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## COMMUNICATION

## Asymmetric Synthesis of the Two Enantiomers of $\beta$ -Phosphorus-containing $\alpha$ -Amino Acids via Hydrophosphinylation and Hydrophosphonylation of Chiral Ni(II)-Complexes

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**A new approach for the asymmetric synthesis of the two enantiomers of  $\beta$ -phosphorus-containing  $\alpha$ -amino acids was developed via Michael addition of secondary phosphine oxides and dialkyl phosphites to chiral Ni(II)-complexes of a dehydroalanine-Schiff base.**

Organophosphorus derivatives are widely found in natural products, pharmaceuticals, ligands and functional materials.<sup>1</sup> In particular, phosphorus-containing  $\alpha$ -amino acids are important classes of tailor-made compounds that have gained considerable attention in peptide design strategies as they enhance stability towards protease degradation and modulate bioactivity. They can also be used for labelling purposes.<sup>2</sup> Notably, it was shown that phosphonic analogues of aminodicarboxylic acids act as group-selective agonists or antagonists for the *N*-methyl-D-aspartate (NMDA) receptor site. Indeed, aminophosphonic acids such as AP-3, AP-4, AP-5 and AP-7 have been demonstrated to be particularly potent when evaluated for the treatment of central nervous system disorders (Figure 1).<sup>3</sup>

Given the prominence of phosphorus-containing  $\alpha$ -amino acids, various P-sources, such as dialkyl/diaryl phosphines, H-phosphonates, or secondary phosphine oxides have been used for C–P bond constructions.<sup>4</sup> However, most of the synthetic methods used so far are based on reactions of air-sensitive (organometallic) reagents or phosphide salts which suffer from limited scope, laborious purification, and low yields. Furthermore, these reactions have typically been catalysed by strong bases, radical initiators, or transition metal catalysts.<sup>4</sup> To address this **aspect, phospho**-Michael addition,<sup>5</sup> i.e. the

addition of P-nucleophiles to an acceptor-substituted alkene or alkyne, certainly represents one of the most versatile, atom-economical and straightforward approaches.

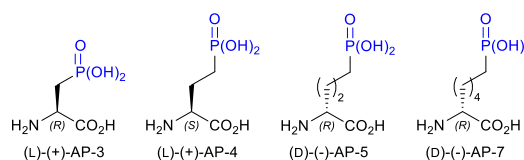


Figure 1. Pharmaceutically important phosphorus-containing  $\alpha$ -amino acids.

However, even though the asymmetric synthesis of phosphorus-containing amino acids has been intensely pursued in recent years,<sup>4b</sup> to the best of our knowledge, the stereoselective Michael addition of phosphide anions to create new phosphorus-carbon bonds remains little explored to date.<sup>4b</sup> Importantly, Feringa and co-workers described the conjugate addition of lithiodiphenylphosphine to optically active butenolide synthon, (5*R*)-menthyloxy-2[5*H*]-furanone, leading to enantiopure *S,S*-CHIRAPOS.<sup>6</sup> Wang and co-workers **also achieved the** asymmetric addition of dialkylphosphine oxides to enones with high enantioselectivity by using Et<sub>2</sub>Zn as a base and dinuclear metal-ProPhenol catalysts.<sup>7</sup> A stereoselective Michael addition of P(X)–H-type nucleophiles to cyclohexen-1-ylphosphine oxide was also described by Stankevič and co-workers.<sup>8</sup> Another point probably worthy of note is that the simple asymmetric activation of P(X)–H moieties via deprotonation with a basic catalyst remains an inaccessible strategy due to the lack of suitable non-racemic chiral molecular entities that exert a sufficiently strong basicity, thus neglecting the intrinsic reactivity of the phosphite form.<sup>7</sup>

In this context and despite significant advances in this field, the stereoselective phospho-Michael reaction on activated alkenes remains a highly desirable alternative. As a consequence, and relying on our long-standing interest in tailor-made amino acids (AAs), including phosphorus-containing derivatives,<sup>9,10</sup> we envisioned **performing** the asymmetric synthesis of  $\beta$ -phosphorus-containing  $\alpha$ -amino acids by taking advantage of chiral trichloro-substituted Ni(II)-complexes of dehydroalanine Schiff bases.<sup>11</sup> An excellent diastereoselectivity was observed upon hydrophosphonylation or

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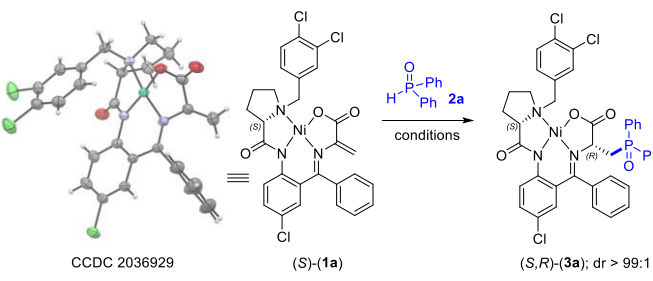
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†Electronic Supplementary Information (ESI) available: General experimental information and procedure for product synthesis, full characterization data,<sup>1</sup>H and <sup>13</sup>C NMR spectra. CCDC 2036929. CCDC 2036930. See DOI: 10.1039/x0xx00000x

hydrophosphinylation of the chiral enone (*S*)-**1a** or (*R*)-**1a**, further providing very simple access to a wide range of enantiopure  $\beta$ -phosphono- and  $\beta$ -phosphino- $\alpha$ -amino acid derivatives through subsequent disassembly and re-construction of the chiral Ni(II)-platform.

At the outset of the study, synthesis of the requisite optically pure Ni(II)-dehydroalanine complex,<sup>12</sup> [(*R*)-**1a** and (*S*)-**1a**] and phosphine oxide reagents (**2**) was performed according to literature procedures. It is worth noting that complexes of type **1** were previously shown to exhibit operational simplicity and an exquisite potential for large-scale applications.<sup>12,13</sup> In addition, the excellent levels of the asymmetric induction during their additions with various *O*-, *N*- and *R*CF<sub>2</sub>- nucleophiles were correlated with the chlorine degree and substitution pattern of the chiral auxiliary.<sup>12,13</sup> It should be emphasized that reactions of the corresponding chiral Ni(II) complexes of dehydroalanine still remain the least well studied area.<sup>13a</sup>

**Table 1.** Optimization of the reaction conditions.<sup>a,b</sup>



| Entry          | K <sub>2</sub> CO <sub>3</sub><br>(eq.) | <b>2a</b><br>(eq.) | t (°C)    | Time<br>(h) | Solvent                         | <b>3a</b><br>(%) <sup>c</sup> | <b>1a</b><br>(%) <sup>c</sup> |
|----------------|---|--------------------|-----------|-------------|---------------------------------|-------------------------------|-------------------------------|
| 1              | 0.25                                    | 2.0                | rt        | 24          | CH <sub>3</sub> CN              | 43                            | 40                            |
| 2              | 0.25                                    | 2.0                | 60        | 4           | CH <sub>3</sub> CN              | 73                            | 0                             |
| 3              | 1.0                                     | 2.0                | 60        | 4           | CH <sub>3</sub> CN              | 65                            | 0                             |
| <b>4</b>       | <b>0.25</b>                             | <b>1.5</b>         | <b>60</b> | <b>4</b>    | <b>CH<sub>3</sub>CN</b>         | <b>89</b>                     | <b>0</b>                      |
| 5              | 0.25                                    | 1.0                | 60        | 4           | CH <sub>3</sub> CN              | 79                            | 5                             |
| 6              | 0.25                                    | 1.5                | 60        | 4           | CH <sub>2</sub> Cl <sub>2</sub> | 44                            | 52                            |
| 7              | 0.25                                    | 1.5                | 60        | 4           | THF                             | 71                            | 5                             |
| 8              | 0                                       | 1.5                | 60        | 4           | CH <sub>3</sub> CN              | 65                            | 34                            |
| 9 <sup>d</sup> | 0.25                                    | 1.5                | 60        | 4           | CH <sub>3</sub> CN              | 73                            | 0                             |

<sup>a</sup> Reaction conditions: (*S*)-(**1a**) (164  $\mu$ mol, 1 eq.), **2a** (246  $\mu$ mol, 1.5 eq.), K<sub>2</sub>CO<sub>3</sub> (41  $\mu$ mol, 0.25 eq.), CH<sub>3</sub>CN (5 mL), heating under air atmosphere in a sealed tube for 4 h. <sup>b</sup> The diastereomeric ratio was determined by <sup>1</sup>H and <sup>31</sup>P NMR analysis of the crude product. <sup>c</sup> Isolated yield. <sup>d</sup> Reaction performed on a 3.0 mmol (ca. 1.8 g) scale of (*S*)-(**1a**).

Complex (*S*)-**1a**, (CCDC 2036929) and diphenylphosphine oxide **2a** were thus selected as model substrates and the conditions for the phospho-Michael addition reaction were optimized. The results are summarized in Table 1. The Michael addition of R<sub>2</sub>P(O)H to simple activated alkenes is usually conducted under basic conditions in polar solvents – either in the presence of a soft basic catalyst (DBU, K<sub>2</sub>CO<sub>3</sub>, etc.), or by using a strong base (e.g., *n*BuLi, NaH) in stoichiometric amount.<sup>14,15</sup> Noteworthy, the R<sub>2</sub>PH/K<sub>2</sub>CO<sub>3</sub> heterogeneous system which provides the phosphide anion only at a low concentration might preclude extensive racemization at the  $\alpha$ -carbon atom of the newly generated chiral phosphorus adducts. To our delight, in the presence of 0.25 equivalent of K<sub>2</sub>CO<sub>3</sub> as a base in acetonitrile at

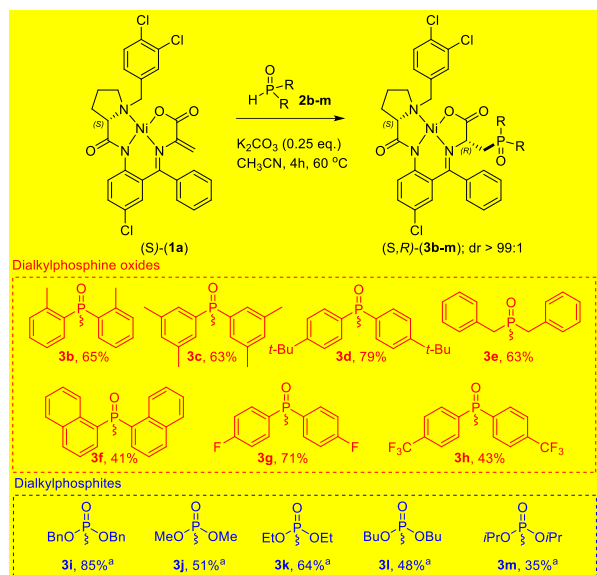
room temperature during 24h, the desired phosphine oxide intermediate (*S,R*)-**3a** was obtained in moderate yield (43%), as a single diastereomer (d.r. > 99:1) (entry 1). Importantly, no epimerization of the newly formed stereocenter could be detected through subsequent purification by SiO<sub>2</sub> chromatography and over prolonged storage under argon atmosphere at/or below 4 °C. Aiming to further improve the product yield (entries 2-5), the reaction temperature was increased, and the screening of the number of equivalents of K<sub>2</sub>CO<sub>3</sub> and of the phosphine oxide **2a** were carried out. A series of common organic solvents was also examined, revealing that acetonitrile is best suited for this transformation (entries 6–7). A control experiment was then conducted without any base producing (*S,R*)-**3a** in moderate yield (65%) along with 34% of recovered starting material (entry 8). Interestingly, this outcome unveils significant information: a base is not essential to promote the phosphorus bond formation, thus providing alternatives for base-sensitive phosphines. Having successfully determined the optimal conditions for the P(O)–H bond addition reaction (entry 4), a gram-scale synthesis of (*S*)-**1** was performed in high diastereoselectivity to deliver (*S,R*)-**3a** without a noticeable decrease in the yield and with recovery of the chiral ligand (entry 9).

As outlined in Scheme 2, the reaction scope was thereafter investigated with a range of secondary phosphine oxides **2b–h** and dialkyl phosphites **2i–m**. The nucleophilicity of these reagents was important in ensuring successful reactivity. We observed that the electronic properties and substitution pattern of the diaryl phosphine oxide reagents did not alter the efficacy of the addition process even with slightly electron-withdrawing groups, such as *p*-F (**3g**) and *p*-CF<sub>3</sub> (**3h**). The corresponding Schiff base products **3b–d** featuring 2-Me, 3,5-diMe and 4-*t*-Bu on the phenyl group were obtained in good yields (e.g., 63–79 %). Naphtyl- and benzyl-phosphinyl derivatives were also allowed, giving **3f** and **3e** in moderate (41%) to good yields (63%) respectively. Of note, the Schiff base products obtained (*S,R*)-(**3a–h**) were all isolated as single diastereomers (d.r > 99:1).

With these promising results in hand, we turned our attention toward the addition of dialkyl phosphites **2i–m** to the chiral enone (*S*)-**1a** under standard conditions. In this case, high diastereoselectivities (d.r > 99:1) were also obtained, but with significantly lower yields. The reaction efficiency was boosted through the use of Cs<sub>2</sub>CO<sub>3</sub> instead of K<sub>2</sub>CO<sub>3</sub> as a base, which provided (*S,R*)-**3i–m** in moderate to good yields (35–85%).

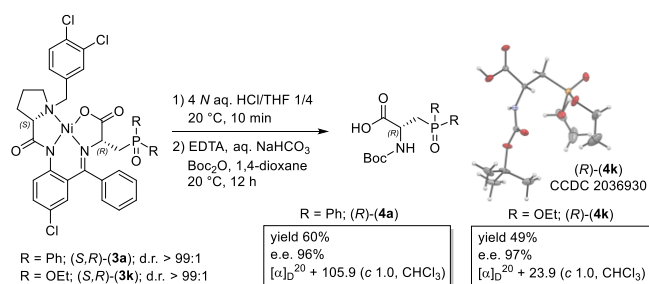
The multi-functionality present in the product provides a further opportunity for post-functionalization. The disassembly of the Ni(II) complexes (*S,R*)-**3a** and (*S,R*)-**3k** (as presented in Scheme 3) was thus performed next, under standard conditions by treatment with 4 *N* aq. HCl in THF (1:4) for 10 minutes at ambient temperature.<sup>16</sup> The red coloured mixture gradually changed to a green solution, indicating disassembly of the starting (*S,R*)-**3a** or (*S,R*)-**3k** complex and formation of NiCl<sub>2</sub>. The mixture was diluted (H<sub>2</sub>O) and the aqueous phase was extracted with EtOAc to recycle the chiral dehydroalanine Schiff base ligand which was obtained as a hydrochloric salt and recovered with 75% yield. The aqueous phase was then treated with EDTA

to chelate the Ni(II) ions and protection of the hydrochloric salt of the *in situ* generated amino acid was performed using Boc<sub>2</sub>O in a mixture of dioxane:H<sub>2</sub>O at ambient temperature in the presence of NaHCO<sub>3</sub>. Compounds (*R*)-**4a** (60%) and (*R*)-**4k** (49%) were respectively obtained in good and moderate yields with 96% enantiomeric purity (SFC analysis, see SI).



**Scheme 2.** Phospha-Michael addition of secondary phosphine oxides (R=Ar) **2b-m** and dialkyl phosphites (R=OAlk) **2i-m** to dehydroalanine complex (*S*)-**1a**.<sup>a</sup> CsCO<sub>3</sub> (0.25 eq.) was used instead of K<sub>2</sub>CO<sub>3</sub>.

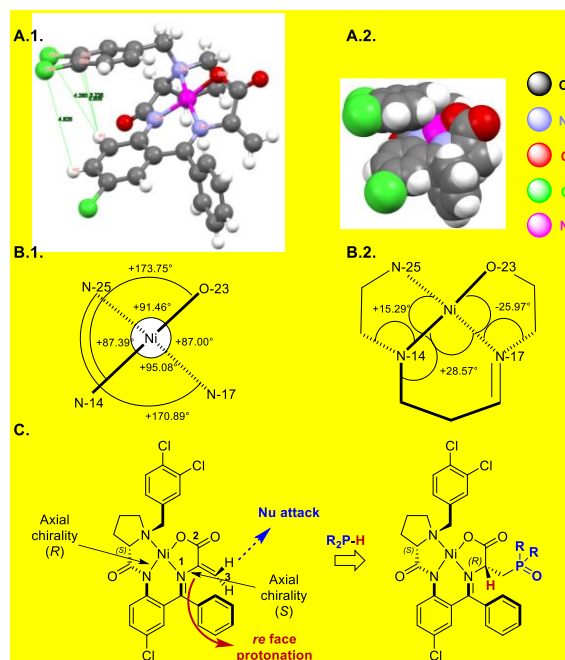
Taking advantage of the high crystallinity of the aminophosphonate derivative (*R*)-**4k**, single crystals were then grown from a solution in dichloromethane at ambient temperature to allow absolute configuration determination of compound (*R*)-**4k** by X-ray spectroscopy (SI) (CCDC 2036930).



**Scheme 3.** Asymmetric Synthesis of Compounds (*R*)-**4a** and (*R*)-**4k** Through Disassembly of Chiral Complex (*S,R*)-**3a** and (*S,R*)-**3k**.

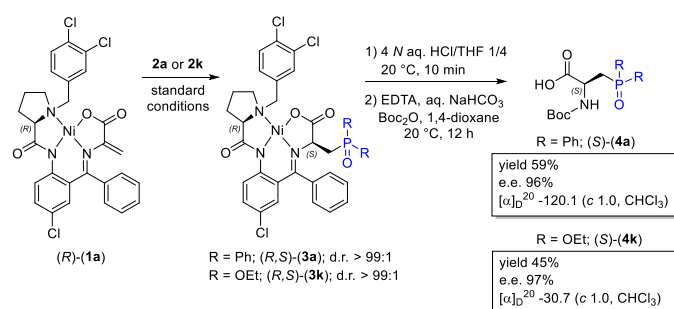
It is interesting to note that this stereochemical outcome could be reasonably rationalized from the crystallographic structure analysis of the Ni(II) complex of the Schiff base of dehydroalanine (*S*)-**1a**. Indeed, as outlined in Figure 2 and the SI, (*S*)-**1a** provides optimal parallel displaced type of aromatic interactions between the *o*-amino-benzophenone moiety, featuring a *p*-chlorine atom, and the Pro *N*-benzyl ring (Fig. 2. A.1. and 2.A.2.). We have observed similar results from the crystallographic analysis of the corresponding Gly Ni(II) complex.<sup>17</sup> These interactions can be defined as a mixed case of

parallel displaced and T-shaped or edge-to-face electrostatic aromatic interactions. This striking evidence has hence a strong impact on the stereochemistry of the chelate rings around the Ni(II), which accordingly adopt bent structures (Fig. 2.B.1. and 2.B.2.) and an axial chirality along the Ni-N (Schiff base) and Ni-N (amide) bonds.



**Figure 2.** Data on dehydroAla Schiff base complex (*S*)-**1a**: **A.1.** Ball and stick crystallographic structure; **A.2.** Spacefill crystallographic structure; **B.1.** Deviation from the planarity of the Ni(II) coordination sphere. **B.2.** Dihedral angles of the chelate rings around the Ni(II). **C.** Axial chirality of the chelate rings and rationale for the scalemic formation of β-phosphorus adducts.

The absolute configuration of these chiral axes is relayed to the 3D rearrangement of the phenyl group and thus to the way of pyramidalization and of protonation (i.e., by the *re* face) of the forthcoming chiral carbon atom (Fig. 2.C.).



**Scheme 4.** Asymmetric Synthesis of Amino Acid Derivatives (*S*)-**4a** and (*S*)-**4k**.

Remarkably, the asymmetric synthesis of the opposite enantiomers (*S*)-**4a** and (*S*)-**4k** was also smoothly achieved (see scheme 4) starting from the Ni(II) complex of the Schiff base of dehydroalanine (*R*)-**1a** using standard conditions. The *entero* derivatives (*S*)-**4a** and (*S*)-**4k** were obtained with the same stereoselectivities and similar overall yields (Scheme 4).

In summary, we have achieved a general and new asymmetric approach for the synthesis of the two enantiomers of  $\beta$ -phosphorus-containing  $\alpha$ -amino acids. The key steps involve first a phospho-Michael addition of either a secondary phosphine oxides or dialkyl phosphites in the presence of a soft basic catalyst to chiral Ni(II)-complexes of dehydroalanine Schiff base leading to the corresponding Schiff base products with a high diastereomeric ratio followed by disassembly and then reconstruction of the chiral Ni(II)-platform. Given the importance of  $\beta$ -phosphono  $\alpha$ -amino acids, and the lack of (catalytic) synthetic approaches that have been reported so far, this protocol appears as a method of choice for the preparation of tailor-made enantiopure  $\alpha$ -amino acids. Further studies on the use of the chiral auxiliary in diverse reactions are currently in progress.

### Conflicts of interest

There are no conflicts to declare.

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