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Tetrahedron Letters 44 (2003) 6469–6473

TETRAHEDRON LETTERS

# Two-fold amino acid-based chiral aminophosphine–oxazolines and use in asymmetric allylic alkylation

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Received 11 April 2003; revised 23 June 2003; accepted 23 June 2003

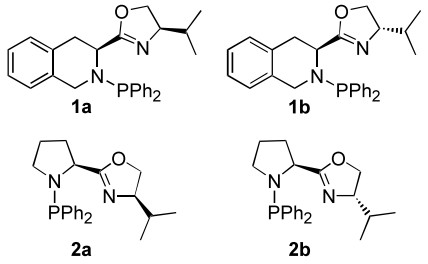
**Abstract**—Chiral aminophosphine–oxazoline ligands derived from two different amino acids (tetrahydroisoquinoline carboxylic acid and proline) have been synthesized and examined as chiral auxiliaries in asymmetric allylic alkylation of three substrates. Stereoisomers **1a** and **2a** are providing the highest enantioselectivities (up to 94% ee) in the allylation of diphenylpropenyl acetate.


Chiral auxiliaries have become key components in a great number of catalyzed enantioselective transformations.[1] As such, phosphorous-based chiral ligands are extremely versatile and have shown stupendous properties in many catalytic reactions.[1] Lately, the chemistry of *P*,*N*-bidentate hybrid ligands has evolved considerably since the original examples reported at the same time by Helmchen,[2] Pfaltz[3] and Williams.[4] This new class of ligands is important in the development of asymmetric catalysis as these auxiliaries have induced high enantiodifferenciations in many reactions including allylation, Heck coupling and other important transformations.[5] Structurally, these auxiliaries are often related to phosphine–oxazolines[5,6] where the chirality is located in the oxazoline moiety, the latter being constructed from chiral natural amino alcohols. Contributions describing *P*-oxazolines containing *P*-heteroatom residues have appeared more scarcely even though the corresponding auxiliaries show equally significant properties.[7–9]

As part of our ongoing exploration of various synthetic approaches to new ligands, we have been using the chiral pool, i.e. amino acids, for the synthesis of aminophosphine–phosphinite ligands and focused on their properties in asymmetric catalysis.[10] The cyclic amino acid-based ligands proved to be the most appropriate for highly enantioselective hydrogenations of ketones.[11] Thus, we sought to use such chiral cyclic amino acids in association with an optically pure amino alcohol to access other types of aminophosphine–oxazoline architectures. During our preliminary study, Gilbertson reported the first efficient ligands of that family where a proline provided the aminophosphine extremity.[12]

Herein we report on our first results on the synthesis of aminophosphine–oxazolines and on their use in asymmetric allylic alkylation.

The aminophosphine–oxazoline ligands **1a** and **1b**, based on tetrahydroisoquinoline carboxylic acid, and **2a** and **2b**, based on proline (Scheme 1),[12] have been synthesized from the corresponding amino acids. Thus, commercial (*S*)-1,2,3,4-tetrahydroisoquinoline carboxylic acid has been first converted into its methyl ester **3**-Q using standard procedures. The following step consisted of preparing the protected aminophosphine residues (Scheme 2). As a matter of fact, among the several pathways which can be considered for the synthesis of the target auxiliaries, it appeared that the most efficient method consisted of preparing the aminophosphine moiety, as a protected unit, in the beginning of the synthesis. We have investigated two protection modes of the phosphorous, i.e. the sulfide and the oxide. The possible phosphinoborane methodology[13]




**Scheme 1.**

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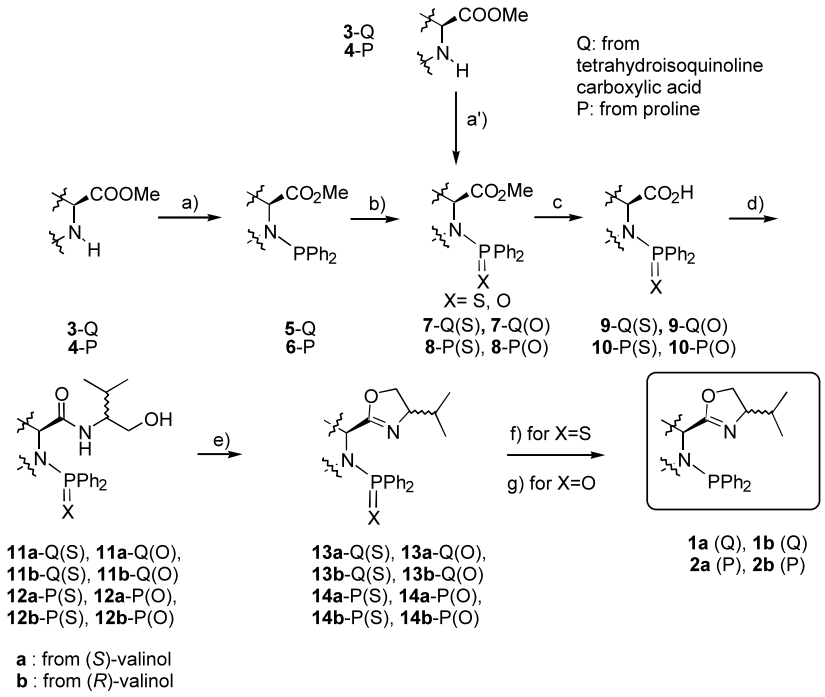
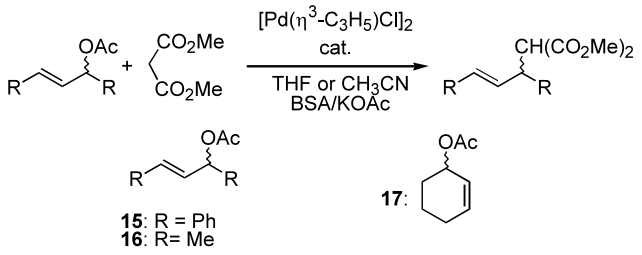
doi:10.1016/S0040-4039(03)01561-2




**Scheme 2.** *Reagents and conditions*: (a) $ClPPh_2$, $NEt_3$, THF, 40°C, 12 h (90%); (a′) $ClP(O)Ph_2$, $NEt_3$, THF (96%); (b) $S_8$, toluene, rt, 1 h (85%); (c) LiOH, MeOH, reflux, 24 h (90%); (d) (*S*)- or (*R*)-valinol, BOP, $NEt_3$, MeCN (99%); (e) *p*-TsCl, DMAP, $CH_2Cl_2$ (90%); (f) Ni Raney, MeCN (95%); (g) $HSiCl_3$, $NEt_3$ (50%).

has not been retained for this study because of the basic conditions required by the following steps of the synthesis which would probably lead to a decomplexation of the $BH_3$ unit from the '$P{\cdot}BH_3$' moiety of the protected intermediate. Thus, the sulfide is obtained in two steps. The intermediate amino–phosphines **5**-Q and **6**-P are prepared via phosphinylation of the esters **3**-Q and **4**-P and then reacted with sulfur providing the P(S) intermediate **7**-Q(S) and **8**-P(S). On the other side, the two esters **5**-Q and **6**-P can be reacted easily with $ClP(O)Ph_2$ providing the corresponding P(O) derivatives **7**-Q(O) and **8**-P(O). Even if the four isolated P(V) residues have been used successfully for the whole synthesis, the sulfide appeared more convenient because of an easier isolation procedure from the final step of the synthesis (vide infra). The acids **9**-Q(S), **9**-Q(O), **10**-P(S), and **10**-P(O) were obtained through hydrolysis of the corresponding esters. Then, a standard peptide coupling[14] between **9**-Q(S), **9**-Q(O), **10**-P(S), and **10**-P(O) and both enantiomers of valinol provided, quantitatively after workup, the phosphine–sulfide and phosphine–oxide amidoalcohols **11a**-Q(S) and **11a**-Q(O), **12a**-P(S), and **12a**-P(O) (from (*S*)-valinol) and **11b**-Q(S) and **11b**-Q(O), **12b**-P(S), and **12b**-P(O) (from (*R*)-valinol). The oxazoline-based compounds **13a**-Q(S), **13a**-Q(O), **13b**-Q(S), **13b**-Q(O), **14a**-P(S), **14a**-P(O), **14b**-P(S), and **14b**-P(O) were reached conveniently via cyclization of the amidoalcohols in the presence of *p*-tosylchloride under basic conditions and isolated in high yields.[15] Finally, the amino–phosphine residues were recovered from **13a**-Q(S), **13b**-Q(S), **14a**-P(S), and **14b**-P(S) through reduction with Ni Raney in acetonitrile providing **1a**, **1b**, **2a**, and **2b** in ca. 95% yield.[16] The phosphine–oxide oxazolines were transformed into the corresponding phosphine–oxazolines **1a**, **1b**, **2a**, and **2b** in the presence of trichlorosilane/$NEt_3$ in toluene.[17,18] The products were isolated in ca. 50% yield. The overall yield of the synthesis of the chiral auxiliaries through the sulfide route starting from the amino ester is 58% which is somewhat higher than the ca. 39% yield obtained while following the oxyde route. Nevertheless, the latter can be applied to the synthesis of new ligands bearing a stereogenic phosphorous atom which can be recovered by a stereoselective reduction.[17] All new compounds have been fully characterized and exhibit classical spectroscopic features.[19]

Asymmmetric allylic alkylation is a standard model reaction for the assessment of new ligands in C–C forming reactions. In order to evaluate these ligands, three substrates (**15**–**17**) have been selected for this initial study (Scheme 3). The precatalysts were obtained by reaction of the chloroallylpalladium dimer with the chosen ligands in the solvent used for catalysis (THF and MeCN).[20]




**Scheme 3.**

For the transformation of 1,3-diphenyl allyl acetate **15**, the solvent had no significant effect on the selectivity of the reaction (Table 1, entries 1–5) as ca. 90% ee or higher were obtained in either acetonitrile or tetrahydrofuran. For the substitution of substrates **15** and **16**, ligands **1a** and **2a** exhibit identical properties (entries 1–8 and 11). For the allylation of **15**, a lowering of the temperature led to a smaller decrease of the enantioselectivity in the presence of **1a** ($\Delta ee = 3\%$) compared to **2a** ($\Delta ee = 7\%$) (entries 3/4 and 11/12). Conversely, an increase of 8% ee was obtained while lowering the temperature during the allylation of **16** in the presence of both chiral auxiliaries **1a** and **2a** (entries 14/15 and 17/18). We could notice that a substrate to catalyst ratio increase to 1000/1 yielded a total transformation within non optimized 65 h with no loss of the enantioselectivity in acetonitrile (entries 2/6). However, a small erosion of the ee occurred in THF (entries 3/8). The steric course of the reaction was different for the diastereomeric pair **1a**/**1b** compared to the pair **2a**/**2b**. As a matter of fact, the two diastereomers **1a** and **1b** are providing both antipodes of the allylation product of **15** with a high level of enantioselectivity. Actually, 78% ee of the (*S*) enantiomer are achieved in the presence of **1b** and 90% ee of the (*R*) product with **1a**. The contribution of **2b** resulted in the production of the (*S*) enantiomer in 22% ee while **2a** gave the (*R*) enantiomer in 94% ee. We think that the chiral auxiliary remains coordinated in a chelate fashion and the allyl residue in a $\eta^3$ mode and that the chlorine atom initially present on the palladium complex does not stay on the metal during the enantioselective step of the process.[21] As a matter of fact, allylic alkylations carried out in the presence of either [Pd(allyl)(**1a**)]$PF_6$ or a combination of $Pd_2dba_3$ and the **1a** ligand are providing enantioselectivities within a ±2% ee of the value given here (entry 3). As reported, the allylic palladium catalytic intermediate exists as two diastereoisomers designated *exo* and *endo*. The addition of a nucleophile on such species can, in theory, follow four pathways arising from a reaction on the two allylic C termini of the two diastereomers. In practice, with *P*,*N* type ligands, it has been proposed that the nucleophile adds preferentially *trans* to the phosphorous. Indeed, the stereoelectronic '*trans*-influence' dictates that the allylic carbon *trans* to the *P*-atom is more electrophylic than the *C*-allylic terminus *trans* to the *N*-atom.[22] The observed major *R* diphenyl product arises from the nucleophilic addition *trans* to *P*,*N* on the *exo* allylic intermediate. In theory, if a similar addition pathway is applied to the corresponding dimethyl allylic diastereomer, the antipode product is obtained.[23] In practice, this is effectively observed in the presence of **1a** for the allylation of **15** and **16** (entries 3 and 14). The chirality of the oxazoline moiety orients the enantiodifferenciation of the addition to **15**. Interestingly, the match/mismatch behavior which could be expected from the diastereomeric pair **1a**/**1b** is not observed as both auxiliaries are providing high ee's into each product antipode. The flexibility of the six membered cycle of ligands **1a** and **1b** is capable of providing equally favored conformations able to induce high enantiodifferenciations in either enantiomer of the product. Conversely, the pair **2a**/**2b** is exhibiting a

**Table 1.** Palladium-catalysed asymmetric allylic allylation[a]

| Entry | Substrate | Ligand | Solvent | Co-catalyst | S/Pd | Time (h) | Temp. (°C) | Conv. (%)[b] | Ee (%) (config.)[c] |
|---|---|---|---|---|---|---|---|---|---|
| 1 | **15** | **1a** | MeCN | KOAc stoich. | 100 | 3 | 20 | 91 | 89 (*R*) |
| 2 | | **1a** | MeCN | KOAc 10% | 100 | 4 | 20 | 100 | 90 (*R*) |
| 3 | | **1a** | THF | KOAc 10% | 100 | 18 | 20 | 100 | 93 (*R*) |
| 4 | | **1a** | THF | KOAc 10% | 100 | 18 | 0 | 100 | 90 (*R*) |
| 5 | | **1a** | MeCN | $Bu_4N^+$ 10% | 100 | 3.75 | 20 | 73 | 90 (*R*) |
| 6 | | **1a** | MeCN | KOAc 10% | 1000 | 18 | 20 | 100 | 90 (*R*) |
| 7 | | **1a** | THF | KOAc 10% | 1000 | 18 | 20 | 100 | 88 (*R*) |
| 8 | | **1a** | THF | KOAc 10% | 1000 | 65 | 0 | 100 | 87 (*R*) |
| 9 | | **1b** | THF | KOAc 10% | 250 | 5.5 | 20 | 97 | 77 (*S*) |
| 10 | | **1b** | MeCN | KOAc 10% | 100 | 18 | 20 | 98 | 78 (*S*) |
| 11 | | **2a** | THF | KOAc 10% | 50 | 18 | 20 | 100 | 94 (*R*) |
| 12 | | **2a** | THF | KOAc 10% | 100 | 18 | 0 | 100 | 87 (*R*) |
| 13 | | **2b** | THF | KOAc 10% | 100 | 18 | 0 | 100 | 22 (*S*) |
| 14 | **16** | **1a** | THF | KOAc 10% | 100 | 18 | 20 | 77 | 39[b] (*S*) |
| 15 | | **1a** | THF | KOAc 10% | 100 | 65 | 0 | 100 | 47 (*S*) |
| 16 | | **1b** | THF | KOAc 10% | 100 | 18 | 20 | 90 | 25[b] (*S*) |
| 17 | | **2a** | THF | KOAc 10% | 100 | 18 | 20 | 100 | 37[b] (*S*) |
| 18 | | **2a** | THF | KOAc 10% | 100 | 18 | 0 | 100 | 45 (*S*) |
| 19 | | **2b** | THF | KOAc 10% | 100 | 18 | 0 | 100 | 5[b] (*S*) |
| 20 | **17** | **1a** | THF | KOAc 10% | 100 | 18 | 20 | 100 | <5[c] (n.d.) |
| 21 | | **2a** | THF | KOAc 10% | 100 | 18 | 20 | 100 | <5[c] (n.d.) |

[a] The catalytic reactions were carried out in the presence of a ligand/Pd ratio = 1.2 under the conditions mentioned in Table 1.

[b] The conversions were determined by $^1H$ NMR on the crude reaction mixture through integration of the methyl residues.

[c] Enantiomeric ratios were determined by HPLC on Chiralpak AD, hexane/isopropyl alcohol = 9/1 for **15**, by NMR spectroscopy using the [Eu(hfc)] shift reagent for **16** and **17**.

match/mismatch behavior (entries 12/13). As well, the same antipode is produced with both diastereomers **1a** and **1b** during the allylation of **16**. Finally, the transformation of the cyclic substrate **17** is occurring with a very low enantioselectivity.

In summary, chiral aminophosphine–oxazoline auxiliaries are easily accessible from natural amino acids and alcohols. The two phosphorous atom protection modes utilized constitute valuable tools for the synthesis of such auxiliaries even those possessing a stereogenic phosphorous atom. The auxiliaries described are efficient in the alkylation of diphenyl allyl acetate. Even if the selectivity is lower with other substrates, it compares well to other systems described. Other ligands of that family and their use in enantioselective transformations will be reported soon.

## Acknowledgements

We thank Professor A. Mortreux and Dr. Lydie Pélinski for fruitful discussions. We also thank Nadia Djelassi for some experiments. We are grateful to CNRS for financial support. C.B. acknowledges MEN for a doctoral fellowship.

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18. The origin of the yield loss experienced during the reduction of the P=O moiety is linked to the purification procedure. Actually, the necessary filtration over silica gel had to be carried out under basic conditions (silica gel washed with $NEt_3$) in order to avoid a cleavage of the P–N bond, the latter being sensitive to the acidic medium produced by the hydrolysis of the excess of $HSiCl_3$ on the silica gel.
19. **1a**: $^1$H NMR (300 MHz, toluene-$d_8$): $\delta$ 0.53 (d, $J=6.8$ Hz, 3H, $CH_3$); 0.59 (d, $J=6.8$ Hz, 3H, $CH_3$); 1.25 (br. hept., $J=6.8$ Hz, 1H, C*H*$(CH_3)_2$); 3.07 (dd, $J=15.9$ and 5.9 Hz, 1H, ArC*H*$_{trans}$CH$_{cis}$CHN); 3.20 (d, $J=16.0$ Hz, 1H, ArCH$_{trans}$C*H*$_{cis}$CHN); 3.45 (m, 2H, C*H*$_2$-O); 3.66 (dd., $J=6.7$ and 7.9 Hz, 1H, NC*H*CH$_2$O); 4.05 (d, $J=$ 16.4 Hz, 1H, ArC*H*H′N); 4.43 (d, $J=16.1$, 1H, ArCH*H*′N); 4.57 (br. t, $J=6.4$ Hz, 1H, C*H*NP); 6.88 (m, 3H, H$_{arom.}$); 6.97–7.13 (m, 7H, H$_{arom.}$); 7.46 (m, 2H, H$_{arom.}$); 7.88 (m, 2H, H$_{arom.}$). $^{31}$P{$^1$H} NMR (121.5 MHz, $CDCl_3$): $\delta$ 64.6 ppm (s).
**2a**: $^1$H NMR (300 MHz, $C_6D_6$): $\delta$ 0.74 (d, $J=6.7$ Hz, 3H, $CH_3$); 0.81 (d, $J=6.7$ Hz, 3H, $CH_3$); 1.36 (m, 1H, C*H*HCH$_2$CH); 1.53 (br. sept., $J=6.6$ Hz, 1H, C*H*$(CH_3)_2$); 1.80 (m, 2H, CH*H*-C*H*HCH); 1.96 (m, 1H, CH*H*-CH); 2.74 (m, 2H, C*H*HN); 3.12 (m, 2H, CH*H*-N); 3.66 (m, 2H, C*H*$_2$O); 3.82 (dd, $J=5.7$ and 7.6 Hz, 1H, NC*H*-CH$_2$O); 4.66 (m, 1H, C*H*); 7.27–7.39 (m, 6H, H$_{arom.}$); 7.93–8.02 (m, 4H, H$_{arom.}$). $^{31}$P{$^1$H} NMR (121.5 MHz, $C_6D_6$): $\delta$ 48.1 ppm (s).
20. *General procedure for the allylic alkylation*: Under nitrogen, in a 100 mL Schlenk tube equiped with a stir bar, the aminophosphine oxazoline and [Pd($\eta^3$-$C_3H_5$)Cl]$_2$ (0.45 equiv.) are reacted in a freshly distilled and degassed solvent. Then, 1,3-diphenyl allyl acetate (100 equiv.) is added to the solution and the mixture is stirred at room temperature for 1 h. In a separate Schlenk tube, a mixture of dimethyl malonate and BSA (both as 3 equiv. with respect to the allylic substrate) and KOAc (catalytic amount) in 3 mL of the solvent is prepared.

This mixture is added dropwise to the catalytic solution. At the end, the reaction mixture was diluted with diethyl ether and quenched by saturated sodium hydrogenocarbonate. The product was extracted with diethyl ether, the organic phase is washed with brine and dried over magnesium sulfate. After filtration and evaporation under reduced pressure, a white solid was isolated in 95% yield. The enantiomeric excess was determined by HPLC using a Chiralpak AD column (*i*PrOH/hexane: 10/90; flow rate: 1 mL/min; detection UV at 254 nm; $t_R(R)=8.4$ min, $t_R(S)=11.6$ min).

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23. Even if the product antipodes are produced depending on the substrate, there is no change of the descriptor of the absolute configuration.