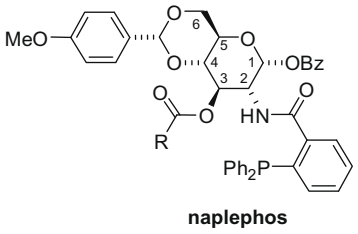
Simple functionalisation of *N*-acetylglucosamine produces the modular ligand library **naplephos**, which combines the performance of 'privileged' ligands based on 1,2-*trans*-cyclohexanediamine with flexibility and accessibility. With the proper choice of substituents, the basic structure was suitably adapted to the Pd-catalysed asymmetric allylic alkylation of *rac*-(*E*)-1,3-diphenyl-2-propenyl acetate with dimethyl malonate, producing the (*S*)-product in ee's of up to 96% ee.

1. Introduction

Homogeneous enantioselective catalysis is a fundamental technology for the production of fine chemicals.[1] In addition to the choice of the active metal, crucial for its effective application is the accurate design of the chiral ligand, which must exhibit a suited and well-defined structure for orienting the stereochemistry of the reaction.

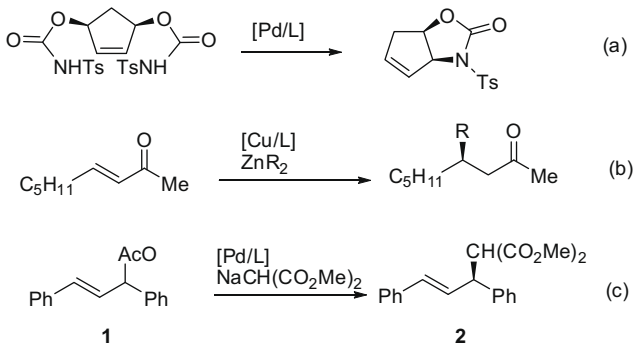
Accordingly, in 2002 Jacobsen[2] a few selected ligands of wide and proven applicability indicated as privileged. Over the years, this original class of privileged ligands has been gradually extended to include other effective structures, and in 2008, the Aldrich Chemical Company has reviewed[3] an entire class comprising more than 30 structures.

A strategy from our group was focussed on the attainment of effective chiral ligands by simple and immediate derivatisation of common carbohydrates,[4] for example, D-glucose. This successful approach[5] has produced the modular ligands' library **naplephos** as shown in Figure 1, which combines the essential structural motifs of the 'privileged' ligands based on 1,2-*trans*-cyclohexanediamine[3] with increased flexibility and accessibility. In fact, by proper choice of the R residue, the basic structure **naplephos** has been already effectively adapted[5b,c] to two different enantioselective processes, affording in all cases the chiral product in high ee's (reactions a and b in Scheme 1). Herein we report its successful application in another relevant reaction, that is, the asymmetric allylic alkylation[6] (AAA) as depicted by reaction c in Scheme 1, which demonstrates the versatility of the structure and its aptitude to afford chiral ligands of broad and established applicability.



naplephos

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



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

2. Results and discussion

The distinctive structure of the **naplephos** ligands is clearly defined, and is optimised for both synthetic convenience and catalytic performance (Scheme 2). Starting from inexpensive

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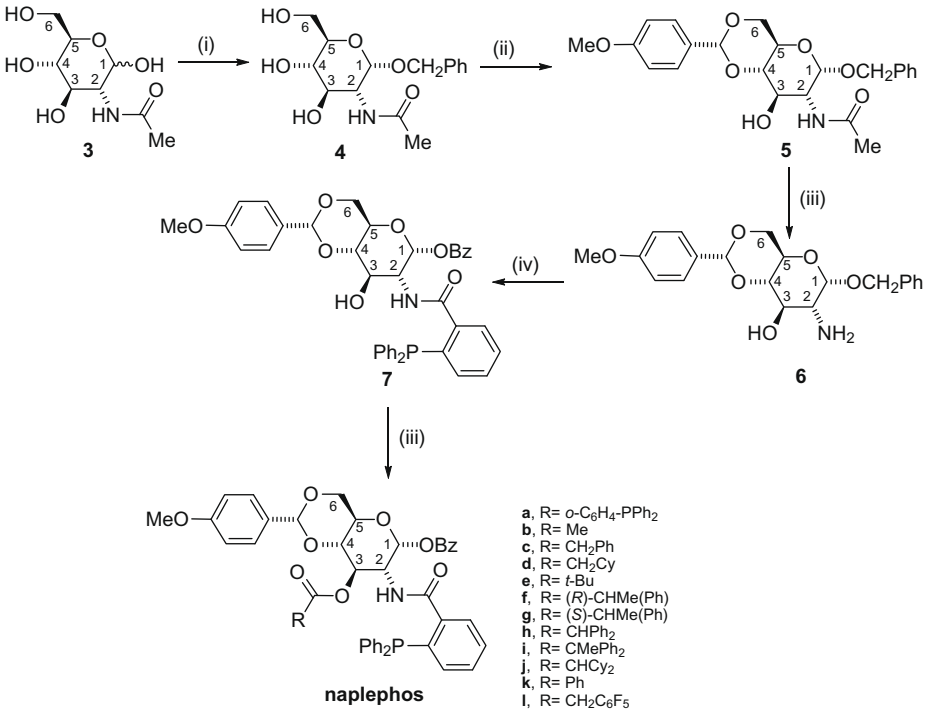


Scheme 2. Synthesis of **naplephos** ligands. Reagents and conditions: (i) BzOH, H^+; (ii) 4-MeO–C_6H_4–CHO, $ZnCl_2$; (iii) KOH, EtOH; (iv) *o*-C_6H_4–PPh_2–CO_2H, DCC, DMAP; (v) RCO_2H, DCC, DMAP.

N-acetylglucosamine, C1 is selectively benzylated at the α-position (i in Scheme 2), thus avoiding a tedious separation of anomers. Positions 4 and 6 are protected with a 4-MeO-benzylidene ring (ii in Scheme 2), which stabilises the chair conformation of the sugar ring, with possible consequent benefit for the outcome of the catalysis.[5c] At the same time, this protection can also be easily removed if a different functionalisation is desired.

At the 2-position, a rigid coordinating diphenylphosphinoamido arm (iii and iv in Scheme 2) is introduced, which reproduces the essential coordinating feature of the privileged Trost ligand.[3] The ester R group is the only variable (v in Scheme 2), and is chosen according to the type of catalytic reaction. When R is again a diphenylphosphino function, the corresponding **naplephos-a** can be productively applied in both the Pd-catalysed desymmetrisation of *meso*-diols[5c] (ee up to 98%) and the Cu-catalysed addition of dialkylzinc to enones[5b] (ee up to 95%).

Within this study, by selecting an R among the simple alkyl and aryl groups (**b**–**l**, see Scheme 2), we demonstrate that the fine tuning of their steric hindrance produces high enantioselectivity in the prototypical Pd asymmetric allylic alkylation (AAA) of *rac*-(*E*)-1,3-diphenyl-2-propenyl acetate **1** with dimethylmalonate (reaction c in Scheme 1).[7]

All the ligands, **naplephos**(**b**–**l**), were characterised via NMR spectroscopy. The sugar protons were assigned according to both their expected chemical shifts and the consistence of the coupling constants within the glucose ring.

The catalytic results are collected in Table 1. After some preliminary runs, the ligand/Pd ratio was conveniently set to 2:1 in most of the experiments (see below). All the reactions were complete within a few hours, affording **2** as the only product. A neat trend was observed, in that both the conversion and the enantioselectivity showed a clear dependence upon the steric hindrance of the ester substituent in **3** (Table 1 also reports both the cone angles[8] and the Charton parameters[9,10] of the R group). The gradual increase in the dimension of the R group along the series **naplephos-b** through **naplephos-h** (entries 1–9) enhances the performance of the catalyst, reaching a maximum which corresponds to a cone angle within 120–126° (entries 5–7). Further enlargement decreases both the activity and the selectivity (entries 8–9).

The presence of an additional stereocenter in the ester group R has little effect on the catalyst performance. In fact, similar enantioselectivity and conversion rate were observed when using **naplephos-f** and **naplephos-g** (entry 5 vs entry 6), which only differ in the configuration of this substituent [R = (*R*)-CH(Et)Ph and (*S*)-CH(Et)Ph, respectively]. In other words, the significant steric role of the substituent is independent of its configuration.

Thus, best results were obtained with **naplephos-h**, which afforded the product in 91% ee under the given experimental conditions. **Naplephos-h** was therefore selected for further refinement of the results, as reported in Table 2.

The performance of the catalyst could be greatly improved upon by increasing the ligand/Pd ratio (entries 1–3), and the conversion was complete in only 10 min with an ee of 96% when 4 equiv of ligand was added (entry 3). The addition of a tetrabutylammonium salt (entry 6) increases the enantioselectivity although the reaction rate did decrease.

The performance of the catalyst was nearly identical when the chloride ion was preliminarily precipitated as a silver salt (entry 4), while the generation of the nucleophile by using BSA resulted in lower reaction rates and ee's (entries 7 and 8).

A key argument for the interpretation of the results collected in Tables 1 and 2 is the strong dependence of the catalyst's performance on (i) the ligand/palladium ratio (entries 1–3 of Table 2) and (ii) the steric hindrance of the R group at the 3-position.

Therefore, some experiments were addressed to study the coordination modes of **naplephos-h** as a function of the ligand/Pd ratio.

In the first test, 1 equiv of **naplephos-h** was added to a THF-d_8 solution of the cationic precursor $[Pd(THF\text{-}d_8)_n(\eta^3\text{-}C_3H_5)]^+(TfO^-)$.[11] The following pieces of diagnostic evidence were observed in the NMR spectra of the resulting complex:

- A shift at high frequency (δ 8.82) of the NH signal in the proton spectrum with respect to the free ligand (δ 7.70).
- The presence of a single resonance at δ 23.3 in the P spectrum.

Table 1
Asymmetric allylic alkylation of *rac*-1,3-diphenyl-2-propenyl acetate with dimethylmalonate[a]

No.	Ligand	Cone angle[b] (°)	Charton parameter[b]	Conversion[c] (%)	Time (h)	ee[d] (*S*) (%)
1	**Naplephos-b**	87	0.52	99	8	39
2	**Naplephos-c**	106	0.70	99	5	85
3	**Naplephos-d**	115		99	2	87
4	**Naplephos-e**	118	1.24	99	2	89
5	**Naplephos-f**	121	1.18	99	2	91
6	**Naplephos-g**	121	1.18	99	2	86
7	**Naplephos-h**	126	1.25	99	2	91
8	**Naplephos-i**	136		99	18	80
9	**Naplephos-j**	144		50	18	80
10	**Naplephos-k**			99	18	45
11	**Naplephos-l**			50	18	60

[a] Reaction conditions: rt, 0.25 mmol of substrate, 0.75 mmol of dimethylmalonate, 0.75 mmol of NaH, 0.0050 mmol of $[Pd(\mu\text{-}Cl)(\eta^3\text{-}C_3H_5)]_2$, 0.022 mmol of **naplephos**.
[b] Relative to the R substituent at the carbonyl α-position. Taken, respectively, from Refs. 8 and 9.
[c] Evaluated by NMR spectroscopy of the crude reaction mixture.
[d] Determined by HPLC on Chiracel OD-H, using 2-propanol/hexane 2:98, 1.0 mL/min, UV, 254 nm.

Table 2
Asymmetric allylic alkylation of *rac*-1,3-diphenyl-2-propenyl acetate with dimethylmalonate and **naplephos-h** as ligand[a]

No.	Nucleophile	**L**/Pd	Additive	Conversion[b] (%)	Time (h)	ee[c] (*S*) (%)
1	$NaCH(CO_2Me)_2$	1.1:1	—	99	18	80
2	$NaCH(CO_2Me)_2$	2:1	—	99	2	91
3	$NaCH(CO_2Me)_2$	4:1	—	99	0.2	96
4[d]	$NaCH(CO_2Me)_2$	2:1	—	99	2	90
5[e]	$NaCH(CO_2Me)_2$	2:1	—	99	2	93
6	$NaCH(CO_2Me)_2$	2:1	Bu_4NBF_4[f]	70	4	95
7	$BSA/CH_2(CO_2Me)_2$	2:1	KOAc[g]	99	5	70
8	$BSA/CH_2(CO_2Me)_2$	2:1	LiOAc[g]	99	5	86

[a] Reaction conditions: rt, 0.25 mmol of substrate, 0.75 mmol of nucleophile, 0.0050 mmol of $[Pd(\mu\text{-}Cl)(\eta^3\text{-}C_3H_5)]_2$.
[b] Evaluated by NMR spectroscopy of the crude reaction mixture.
[c] Determined by HPLC on Chiracel OD-H, using 2-propanol/hexane 2:98, 1.0 mL/min, UV, 254 nm.
[d] The catalyst was treated with a stoichiometric amount of $AgBF_4$ prior the addition of the reagents.
[e] Reaction conditions: rt, 0.10 mmol of substrate, 0.30 mmol of nucleophile, 0.0050 mmol of $[Pd(\mu\text{-}Cl)(\eta^3\text{-}C_3H_5)]_2$.
[f] 0.75 mmol.
[g] 0.010 mmol.

– A shift at high frequency from δ 169.4 to δ 173.2 of the amido carbonyl group in the carbon spectrum.

According to previous literature,[7a,12a,13,14] all these features do clearly indicate P,O-chelation through the amide carbonyl function at the 2-position (Fig. 2), and, hence, in the presence of only 1 equiv of ligand, the active species are plausibly cationic chelated complexes $[Pd(\eta^3\text{-allyl})(P,O\text{-}\mathbf{naplephos})]^+$.

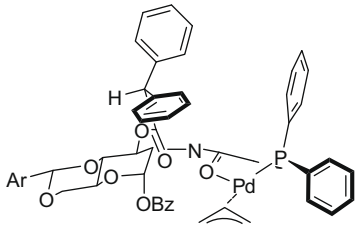


Figure 2. Structure of complex $[Pd(\eta^3\text{-}C_3H_5)(P,O\text{-}\mathbf{naplephos\text{-}h})]^+$.

More interesting within this context is what happened upon the addition of the second equivalent of ligand to $[Pd(\eta^3\text{-}C_3H_5)(P,O\text{-}\mathbf{naplephos\text{-}h})]^+$, because these are the conditions which largely favour both conversion and ee (e.g., entry 1 vs entry 2 of Table 2).

The immediate phosphorous spectrum displayed the signal of the free ligand at δ −9.5, along with the aforementioned signal at δ 23.3. On standing, the former signal gradually decreased, while a new singlet at δ 28.5 grew. After a few hours this was by far the prevailing species. The contemporaneous shift of the NH signal from δ 8.82 to the original region at around δ 7.7 was also observed.

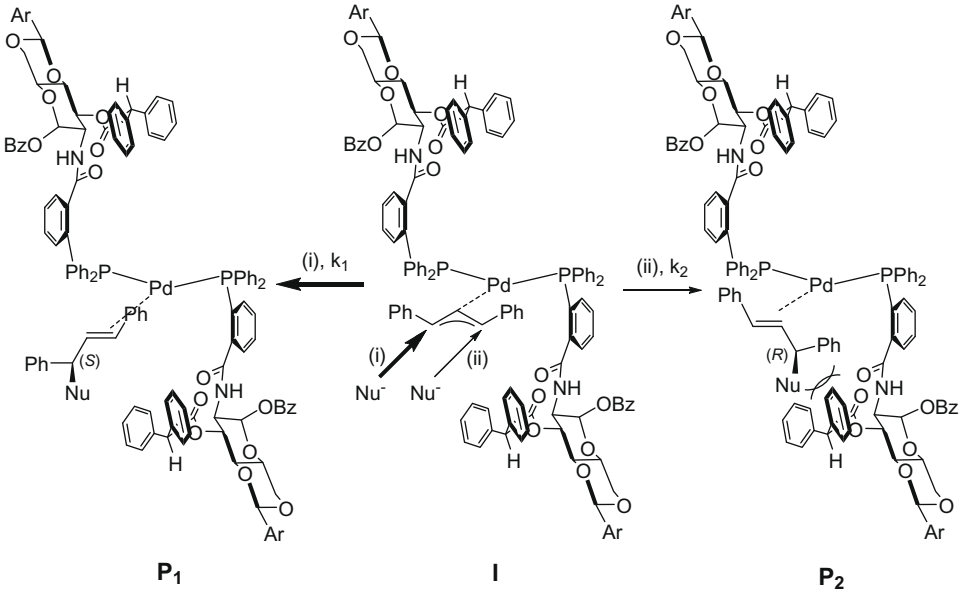
This finding strongly indicates[12a] competitive coordination of two phosphines in a C_2-symmetrical fashion affording a more active catalytic species when the ligand/Pd ratio is equal to two or higher.

By combining these pieces of evidence with the aforementioned dependence of the enantioselectivity on the hindrance of R, the results can be interpreted by assuming that two phosphines coordinate as illustrated in **I**, which represents the most active π-allyl intermediate of the catalytic cycle (Scheme 3).[6d]

According to the mechanism proposed by Pfaltz for C_2-symmetrical ligands,[6d] the enantioselectivity originates from the different rates of nucleophilic attacks (i and ii) at the allyl carbon termini. These are governed by the rotation[6d] of the allyl fragment to give (*S*)-**2** and (*R*)-**2**, respectively, coordinated in an η^2-fashion in $\mathbf{P_1}$ and $\mathbf{P_2}$. In this case, it is clear how the attainment of $\mathbf{P_2}$ is hampered by steric repulsion between the substituents on (*R*)-**2** and R, and, as a consequence, a gradual increase of the cone angle of R regularly favours the formation of (*S*)-**2**.

Furthermore, in the P,P-coordination mode, the N–H units are available for hydrogen-bond interactions with the carbonyl nucleophile, an additional feature which can be beneficial for both rate and selectivity.[15]

This is also in agreement with the fact that the R group is sterically effective, but stereochemically inactive (see above, entry 5 vs entry 6), and with the observation that the enantioselectivity of the reaction is mainly governed by the pocket created by the chiral ligands.



Scheme 3. Possible intermediates in the allylic alkylation of 1,3-diphenyl-2-propenyl acetate with dimethyl malonate by using 2 equiv of **naplephos** ligands.

The fact that very large substituents (cone angle of R >126°) lower the performance of the catalysts can be ascribed to the poor coordination ability of the crowded ligands. In fact, when the cationic precursor $[Pd(THF\text{-}d_8)_n(\eta^3\text{-}C_3H_5)]^+(TfO^-)$ was treated with 2 equiv of **naplephos-j**, very slow coordination was seen by the recording spectra. This means that under catalytic conditions the active species are present at very low concentration, which is in agreement with the observed reduction of the rate of reaction (e.g., entry 7 vs entry 8 in Table 1).

Notably, the importance of the sugar backbone for the catalyst's performance was confirmed by preparing ligand **8** based on *trans*-(1*S*,2*S*)-aminocyclohexanol (Fig. 3),[16] which reproduces the essential coordinating features of **naplephos-h**. By using **8**, product (*S*)-**2** was again obtained in 91% ee, but the conversion was only 25% after 18 h (compare with entry 2 of Table 2). This demonstrates the prominent role played by the sugar scaffold (and its substituents) in enhancing the activity of the catalysts.

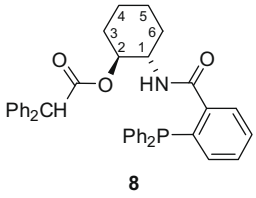


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Figure 3. Formula of (1*S*,2*S*)-2-[(diphenylphosphino)benzoyl]amino cyclohexyl diphenylacetate **8**.

3. Conclusion

The simple functionalisation of commercially available *N*-acetylglucosamine provides an efficient library of chiral ligands **naplephos**. Along with an anomeric α-benzyl group and the rigid benzylidene ring in C4 and C6, the distinctive feature of the ligands is a coordinating diphenylphoshino arm in the equatorial 2-position. Esterification at the 3-position with readily accessible carboxylic acid RCO_2H allows us to functionalise the ligands with fine control of the steric hindrance.

By the appropriate choice of the R residue, the basic structure **naplephos** has already been effectively adapted to three different enantioselective processes, affording in all cases the chiral product in high ee's. This demonstrates the convenience and the flexibility of the ligand structure, and its prospective ability for a wider and established applicability.

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 spectrometers (Varian Model Gemini). 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). Benzyl-4,6-*O*-[(4-MeO)-benzylidene]-2-deoxy-2-amino-α-D-glucoside **6** was prepared according to literature methods.[5c] THF was distilled from $LiAlH_4$, dichloromethane from CaH_2.

4.2. Preparation of 7

A solution of **6** (1.22 g, 2.0 mmol), 2-diphenylphosphinobenzoic acid (2.0 mmol), 4-dimethylaminopyridine (0.024 g, 0.2 mmol) and 1,3-dicyclohexylcarbodiimide (0.82 g, 4.0 mmol) in dry dichloromethane (20 mL) was stirred for 12 h at room temperature under an inert atmosphere to afford a suspension. The residue was removed by filtration. The resulting solution was evaporated under vacuum, and the residue was chromatographed on silica gel (2:1 ethyl acetate/hexane) affording the pure product as a white solid (yield: 85%).

Detailed presentation of physical data for **7**: [α] = +6.7 (*c* 1, $CHCl_3$); selected ^{1}H NMR data: 6.41 (d, 1H, $^3J_{NH-H2}$ = 9.2 Hz, NH), 5.70 (s, 1H, OCHO), 5.05 (d, 1H, $^3J_{H1-H2}$ = 4.2 Hz, H1), 4.80 (d, 1H, $^2J_{gem}$ = 11.7 Hz, C*H*HPh), 4.58 (d, 1H, CH*H*Ph), 4.52 (dt, 1H, $^3J_{H2-H3}$ = 10.2 Hz, H2), 4.35 (dd, 1H, $^3J_{H6eq-H5}$ = 4.2 Hz, $^2J_{H6eq-H6ax}$ = 9.0 Hz, H6eq), 4.07 (t, 1H, $^3J_{H3-H4}$ = 10.2 Hz, H3), 4.02 (dt overlapped, 1H, $^3J_{H5-H4}$ = $^3J_{H5-H6ax}$ = 9.9 Hz, H5), 3.97 (s, 3H, OMe), 3.91 (t, 1H, H4), 3.80 (t, 1H, H6ax); selected ^{13}C NMR data: δ = 170.0, 102.2,

97.4, 82.0, 70.9, 70.0, 69.2, 63.3, 55.5, 55.2. Anal. Calcd for $C_{40}H_{38}NO_7P$: C, 71.10; H, 5.67; N, 2.07. Found: C, 70.89; H, 5.45; N, 2.11.

4.3. General procedure for the preparation of naplephos(b-l) ligands

A solution of **7** (1.15 g, 2.0 mmol), the appropriate RCO_2H acid (2.5 mmol), 4-dimethylaminopyridine (0.24 g, 2.0 mmol) and 1,3-dicyclohexylcarbodiimide (0.82 g, 4.0 mmol) in dry dichloromethane (10 mL) was stirred for 12 h at room temperature under an inert atmosphere affording a suspension. The residue was removed by filtration. The resulting solution was evaporated under vacuum, and the residue was chromatographed on silica gel (1:2 ethyl acetate/hexane) affording the pure product as a white solid (yield: 80–85%).

Detailed presentation of physical data for **naplephos-b**: $[\alpha] = -7.9$ (c 1, $CHCl_3$); selected ^{1}H NMR data: 6.30 (d, 1H, $^3J_{NH-H2}$ = 9.4 Hz, NH), 5.49 (s, 1H, OCHO), 5.42 (t, 1H, $^3J_{H3-H2} = {}^3J_{H3-H4}$ = 9.8 Hz, H3), 4.86 (d, 1H, $^3J_{H1-H2}$ = 3.4 Hz, H1), 4.70 (d, 1H, $^2J_{gem}$ = 11.8 Hz, C*H*HPh), 4.50 (m, 2H, CH*H*Ph and H2), 4.21 (dd, 1H, $^3J_{H6eq-H5}$ = 4.0 Hz, $^2J_{H6eq-H6ax}$ = 10.0 Hz, H6eq), 3.92 (dt, 1H, $^3J_{H5-H4} = {}^3J_{H5-H6ax}$ = 9.6 Hz, H5), 3.80 (s, 3H, OMe), 3.76 (t, 1H, H4), 3.75 (t, 1H, H6ax), 2.36 (s, 3H, Me); selected ^{13}C NMR data: δ = 169.0, 166.3, 99.3, 95.1, 76.6, 67.7, 66.3, 60.6, 52.8, 50.2, 18.7. Anal. Calcd for $C_{42}H_{40}NO_8P$: C, 70.28; H, 5.62; N, 1.95. Found: C, 70.48; H, 5.59; N, 1.88.

Detailed presentation of physical data for **naplephos-c**: $[\alpha] = +7.8$ (c 1, $CHCl_3$); selected ^{1}H NMR data: δ = 6.27 (d, 1H, $^3J_{NH-H2}$ = 9.8 Hz, NH), 5.41 (t, 1H, $^3J_{H3-H2} = {}^3J_{H3-H4}$ = 9.9 Hz, H3), 5.40 (s, 1H, OCHO), 4.87 (d, 1H, $^3J_{H1-H2}$ = 3.4 Hz, H1), 4.68 (d, 1H, $^2J_{gem}$ = 11.6 Hz, C*H*HPh), 4.60 (dt, 1H, H2), 4.47 (d, 1H, CH*H*Ph), 4.19 (dd, 1H, $^3J_{H6eq-H5}$ = 4.4 Hz, $^2J_{H6eq-H6ax}$ = 9.8 Hz, H6eq), 3.92 (dt, 1H, $^3J_{H5-H4} = {}^3J_{H5-H6ax}$ = 10.0 Hz, H5), 3.81, (s, 3H, OMe), 3.76 (t, 1H, H4), 3.72 (t, 1H, H6ax), 3.65 (app d, 2H, CH_2Ph); selected ^{13}C NMR data: δ = 172.3, 168.7, 101.6, 97.9, 79.8, 70.8, 70.4, 69.0, 63.4, 55.5, 52.9, 41.5. Anal. Calcd for $C_{48}H_{44}NO_8P$: C, 72.62; H, 5.59; N, 1.76. Found: C, 72.87; H, 5.50; N, 1.65.

Detailed presentation of physical data for **naplephos-d**: $[\alpha] = +20.8$ (c 1, $CHCl_3$); selected ^{1}H NMR data: 6.35 (d, 1H, $^3J_{NH-H2}$ = 10.0 Hz, NH), 5.48 (s, 1H, OCHO), 5.43 (t, 1H, $^3J_{H3-H2} = {}^3J_{H3-H4}$ = 9.4 Hz, H3), 4.88 (d, 1H, $^3J_{H1-H2}$ = 4.2 Hz, H1), 4.68 (d, 1H, $^2J_{gem}$ = 11.6 Hz, C*H*HPh), 4.47 (m, 2H, CH*H*Ph and H2), 4.18 (dd, 1H, $^3J_{H6eq-H5}$ = 4.2 Hz, $^2J_{H6eq-H6ax}$ = 9.2 Hz, H6eq), 3.89 (dt, 1H, $^3J_{H5-H4} = {}^3J_{H5-H6ax}$ = 9.6 Hz, H5), 3.79 (s, 3H, OMe), 3.74 (t, 1H, H4), 3.70 (t, 1H, H6ax), 2.21 (m, 2H, CH_2Cy); selected ^{13}C NMR data: δ = 173.0, 164.4, 99.6, 97.5, 94.0, 75.4, 65.9, 64.9, 59.4, 51.4, 49.9, 38.3, 30.9, 28.9, 21.9. Anal. Calcd for $C_{48}H_{50}NO_8P$: C, 72.07; H, 6.30; N, 1.75. Found: C, 71.69; H, 6.36; N, 1.82.

Detailed presentation of physical data for **naplephos-e**: $[\alpha] = -2.2$ (c 1, $CHCl_3$); selected ^{1}H NMR data: δ = 6.47 (d, 1H, $^3J_{NH-H2}$ = 9.6 Hz, NH), 5.67 (s, 1H, OCHO), 5.59 (t, 1H, $^3J_{H3-H2} = {}^3J_{H3-H4}$ = 10.0 Hz, H3), 4.98 (d, 1H, $^3J_{H1-H2}$ = 3.6 Hz, H1), 4.84 (d, 1H, $^2J_{gem}$ = 11.7 Hz, C*H*HPh), 4.68 (dt, 1H, H2), 4.63 (d, 1H, CH*H*Ph), 4.22 (dd, 1H, $^3J_{H6eq-H5}$ = 4.5 Hz, $^2J_{H6eq-H6ax}$ = 9.9 Hz, H6eq), 4.08 (dt, 1H, $^3J_{H5-H4} = {}^3J_{H5-H6ax}$ = 10.2 Hz, H5), 3.96 (s, 3H, OMe), 3.91 (t, 1H, H4), 3.89 (t, 1H, H6ax), 1.29 (s, 9H, *t*-Bu); selected ^{13}C NMR data: δ = 180.7, 168.4, 101.3, 98.2, 79.6, 70.5, 70.0, 69.0, 63.4, 55.5, 52.8, 39.2, 27.3. Anal. Calcd for $C_{45}H_{46}NO_8P$: C, 71.13; H, 6.10; N, 1.84. Found: C, 71.46; H, 6.29; N, 1.89.

Detailed presentation of physical data for **naplephos-f**: $[\alpha] = -16.6$ (c 1, $CHCl_3$); selected ^{1}H NMR data: 6.30 (d, 1H, $^3J_{NH-H2}$ = 9.6 Hz, NH), 5.43 (t, 1H, $^3J_{H3-H2} = {}^3J_{H3-H4}$ = 10.0 Hz, H3), 5.33 (s, 1H, OCHO), 4.86 (d, 1H, $^3J_{H1-H2}$ = 3.6 Hz, H1), 4.65 (d, 1H, $^2J_{gem}$ = 11.4 Hz, C*H*HPh), 4.49 (dt, 1H, H2), 4.45 (d, 1H, CH*H*Ph), 4.15 (dd, 1H, $^3J_{H6eq-H5}$ = 4.4 Hz, $^2J_{H6eq-H6ax}$ = 9.8 Hz, H6eq), 3.81 (dt, 1H, $^3J_{H5-H4} = {}^3J_{H5-H6ax}$ = 10.0 Hz, H5), 3.80 (s, 3H, OMe), 3.72 (t, 1H, H4), 3.66 (t, 1H, H6ax), 3.51 (t, 1H, $^3J_{H-H}$ = 7.4 Hz, CHEtPh), 2.10 (m, 1H, C*H*HMe), 1.71 (m, 1H, CH*H*Me), 0.75 (t, 3H, $^3J_{H-H}$ = 8.0 Hz, Me); selected ^{13}C NMR data: δ = 174.6, 168.5, 101.2, 98.1, 79.4, 70.4, 69.8, 68.9, 63.3, 55.5, 53.5, 52.7, 26.5, 12.2. Anal. Calcd for $C_{50}H_{48}NO_8P$: C, 73.07; H, 5.89; N, 1.70. Found: C, 73.22; H, 5.83; N, 1.61.

Detailed presentation of physical data for **naplephos-g**: $[\alpha] = +41.1$ (c 1, $CHCl_3$); selected ^{1}H NMR data: 6.38 (d, 1H, $^3J_{NH-H2}$ = 9.5 Hz, NH), 5.66 (s, 1H, OCHO), 5.64 (t, 1H, $^3J_{H3-H2} = {}^3J_{H3-H4}$ = 10.4 Hz, H3), 5.07 (d, 1H, $^3J_{H1-H2}$ = 3.6 Hz, H1), 4.82 (d, 1H, $^2J_{gem}$ = 12.0 Hz, C*H*HPh), 4.70 (dt, 1H, H2), 4.61 (d, 1H, CH*H*Ph), 4.35 (dd, 1H, $^3J_{H6eq-H5}$ = 4.8 Hz, $^2J_{H6eq-H6ax}$ = 10.4 Hz, H6eq), 4.07 (dt, 1H, $^3J_{H5-H4} = {}^3J_{H5-H6ax}$ = 9.6 Hz, H5), 3.97 (s, 3H, OMe), 3.94 (t, 1H, H4), 3.92 (t, 1H, H6ax), 3.68 (t, 1H, $^3J_{H-H}$ = 7.2 Hz, CHEtPh), 2.52 (m, 1H, C*H*HMe), 1.93 (m, 1H, CH*H*Me), 0.98 (t, 3H, $^3J_{H-H}$ = 7.2 Hz, Me); selected ^{13}C NMR data: δ = 170.6, 164.4, 97.4, 95.2, 75.5, 66.3, 64.8, 59.3, 51.3, 49.7, 48.8, 22.9, 8.1. Anal. Calcd for $C_{50}H_{48}NO_8P$: C, 73.07; H, 5.89; N, 1.70. Found: C, 71.93; H, 5.68; N, 1.81.

Detailed presentation of physical data for **naplephos-h**: $[\alpha] = -23.0$ (c 1, $CHCl_3$); selected ^{1}H NMR data: δ = 6.34 (d, 1H, $^3J_{NH-H2}$ = 9.8 Hz, NH), 5.64 (t, 1H, $^3J_{H3-H2} = {}^3J_{H3-H4}$ = 10.2 Hz, H3), 5.46 (s, 1H, OCHO), 5.16 (s, 1H, $CHPh_2$), 4.95 (d, 1H, $^3J_{H1-H2}$ = 3.6 Hz, H1), 4.71 (d, 1H, $^2J_{gem}$ = 11.6 Hz, C*H*HPh), 4.61 (dt, 1H, H2), 4.48 (d, 1H, CH*H*Ph), 4.30 (dd, 1H, $^3J_{H6eq-H5}$ = 4.6 Hz, $^2J_{H6eq-H6ax}$ = 10.2 Hz, H6eq), 3.96 (dt, 1H, $^3J_{H5-H4} = {}^3J_{H5-H6ax}$ = 9.6 Hz, H5), 3.85 (s, 3H, OMe), 3.75 (t, 1H, H4), 3.75 (t, 1H, H6ax); selected ^{13}C NMR data: δ = 173.3, 168.1, 101.3, 97.9, 79.2, 70.7, 70.3, 68.8, 63.3, 56.9, 55.5, 52.5. Anal. Calcd for $C_{54}H_{48}NO_8P$: C, 74.55; H, 5.56; N, 1.61. Found: C, 74.10; H, 5.49; N, 1.62.

Detailed presentation of physical data for **naplephos-i**: $[\alpha] = -28.6$ (c 1, $CHCl_3$); selected ^{1}H NMR data: δ = 6.25 (d, 1H, $^3J_{NH-H2}$ = 9.6 Hz, NH), 5.55 (t, 1H, $^3J_{H3-H2} = {}^3J_{H3-H4}$ = 9.4 Hz, H3), 5.39 (s, 1H, OCHO), 4.82 (d, 1H, $^3J_{H1-H2}$ = 3.3 Hz, H1), 4.62 (d, 1H, $^2J_{gem}$ = 11.7 Hz, C*H*HPh), 4.48 (dt, 1H, H2), 4.42 (d, 1H, CH*H*Ph), 4.13 (dd, 1H, $^3J_{H6eq-H5}$ = 5.1 Hz, $^2J_{H6eq-H6ax}$ = 10.2 Hz, H6eq), 3.89 (dt, 1H, $^3J_{H5-H4} = {}^3J_{H5-H6ax}$ = 10.2 Hz, H5), 3.85 (s, 3H, OMe), 3.67 (t, 1H, H4), 3.65 (t, 1H, H6ax), 1.85 (s, 3H, Me); selected ^{13}C NMR data: δ = 175.9, 168.3, 101.7, 98.2, 79.4, 71.0, 70.5, 69.0, 63.4, 57.0, 57.6, 52.7, 27.1. Anal. Calcd for $C_{55}H_{50}NO_8P$: C, 74.73; H, 5.70; N, 1.58. Found: C, 72.28; H, 5.81; N, 1.54.

Detailed presentation of physical data for **naplephos-j**: $[\alpha] = +14.5$ (c 1, $CHCl_3$); selected ^{1}H NMR data: 6.54 (d, 1H, $^3J_{NH-H2}$ = 9.0 Hz, NH), 5.46 (t, 1H, $^3J_{H3-H2} = {}^3J_{H3-H4}$ = 10.2 Hz, H3), 5.44 (s, 1H, OCHO), 4.92 (d, 1H, $^3J_{H1-H2}$ = 3.3 Hz, H1), 4.66 (d, 1H, $^2J_{gem}$ = 11.7 Hz, C*H*HPh), 4.48 (m, 2H, CH*H*Ph and H2), 4.14 (dd, 1H, $^3J_{H6eq-H5}$ = 4.8 Hz, $^2J_{H6eq-H6ax}$ = 10.2 Hz, H6eq), 3.92 (dt, 1H, $^3J_{H5-H4} = {}^3J_{H5-H6ax}$ = 9.6 Hz, H5), 3.74 (s, 3H, OMe), 3.70 (t, 1H, H4), 3.65 (t, 1H, H6ax), 2.02 (t, 1H, $^3J_{H-H}$ = 6.6 Hz, $CHCy_2$); selected ^{13}C NMR data: δ = 175.7, 167.5, 101.7, 97.9, 79.5, 70.3, 69.3, 68.9, 63.2, 57.4, 55.3, 52.9, 36.5. Anal. Calcd for $C_{54}H_{60}NO_8P$: C, 73.53; H, 6.86; N, 1.59. Found: C, 73.77; H, 6.76; N, 1.55.

Detailed presentation of physical data for **naplephos-k**: $[\alpha] = -2.0$ (c 1, $CHCl_3$); selected ^{1}H NMR data: 6.38 (d, 1H, $^3J_{NH-H2}$ = 9.6 Hz, NH), 5.68 (t, 1H, $^3J_{H3-H2} = {}^3J_{H3-H4}$ = 10.0 Hz, H3), 5.55 (s, 1H, OCHO), 4.91 (d, 1H, $^3J_{H1-H2}$ = 3.6 Hz, H1), 4.71 (d, 1H, $^2J_{gem}$ = 11.8 Hz, C*H*HPh), 4.66 (dt, 1H, H2), 4.48 (d, 1H, CH*H*Ph), 4.22 (dd, 1H, $^3J_{H6eq-H5}$ = 4.2 Hz, $^2J_{H6eq-H6ax}$ = 9.6 Hz, H6eq), 4.10 (dt, 1H, $^3J_{H5-H4} = {}^3J_{H5-H6ax}$ = 9.6 Hz, H5), 3.85 (t, 1H, H4), 3.83 (t, 1H, H6ax), 3.75 (s, 3H, OMe); selected ^{13}C NMR data: δ = 168.7, 160.1, 101.4, 97.9, 79.5, 70.7, 70.3, 68.8, 63.3, 55.3, 52.7. Anal. Calcd for $C_{47}H_{42}NO_8P$: C, 72.39; H, 5.43; N, 1.80. Found: C, 72.73; H, 5.48; N, 1.84.

Detailed presentation of physical data for **naplephos-l**: $[\alpha] = +12.7$ (c 1, $CHCl_3$); selected ^{1}H NMR data: 6.26 (d, 1H, $^3J_{NH-H2}$ =

9.2 Hz, NH), 5.47 (s, 1H, OCHO), 5.41 (t, 1H, $^3J_{H3-H2} = {}^3J_{H3-H4}$ = 9.8 Hz, H3), 4.84 (d, 1H, $^3J_{H1-H2}$ = 4.2 Hz, H1), 4.66 (d, 1H, $^2J_{gem}$ = 11.6 Hz, C*H*HPh), 4.60 (dt, 1H, H2), 4.47 (d, 1H, CH*H*Ph), 4.18 (dd, 1H, $^3J_{H6eq-H5}$ = 4.4 Hz, $^2J_{H6eq-H6ax}$ = 9.6 Hz, H6eq), 3.91 (dt, 1H, $^3J_{H5-H4} = {}^3J_{H5-H6ax}$ = 10.0 Hz, H5), 3.80 (s, 3H, OMe), 3.70 (t, 1H, H4), 3.65 (t, 1H, H6ax); selected ^{13}C NMR data: δ = 168.8, 160.2, 101.4, 97.6, 79.1, 71.9, 70.2, 68.7, 63.2, 55.3, 52.3, 28.0. Anal. Calcd for $C_{48}H_{39}F_5NO_8P$: C, 65.23; H, 4.45; N, 1.58. Found: C, 65.15; H, 4.44; N, 1.50.

4.4. Preparation of 8

A solution of 2-(diphenylphosphino)-*N*-[(1*S*,2*S*)-2-hydroxycyclohexyl]benzamide[16] (0.46 g, 1.0 mmol), diphenylacetic acid (0.42 g, 2.0 mmol), 4-dimethylaminopyridine (0.24 g, 2.0 mmol) and 1,3-dicyclohexylcarbodiimide (0.41 g, 2.0 mmol) in dry dichloromethane (10 mL) was stirred for 12 h at room temperature under inert atmosphere to afford a suspension. The residue was removed by filtration. The resulting solution was evaporated under vacuum, and the residue was chromatographed on silica gel (1:2 ethyl acetate/hexane) affording the pure product as a white solid (yield: 85%).

Detailed presentation of physical data for **8**: $[\alpha] = -59.4$ (*c* 1, $CHCl_3$); selected ^{1}H NMR data: 5.92 (d, 1H, $^3J_{NH-H1}$ = 8.4 Hz, NH), 5.04 (s, 1H, $CHPh_2$), 4.66 (dt, 1H, $^3J_{H2-H1} = {}^3J_{H2-H3ax}$ = 12 Hz, $^3J_{H2-H3eq}$ = 4.4 Hz, H2), 4.01 (m, 1H, H1); selected ^{13}C NMR data: δ = 173.6, 168.3, 75.3, 57.1, 53.0, 31.6, 30.9, 24.0. Anal. Calcd for $C_{39}H_{36}NO_3P$: C, 78.37; H, 6.07; N, 2.34. Found: C, 78.89; H, 6.21; N, 2.19.

4.5. General procedure for the catalytic reaction

With the sodium salt of dimethylmalonate: a solution of [Pd(μ-Cl)-(η^3-allyl)]$_2$ (0.0020 g, 0.0050 mmol) and the appropriate **naplephos** (0.022 mmol) in 0.5 mL of dry THF was stirred under nitrogen for 0.5 h. A solution of (*E*)-1,3-diphenyl-2-propenyl acetate (0.063 g, 0.25 mmol) in 0.5 mL of the same solvent was then added. After stirring the resulting light yellow solution for additional 0.5 h, a solution of the sodium salt of dimethylmalonate (0.116 g, 0.750 mmol) (and the additive when present, see Table 2) in 4 mL of dry THF was added. After the required reaction time, the system was quenched by the addition of aqueous ammonium chloride. The product was extracted with dichloromethane and, after drying over sodium sulphate, the product was isolated by column chromatography on silica gel (dichloromethane).

With BSA/dimehylmalonate: a solution of [Pd(μ-Cl)(η^3-allyl)]$_2$ (0.0020 g, 0.0050 mmol) and the appropriate **naplephos** (0.022 mmol) in 0.5 mL of dry dichloromethane was stirred under nitrogen for 0.5 h. A solution of (*E*)-1,3-diphenyl-2-propenyl acetate (0.063 g, 0.25 mmol) in 0.5 mL of the same solvent was then added. After stirring the resulting light yellow solution for additional 0.5 h, a solution of dimethylmalonate (0.0997 g, 0.750 mmol), BSA (0.152 g, 0.750 mmol) and a pinch of the acetate salt in 2 mL of dry dichloromethane was added. After the required reaction time, the system was quenched by the addition of aqueous ammonium chloride. The organic phase was dried over sodium sulphate, and the product was isolated by column chromatography on silica gel (dichloromethane).

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