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# Asymmetric synthesis of proline and pipecolic acid phosphorous analogues using enantioselective deprotonation–carboxylation reactions

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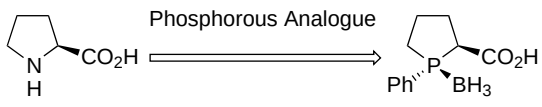
**Abstract**—The first synthesis of an optically active 1-phenylphospholane-2-carboxylic acid–borane complex and a 1-phenylphosphorinane-2-carboxylic acid–borane complex, which are proline and pipecolic acid phosphorous analogues, has been accomplished. The key to the synthesis is the enantioselective deprotonation accompanied with diastereoselective carboxylation. 

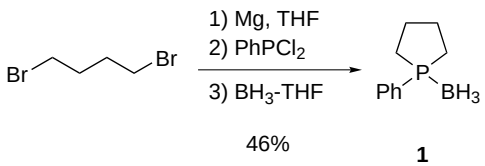
Catalytic asymmetric synthesis has been developed to meet the increasing need for optically active compounds, particularly biologically important chiral compounds in the pharmaceutical fields. In this area the development of new efficient chiral ligands for metal-catalyzed asymmetric reactions has received much attention.

On the other hand, chiral bidentate ligands derived from proline have been shown to be highly efficient ligands in many asymmetric reactions[1] and have revealed that the rigid bicyclo[3.3.0]systems created by the metal–ligand chelate complexes play very important roles for high enantioselectivity.[2] If the rigid bicyclo[3.3.0]systems were applied to transition metals (soft metals), the categories of applied asymmetric reactions are expected to spread widely. Therefore, we initiated investigation of the synthesis of proline phosphorous analogues and their application to transition metal-catalyzed asymmetric reactions. We herein report that the enantioselective synthesis of the proline phosphorous analogue using *sec*-butyllithium and (–)-sparteine has been achieved and that a pipecolic acid phosphorous analogue has also been synthesized.




Enantioselective deprotonation at the α-position of the phosphorous atom in phosphine–borane complexes[3] was examined as a synthetic strategy for the preparation of the proline phosphorous analogue. For the synthesis, it was also necessary to control diastereoselectivity of the stereogenic centers created at the α-position of the phosphorous atom and at the phosphorous atom itself.

The reaction of the 1,4-Grignard compound of 1,4-dibromobutane with dichlorophenylphosphine[4] followed by protection using borane–tetrahydrofuran[5] constituted 1-phenylphospholane–borane (**1**) (Scheme 1). The proline phosphorous analogue was synthesized by dry-ice quenching after the enantioselective deprotonation of **1** using *sec*-butyllithium and (–)-sparteine[6] as a chiral source. At this stage, it was found that a subtle difference in the reaction conditions drastically affected the enantioselectivity of the product. The effects of the reaction conditions of the enantioselective deprotonation using *sec*-butyllithium and (–)-sparteine are shown in Table 1.




**Scheme 1.**

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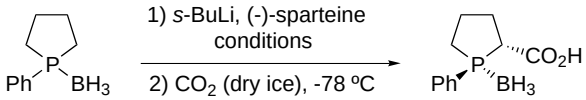
**Table 1.** Carboxylic acid formation via enantioselective deprotonation of **1**




**1** **2**

| Entry[a] | *s*-BuLi (equiv.) | (−)-Sparteine (equiv.) | Conditions | Yield (%) | *trans*/*cis*[d] | ee (%, *trans*)[e] |
|---|---|---|---|---|---|---|
| 1 | 1.0 | 1.0 | −78°C, 3 h | 24 | 3.0 | 83 |
| 2 | 1.5 | 1.5 | −78°C, 3 h | 62 | 2.2 | 32 |
| 3 | 1.5 | 1.5 | 0°C, 2 h | 76 | 1.5 | 34 |
| 4 | 1.5 | 1.5 | 0°C, 3 h | 59 | 1.5 | 55 |
| 5 | 1.5 | 1.5 | 0°C, 4 h | 48 | 1.6 | 85 |
| 6 | 1.5 | 1.5 | 0°C, 6 h | 45 | 1.5 | 87 |
| 7 | 1.5 | 1.5 | rt, 2 h | 41 | 2.0 | 92 |
| 8[b] | 1.2 | 1.2 | 0°C, 4 h | 52 | 3.1 | 75 |
| 9[c] | 1.0 | 1.0 | 25°C, 8 h | 55 | 4.0 | 92 |

[a] 0.50 mmol scale.
[b] 5.0 mmol scale.
[c] 25 mmol scale.
[d] Determined by $^1$H NMR analysis after conversion to the corresponding methyl ester by treatment with $TMSCHN_2$.
[e] Determined by chiral HPLC analysis on Chiracel AD after conversion to the corresponding methyl ester by treatment with $TMSCHN_2$.

As a result of optimization, use of equal equivalents of the substrate (**1**), *sec*-butyllithium, and (−)-sparteine showed high enantioselectivity[7] but low yield (entry 1), while excess use of *sec*-butyllithium showed high yield but low enantioselectivity (entry 2). It was revealed that excess use of *sec*-butyllithium at higher temperature improved the results. Thus, dry-ice quenching at −78°C after 1.5 equiv. of *sec*-butyllithium and (−)-sparteine were added and the mixture was stirred at 0°C for 4–6 h or at room temperature for 2 h achieved high enantioselectivity (entry 4–6). In a large-scale synthesis, on the other hand, the conditions optimized in the small-scale experiments did not satisfy enantioselectivity and minor tuning of the reaction conditions was needed (entries 8 and 9). In this case, the precise control of reaction temperature (25°C) was found to be effective, and satisfactory yield, diastereoselectivity, and enantioselectivity were obtained (entry 9).

The five-membered ring frame of 1-phenylphospholane–borane (**1**) was thought to be flip-flexible and the flexibility might induce low selectivity, while the six-membered ring flame was thought to be more rigidly stable due to a chair conformation. Therefore, we next decided to investigate enantioselective deprotonation of a six-membered ring system.

The synthesis of 1-phenylphosphorinane–borane (**3**) was related to that of **1**; namely, the reaction of the bis Grignard reagent of 1,5-dibromopentane with dichlorophenylphosphine[8] followed by protection using borane–tetrahydrofuran[5] gave **3** (Scheme 2).

As a result of optimization of the enantioselective deprotonation–carboxylation of **3** (Table 2), use of equal equivalents of the substrate (**3**), *sec*-butyllithium, and (−)-sparteine showed high enantioselectivity with a moderate yield (entry 1), while excess use of *sec*-butyllithium did not show significant decrease of the enantioselectivity, different from a similar reaction of **1**. Interestingly, diastereoselectivity was higher than that in the reaction of **1** as expected. Finally, in a 5 mmol-scale synthesis, high yield, diastereoselectivity, and enantioselectivity were obtained (entry 6).

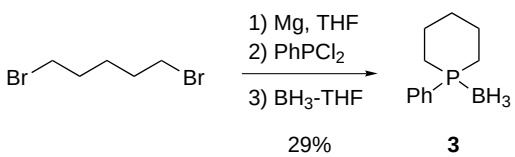
Direct recrystallization of the enantiomerically enriched products enhanced the enantiomeric excess and the diastereomer ratio (Scheme 3).

The absolute configurations of **2** and **4** were determined by X-ray analysis of the menthyl ester of **2** and the quinidine salt of **4**.

In conclusion, the first syntheses of 1-phenylphospholane-2-carboxylic acid–borane complex (**2**) and 1-phenylphosphorinane-2-carboxylic acid–borane complex (**4**), which are proline phosphorous and pipecolic acid phosphorous analogues, have been accomplished.[9] These compounds are expected to be important key skeletons for development of novel chiral phosphine ligands. Synthesis of these chiral ligands as well as their application to catalytic asymmetric synthesis are now in progress.

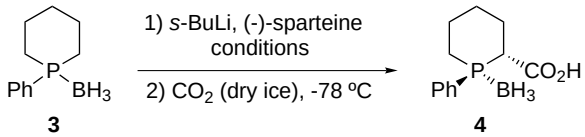
**Experimental procedure for the synthesis of 2:**

To a stirred solution of substrate **1** (4.5 g, 25 mmol) and (−)-sparteine (5.8 mL, 25 mmol) in ether (100 mL)




**Scheme 2.**

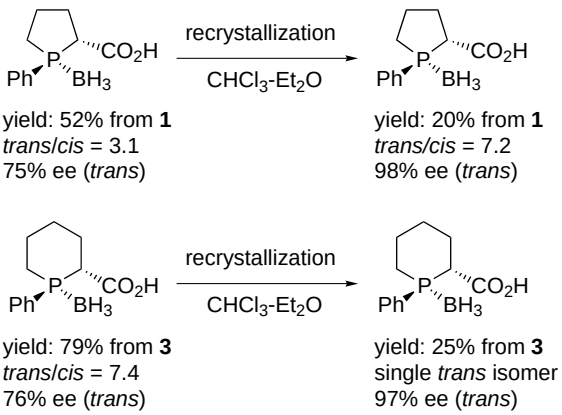
**Table 2.** Carboxylic acid formation via enantioselective deprotonation of **3**




**3** **4**

| Entry[a] | *s*-BuLi (equiv.) | (−)-Sparteine (equiv.) | Conditions | Yield (%) | *trans*/*cis*[c] | ee (%, *trans*)[d] |
|---|---|---|---|---|---|---|
| 1 | 1.0 | 1.0 | −78°C, 3 h | 40 | 18 | 90 |
| 2 | 3.0 | 1.5 | −78°C, 3 h | 64 | 14 | 81 |
| 3 | 1.5 | 1.5 | −78°C, 1 h | 65 | 7.1 | 80 |
| 4 | 1.5 | 1.5 | −78°C, 3 h | 57 | 36 | 83 |
| 5 | 1.5 | 1.5 | −78°C, 6 h | 36 | 8.1 | 89 |
| 6[b] | 1.2 | 1.2 | −78°C, 3 h | 79 | 7.4 | 76 |

[a] 0.50 mmol scale.
[b] 5.0 mmol scale.
[c] Determined by $^1$H NMR analysis after conversion to the corresponding methyl ester by treatment with $TMSCHN_2$.
[d] Determined by chiral HPLC analysis on Chiracel AD after conversion to the corresponding methyl ester by treatment with $TMSCHN_2$.




**Scheme 3.**

under argon atmosphere at room temperature was added a 1.0 M solution of *sec*-butyllithium in hexane (25 mL, 25 mmol), and the mixture was stirred at 25°C for 8 h. After cooling to −78°C, several pieces of dry ice were poured into the yellow suspension. After stirring for additional 30 min, the reaction mixture was allowed to warm to room temperature. White suspension of the mixture was acidified to <pH 4 with 1N aq. HCl, and the product was extracted with ethyl acetate. The extracts were dried over $Na_2SO_4$, filtered, and concentrated to give the crude product. Column chromatography on silica gel eluted with hexane/ethyl acetate (1/1) furnished the product as a white solid (3.03 g, 13.6 mmol, 55%); IR (KBr): 3396, 2936, 2376, 1704, 1420, 1335, 1297, 1248, 1219, 1069 $cm^{-1}$; $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ 03–1.3 (brq, $J=87$ Hz, 3H), 1.96–2.00 (m, 1H), 2.16–2.37 (m, 5H), 3.26–3.34 (m, 1H), 7.47–7.53 (m, 3H), 7.75–7.79 (m, 2H); $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta$ 26.2, 26.3, 29.9, 46.6, 129.1, 129.8, 131.4, 131.7, 175.4; $^{31}$P NMR (121 MHz, $CDCl_3$) $\delta$ 45.0; EI-MS *m*/*z*: 222 ($M-1^+$, 1%), 208 ($[M-BH_3]^+$, 100), 191 (16), 179 (16), 163 (72), 152 (33), 133 (30), 115 (17), 109 (79). Anal. calcd for $C_{31}H_{16}BO_2P$: C, 59.51; H, 7.26. Found: C, 59.29; H, 7.40%.

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