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Alternative synthesis of α-substituted β-amidophosphines by [1,4]-addition. A new route to chiral ligands

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Abstract—Phosphine–borane can be diastereoselectively added to chiral α,β-unsaturated amides **3**, using amino-alcohols as chiral inducers, leading to α-substituted β-amidophosphine boranes **4** with up to 74% diastereomeric excess. Selective deprotection afforded optically pure carboxylic derivatives **5** which are key intermediates for the synthesis of various potential chiral ligands for asymmetric catalysis. © 2002 Published by Elsevier Science Ltd.

1. Introduction

All phosphorus containing ligands employed in asymmetric catalysis[1] can be classified into two types depending on the location of the stereogenic information, which may be found on the phosphorus atom (DIPAMP[2]) or on a side chain. For the latter case, the chirality can be carbon centered (VALAP,[3] CHIRAPHOS[4]) or of axial type (BINAP[5]).

When the chirality is carbon centered, most of the ligands in frequent use are derived from amino acids or from the chiral pool,[6] which limits their structural diversity. To the best of our knowledge, very few of them were obtained by creation of a stereogenic center. In the rare examples, their syntheses are based or on racemic starting materials, and need a difficult resolution[7] (Fig. 1: Minami and Gilbertson's ligands) or on a enantioselective synthesis[8] (Fig. 1: Kobayashi's ligands).

The development of new asymmetric phosphine ligands is of great interest. Since the phosphorus atom is directly associated with the transition metal in the catalytic species, the creation of the chiral center at the neighboring α-position is particularly apt to enhance facial discrimination and thus lead to improved level of enantioselectivity.

For this reason, we became interested in the synthesis of new potential ligands possessing a stereogenic center at the α-position to the phosphorus atom. In a previous paper,[9] we described a diastereoselective alkylation process to access compound **1** (d.e. up to 72%), a key intermediate for the synthesis of a broad range of chiral ligands via acid **2** (Scheme 1). A disadvantage of this approach is the limited number of suitable electrophiles. Indeed, several important α-substituents such as ethyl, isopropyl or aryl (which are needed for mechanistic studies of asymmetric catalysis) cannot be introduced in this way.

In this paper, we wish to report alternative and complementary routes to chiral α-substituted β-amidophosphines.

In the course of our study on the synthesis of chiral amidophosphonates[10] we described a diastereoselective version of one of the most versatile pathways for the formation of carbon phosphorus bonds, namely, the Pudovik reaction.[11] This reaction involves the addition of compounds containing a labile P–H bond to α,β-unsaturated optically active amides, providing an easy access to the biologically-interesting α-substituted β-amidophosphonates. Therefore, we decided to apply this methodology to the synthesis of chiral phosphines.

Keywords: diastereoselective Michael addition; chiral ligands; asymmetric catalysis.

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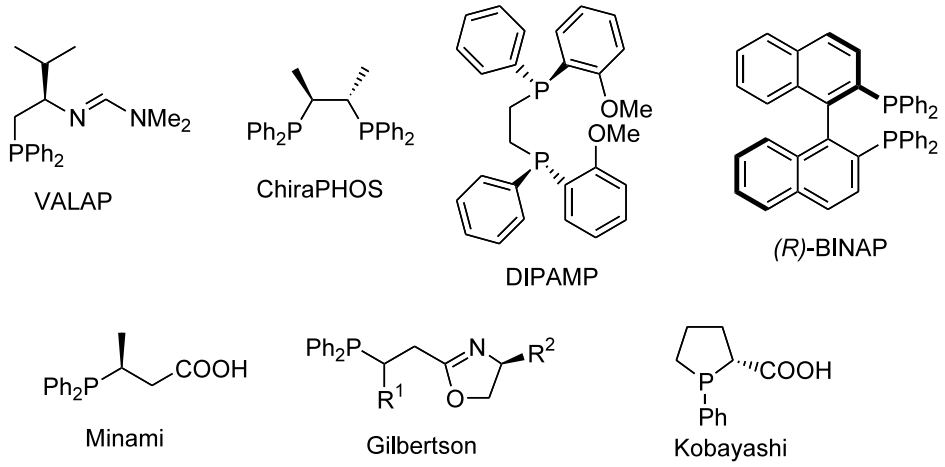
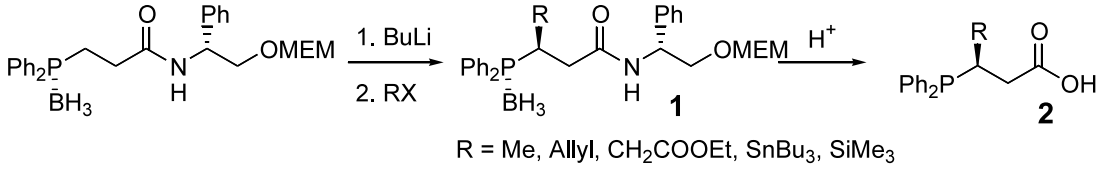


Figure 1.



Scheme 1.

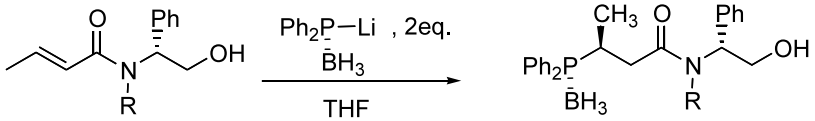
2. Results and discussion

In a first attempt we investigated the influence of the substituent on the nitrogen atom. Secondary and tertiary chiral crotonyl amides **3a**–**c** derived from *O*-unprotected-(*R*)-phenylglycinol were subjected to the conditions already optimized for the phosphonate series[10] (i.e. addition at low temperature of the crotonyl amide to a solution of the lithium salt of diphenylphosphine–borane in THF previously formed at 0°C over 30 min by action of butyllithium on diphenylphosphine borane). The Michael adducts **4a**–**c** were obtained in good yields. Surprisingly, contrary to the phosphonate series, the best diastereoselectivity was obtained with secondary amide **3a** with a 68% d.e. (Table 1, entry 1) whereas, with tertiary amides **3b** and **3c**, the d.e. never exceeded 48%. The sodium salt of diphenylphosphine–borane was also prepared and subjected to the 1,4-addition conditions above, but this led to products with much lower d.e.

We then turned our attention to the influence of the chiral auxiliary (Table 2). A series of chiral amines were used to prepare crotonyl amides **3d**–**f** which were employed in a Michael addition reaction with the diphenylphosphine–borane anion.

With aminoalcohol as chiral auxiliary (entries 1 and 2), the diastereoselection was reasonable, the best d.e. of 68% being observed with phenylglycinol (entry 1). However, introduction of a substituent α to the oxygen atom of the aminoalcohol dramatically decreased the

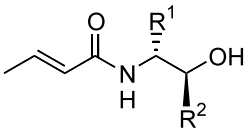
Table 1. Diastereoselective 1,4-addition of diphenylphosphine–borane to crotonyl amides **3a**–**c**



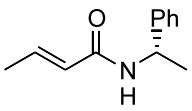
Entry	Amide	Product (yield %)[a]	% d.e.[b]
1	**3a**	**4a** (61)	68
2	**3b**	**4b** (62)	48
3	**3c**	**4c** (66)	20

[a] Isolated yield.
[b] Measured on the crude product by ^{31}P NMR.

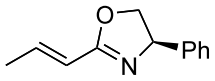
Table 2. Diastereoselective 1,4-addition of diphenylphosphine–borane to crotonyl amides **3d–g**: influence of the chiral auxiliary



3d : R^1=Et; R^2=H
3e : R^1=Me; R^2=Ph



3f

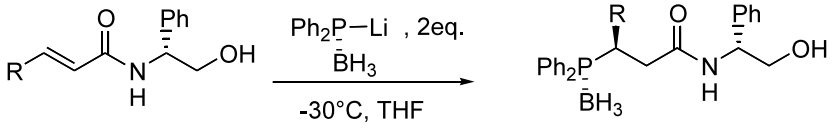


3g

Entry	Amide	Product (yield %)[a]	% d.e.[b]
1	**3a**	**4a** (61)	68
2	**3d**	**4d** (55)	60
3	**3e**	**4e** (69)	30
4	**3f**	**4f** (88)	7
5	**3g**	–	–

[a] Isolated yield.
[b] Measured on the crude product by ^{31}P NMR or by HPLC (column: Omnispher 10C18 250×4.6 mm).

Table 3. Diastereoselective 1,4-addition of diphenylphosphine–borane to crotonyl amides **3h–j**: influence of the β-substituent[12]



3h : R=Et
3i : R=*i*-Pr
3j : R=Ph

4h-j

Entry	Amide	Product (yield %)[a]	% d.e.[b]
1	**3h**	**4h** (62)	74
2	**3i**	**4i** (75)	64
3	**3j**	**4j** (76)	45

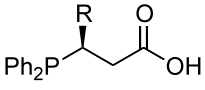
[a] Isolated yield.
[b] Measured on the crude product by ^{31}P NMR or by HPLC (column: Omnispher 10C18 250×4.6 mm).

diastereoselectivity (entry 3). The same results were observed when α-methylbenzylamine was used (entry 4), confirming that the presence of a free hydroxy group is necessary for high diastereoselection.[10] In all cases where oxazoline **3g** was used as chiral inductor, no Michael adducts were observed. The effect of temperature on the crotonyl amide addition reaction was then investigated. Temperatures between −85 and 0°C were assayed; the best result was obtained at −30°C with a yield of 61% and a diastereomeric excess of 68%. At lower or higher temperatures, the d.e. dropped. An exception was observed at −85°C, where we observed almost the same d.e. as that achieved at −30°C, but only after 4 days, and with a lower yield.

To evaluate the scope of the reaction, we then studied the influence of the double bond substituent on the diastereoselectivity. Unsaturated amides derived from (*R*)-phenylglycinol were prepared by condensation with the corresponding acyl chlorides. The results of Michael addition are given in Table 3.

All of these Michael additions proceeded in relatively good yields and gave moderate to good diastereoselectivities. Moreover, the diastereomers can be separated by simple column chromatography (**4j**) or by C18-HPLC (**4a**, **4h**, **4i**). The removal of the chiral auxiliary can be readily achieved by acidic treatment[9] to give phosphine–acid **5** in good yield (Fig. 2). The enantiomers can also be separated, at that stage, by chiral HPLC (column: CHIRALCEL® AD-H 5 μm 250×4.6 mm).

To determine the absolute configuration of the newly created chiral center, we compared the optical rotation of an enriched solution of the major isomer of **4a**



5

Figure 2.

obtained from 1,4-addition with an enantiomerically pure solution of **4a** obtained from diastereoselective alkylation process, which indicated an (*S*) configuration for the created center. This result is in accordance with those in the phosphonate series, but the relative configuration is opposite to the one observed by Mukaiyama and Brown for their 1,4-addition of alkyl- and aryl-magnesium bromides.[13]

In conclusion, a new and alternative asymmetric synthesis of substituted amidophosphines has been developed which allows the preparation of a large variety of functionalized derivatives. Particularly attractive is the possibility of gaining access to new substituted amidophosphines (for example with ethyl, *iso*-propyl and phenyl substituents) in enantiomerically pure form, which are not obtainable by diastereoselective alkylation. The carboxylic acid **5** as well as substituted amides **4a**, **4h**–**j** are potential chiral ligands and useful intermediates for the preparation of chiral catalysts. Their synthesis is currently being investigated and will be reported shortly.

Acknowledgements

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12. *Typical procedure for the 1,4-addition step. Synthesis of **4j***: Butyllithium in hexane (1.6 mL, 2.5 mmol) was added to a solution of diphenylphosphine borane (0.5 g, 2.5 mmol) in anhydrous THF (10 mL) under inert atmosphere at −78°C. The solution was warmed to 0°C. After stirring for 30 min at 0°C, the mixture was cooled to −30°C, and a solution of amide **3j** (0.33 g, 1.25 mmol) diluted in THF (1 mL), was added. After stirring for 4 h at −30°C, water (5 mL) was added, and the compound was extracted with dichloromethane (3×10 mL). The combined organic layers were dried over magnesium sulfate, filtered and concentrated. The crude mixture was purified by column chromatography on silica gel (EtOAc/cyclohexane 1/1) to provide **4j** (0.44 g) with 76% yield and 45% d.e.
Description of the major diastereomer obtained from flash chromatography: White powder; mp 146°C; $[\alpha]_D^{20}=+103$ (*c* 0.5, $CHCl_3$); ^1H NMR: δ 0.5–0.8 (m, 3H), 1.9 (s, 1H), 2.6–2.7 (m, 1H), 2.85–3.0 (m, 1H), 3.35–3.5 (m, 2H), 4.25–4.4 (m, 1H), 4.65–4.75 (m, 1H), 5.87 (d, 6.9, 1H), 6.9–7.7 (m, 20H); ^{31}P NMR: δ 24.4; ^{13}C NMR: δ 22.0, 38.3 (d, $J=5.7$ Hz), 40.0 (d, $J=33.7$ Hz), 48.9, 126.0–133.4, 135.5, 143.3, 169.7 (d, $J=16.0$ Hz); IR (neat): 3265, 2397, 1654, 1546, 1436, 1071–1040, 740–694 cm^{-1}. Anal. calcd for $C_{29}H_{31}BNO_2P$ (467.36): C, 74.53; H, 6.69; N, 3.00. Found: C, 74.21; H, 6.76; N, 2.94%.
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