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# Pyridylseleno Group in Organic Synthesis. Part 7.[1] Asymmetric Reduction of (2-Pyridylseleno)methyl Aryl Ketones

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The reduction of (2-pyridylseleno)methyl aryl ketones using (−)-diisopinocamphenylchloroborane was found to produce *R*-1-aryl-2-(2-pyridylseleno)ethanols with satisfactory enantiomeric excesses.

KEY WORDS: Asymmetric reduction / 2-Pyridylseleno group / Chiral alcohol

We have already reported the difference in the nature of neighboring group participation by 2-pyridylseleno group and that by phenylseleno group.[1] Thus, we investigated the stereochemistry and observed the retention of configuration in the Ritter-type substitution of hydroxy group in chiral alcohol bearing 2-pyridylseleno group on $\beta$ carbon atom (through the neighboring group participation by 2-pyridylseleno group). On the other hand, racemic amide was produced in the similar reaction through the anchimeric assistance by phenylseleno group. For the synthesis of various kinds of optically active amides by this procedure, it is important to prepare chiral alcohols bearing 2-pyridylseleno group on $\beta$ carbon atom. However, the way to the chiral alcohols has so far been limited to the reaction of optically active oxiranes with sodium 2-pyridineselenolate. As another way to the chiral alcohols, we tried the asymmetric reduction of ketones bearing (2-pyridylseleno)methyl group. As a result, we found that the reduction of (2-pyridylseleno)methyl aryl ketones using (−)-diisopinocamphenylchloroborane (**4**) affords 1-aryl-2-(2-pyridylseleno)ethanols in moderate yields with satisfactory enantiomeric excesses. We describe herein the ditails of this reaction.

## Results and Discussions

(2-Pyridylseleno)methyl aryl ketones (**1**) were prepared from *para*-substituted acetophenone derivatives using the known procedrue[2] *via* enol silyl ethers (Scheme 1). (2-Pyridylseleno)methyl phenyl ketone (**1a**), thus prepared, was reduced to

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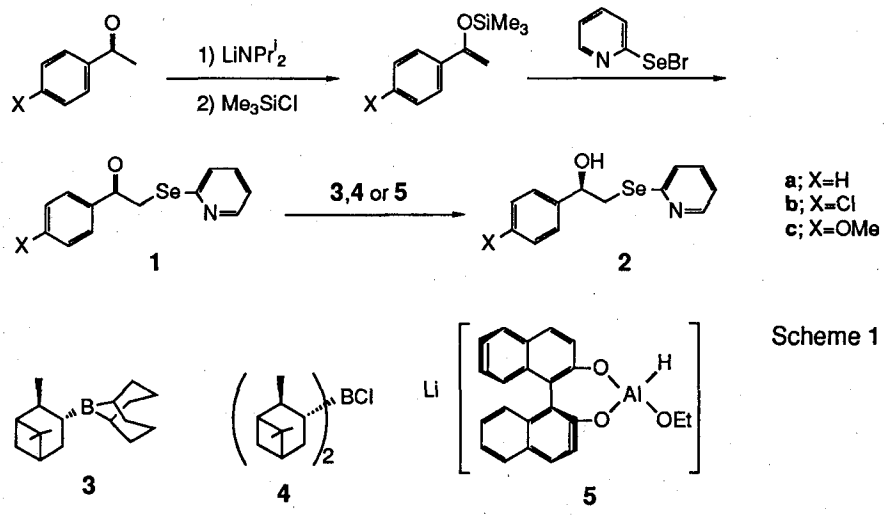
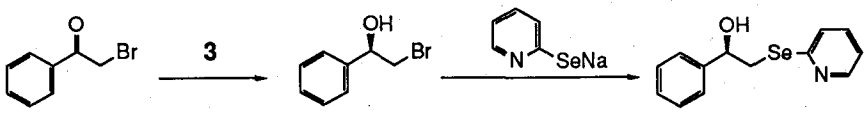



Table 1. Asymmetric Reduction of **1a** Using Various Reducing Agents.[a)]

| Entry | Reducing Agent (equivalent) | Solvent (ml) | Temp (℃) | Time (h) | **2a** Yield (%) | e. e. (%) | Configuration |
|---|---|---|---|---|---|---|---|
| 1 | **3** (2 eq.) | — | 25 | 120 | 41 | 88 | R |
| 2 | **4** (3 eq.) | THF (2.6) | −25 | 24 | 55 | 92 | R |
| 3 | **5** (3 eq.) | THF (18) | −78 | 3.5 | 78 | 41 | R |
| 4 | **5** (3 eq.) | THF (18) | −100 | 5 | 76 | 62 | R |

[a)] Carried out usimng **1a** (1 mmol).

the alcohol (**2a**) using various kinds of reducing agents, namely, (+)-*B*-pinan-3-yl-9-borabicyclo[3.3.1]nonane (**3**),[3)] (−)-diisopinocamphenylchloroborane (**4**),[4)] and (*S*)-binaphthol-modified lithium aluminum hydride reagent (**5**).[5)] The optical purities of the products were assayed by 200 MHz $^1$H NMR spectroscopy from the integrals of the proton geminal to the oxygen atom after conversion of the products to the diastereomeric (*S*)-2, 2, 2-trifluroro-1-methoxy-1-phenylpropanoates [(*S*)-MTPA esters].[6)] Typical results are summarized in Table 1. The reduction using **3** afforded the alcohol with satisfactory enantiomeric excess (88 %), but the reaction required long time in spite of the conditions without solvent. The reductions using **5** were carried out at low tempreatures (Entries 3 and 4). Although the alcohol was obtained in fairly good chemical yields, enantiomeric excess was not improved to satisfactory even by cooling to −100℃. The best result (92% e.e.) was obtained by the reduction using **4** under reasonable reaction conditions (Entry 2). In order to determine the absolute configuration of the products, we have carried out the reduction of phenacyl bromide using **3** which has been reported[3)] to give (*R*)-1-phenyl-2-bromoethanol. The replacement of the bromine atom by 2-pyridylseleno group afforded the authentic sample of (*R*)-1-phenyl-2-(2-pyridylseleno)ethanol (Scheme 2). By the comparison of the $^1$H NMR spectra of their (*S*)-MTPA esters,




Scheme 2

Table 2. Asymmetric Reduction of Various Ketones Using **4**.[a)]

| Entry | Ketone | Time (h) | **2** Product | **2** Yield (%) | e. e. (%) |
|---|---|---|---|---|---|
| 5 | **1a** | 7.5 | **2a** | 38 | 95 |
| 6 | **1a** | 24 | **2a** | 54 | 92 |
| 7 | **1b** | 24 | **2b** | 28 | 95 |
| 8 | **1c** | 42 | **2c** | 49 | 92 |

[a)] Carried out using **1** (1 mmol) and **4** (3 mmol) in THF (2.6ml) at -25℃.

all of the major isomers in Talbe 1 have been confirmed to have *R* configuration.

As we found that **4** is a suitable reducing agent for our substrate, we tried the reduction of other (2-pyridylseleno)methyl aryl ketones (**1**) using **4**. The results are summarized in Table 2. It has been reported[4)] that the reduction of acetophenone by **4** affords the alcohol in 72% yield after 7 h at − 25℃. As compared to this result, it is clear that the reductions were retarded considerably by the introduction of 2-pyridylseleno group into the methyl carbon (Entries 5 and 6). By the introduction of electron withdrawing or donating substituent into the phenyl ring (**1b** or **1c**), the reductions were further retarded to afford the alcohols only in moderate yields (Entries 7 and 8). However, the enantiomeric excesses were satisfactory for all substrates (>92 % e.e.) allowing the subsequent use of these alcohols as chiral source.

Thus, the asymmetric reduction usnig **4** of ketones bearing 2-pyridylseleno group on $\alpha$ carbon atom was shown to be a effective method for the preparation of optically active alcohols having 2-pyridylseleno group on $\beta$ carbon atom. The effects of electron donating or withdrawing substituent in the phenyl ring on the anchimeric assistance by the selenium atom are under investigation in our laboratory and will be reported in due course.

## Experimental

The IR spectra were taken with a JASCO IR-810 spectrometer. $^1$H NMR spectra were recorded with a Varian VXR-200 (200 MHz) instrument in $CDCl_3$ using TMS as internal standard.

**Materials.** Tetrahydrofuran (THF) and diethyl ether were dried over benzophenone ketyl and dichloromethane was dried over calcium hydride and they were distilled under nitrogen just before use. 2,2'-Dipyridyl diselenide[2)] and (*R*)-2,2,2-trifluoro-1-methoxy-1-phenylpropanoyl chloride[6)] were prepared according to

the reported procedures. (2-Pyridylseleno)methyl aryl ketones (**1**) were prepared by the reported procedure *via* enol silyl ethers.[2] (2-Pyridylseleno)methyl phenyl ketone (**1a**); pale yellow oil, $^1$H NMR $\delta$ 4.65 (s. 2H), 7.0-7.1 (m. 1H), 7.3-7.6 (m. 5H), 8.0-8.1 (m. 2H), and 8.4-8.5 (m. 1H): (2-Pyridylseleno)methyl 4-chlorophenyl ketone (**1b**); yellow oil, $^1$H NMR $\delta$ 4.58 (s. 2H), 6.9-7.1 (m. 1H), 7.2-7.6 (m. 2H), 7.34 (d. 2H, J=8.7 Hz), 7.94 (d. 2H, J=8.7 Hz), and 8.3-8.5 (m. 1H): (2-Pyridylseleno)methyl 4-methoxyphenyl ketone(**1c**); pale yellow oil, $^1$H NMR $\delta$ 3.85 (s. 3H), 4.60 (s. 2H), 6.90 (d. 2H, J=9.0 Hz), 7.0-7.1 (m. 1H), 7.3-7.6 (m. 2H), 8.02 (d. 2H, J = 9.0 Hz), and 8.4-8.5 (m. 1H). (+)-*B*-Pinan-3-yl-9-borabicyclo-[3.3.1]nonane (**3**) in THF (0.5 M) and (−)-diisopinocamphenylchloroborane (**4**) were commercially available and were used without further purification. All other organic materials were commercial products and were purified before use by distillation.

**Asymmetric Reduction of 1a by (+)-*B*-Pinan-3-yl-9-borabicyclo [3.3.1]-nonane (3).** Solvent was removed from the commercial solution of **3** in THF (0.5 M) (15 ml, 7.5 mmol) under nitrogen atmosphere. Thus prepared **3** was added to **1a** (0.99 g, 3.6 mmol) to afford two-layer (orange and colorless) mixture, which was stirred under nitrogen atmosphere at ambient temperature for 120 h. The mixture gradually turned to red-orange suspension. Acetaldehyde (0.6 ml, 11 mmol) was added to the suspension under ice-bath cooling and the resulting mixture was stirred for 20 min. Volatile compounds were removed from this mixture by heating at 60℃ under reduced pressure for 50 min. After cooling down, the residual oil was dissolved in diethyl ether (10 ml) and 2-aminoethanol (0.46 ml, 7.6 mmol) was added under ice bath cooling. The mixture was stirred for 15 min to form yellow precipitate. The precipitate was filtered and washed with cold ether (20 ml). The filtrate and washing were combined and washed with brine (5 ml×2), dried ($MgSO_4$), and evaporated *in vacuo* to leave red-orange oil. Column chromatography [silica gel, hexane-ethyl acetate (4 : 1) as eluant] afforded 1-phenyl-2-(2-pyridylseleno)-ethanol (**2a**) (0.41 g, 1.5 mmol; 41%) as yellow oil. **2a**: $^1$H NMR $\delta$ 3.41 (dd. 1H, J= 13.8 and 7.4 Hz), 3.50 (dd. 1H, J=13.8 and 3.4 Hz), 5.18 (dd. 1H, J=7.4 and 3.4 Hz), 6.55 (s. 1H), 7.0-7.2 (m. 1H), 7.2-7.6 (m. 7H), and 8.4-8.5 (m. 1H). To determine the optical purity, this alcohol was converted to the (*S*)-MTPA ester. (*R*)-1-Phenyl-2-(2-pyridylseleno)ethyl (*S*)-2,2,2-trifluoro-1-methoxy-1-phenylpropanoate [(*S*)-MTPA ester of (*R*)-**2a**]: $^1$H NMR $\delta$ 3.46 (s. 3H), 3.58 (dd. 1H, J=13.0 and 8.6 Hz), 3.73 (dd. 1H, J=13.0 and 5.3 Hz), 6.26 (dd. 1H, J=8.5 and 5.3 Hz), 6.9-7.1 (m. 1H), 7.2-7.6 (m. 12H), and 8.4-8.5 (m. 1H). Proton geminal to oxygen in (*S*)-MTPA ester of (*S*)-**2a** resonanced at 6.16 (dd. 1H, J=8.9 and 4.5 Hz) ppm. Comparison of the integrals of these protons (6.26 and 6.16 ppm) revealed that the enantiomeric excess of the alcohol is 88%.

**Asymmetric Reduction of 1a by (−)-Diisopinocamphenylchloroborane (4).** To a solution of **4** (1.07 g, 3.3 mmol) in THF (1.6 ml) was added a solution of **1a** (0.28 g, 1 mmol) in THF (1 ml) at −42℃ under nitrogen atmosphere to give a pale

yellow solution. The solution was stirred at −42℃ for 3.5 h and then −25℃ for 24 h. The reaction was quenched by the addition of acetaldehyde (0.15 ml, 2.4 mmol) in two portions during 4 h and the resulting yellow suspension was further stirred for 8 h. Then, the volatile compounds were removed under reduced pressure (ca. 1 mmHg, 2 h) and diethyl ether was added to the residual oil to give yellow suspension. Diethanolamine (0.62 ml, 6.5 mmol) was added and the resulting mixture was stirred for 6 h to form orange precipitate. The precipitate was filtered and washed twice with a small amount of pentane. The combined filtrate and washings was evaporated *in vacuo* to leave orange oil which was subjected to column chromatography [silica gel, hexane–ethyl acetate (4 : 1) as eluant] to afford **2a** (0.15 g, 0.55 mmol; 55%). By the same procedure as described above, (*R*)-**2a** was confirmed to be a major isomer with an enantiomeric excess of 92%.

**Asymmetric Reduction of 1a by (*S*)-Binaphthol-modified Lithium Aluminum Hydride Reagent (5).** To a solution of lithium aluminum hydride in THF (1.05 M, 2.9 ml; 3 mmol) was added slowly a solution of ethanol (0.18 ml; 3 mmol) in THF (3 ml) at ambient temperature. After 25 min, a solution of (*S*)-(−)-1,1'-bi-2-naphthol (0.86 g, 3 mmol) in THF (9 ml) was added during 40 min to give slightly white-turbid solution. After 30 min, the solution was cooled to −100℃ and further stirred for 45 min. A solution of **1a** (0.28 g, 1 mmol) in THF (3 ml) was added and the resulting orange solution was stirred for 3 h. Then, the bath temperature was raised to −78℃ and the solution was stirred for 2 h. Methanol was added (0.3 ml) and after 10 min water (0.3 ml) and diethyl ether (5 ml) were added. The cooling bath was removed and the stirring was continued for 10 min. The solution was dried over $MgSO_4$ and evaporated *in vacuo*. The residue was again dissolved in diethyl ether (100 ml) and the solution was washed by 3N NaOH (10 ml×5). After filtration, the filtrate was evaporated *in vacuo* to leave an oil which was subjected to column chromatography [silica gel, hexane–ethyl acetate (7 : 3) as eluant] to afford **2a** (0.21 g, 0.76 mmol; 76%). By the same procedure as described above, (*R*)-**2a** was confirmed to be the major isomer with 62% e.e..

Spectral data of other chiral alcohols and their (*S*)-MTPA esters are as follows.

**1-(4-Chlrophenyl)-2-(2-pyridylseleno)ethanol (2b)**: $^1$H NMR $\delta$ 3.33 (dd. 1H, J =13.9 and 7.2 Hz), 3.47 (dd. 1H, J=13.9 and 3.1 Hz), 5.16 (dd. 1H, J=7.2 and 3.1 Hz), 6.79 (s. 1H), 7.0–7.2 (m. 1H), 7.2–7.6 (m. 6H), and 8.4–8.5 (m. 1H).

**(*R*)-1-(4-Chlrophenyl)-2-(2-pyridylseleno)ethyl (*S*)-2,2,2-trifluoro-1-methoxy-1-phenylpropanoate [(*S*)-MTPA ester of (*R*)-2b)]**: $^1$H NMR $\delta$ 3.47 (s. 3H), 3.59 (dd. 1H, J=13.0 and 8.4 Hz), 3.74 (dd. 1H, J=13.0 and 5.4 Hz), 6.28 (dd. 1H, J=8.4 and 5.4 Hz), 6.9–7.1 (m. 1H), 7.2–7.6 (m. 11H), and 8.4–8.5 (m. 1H). Proton geminal to oxygen in (*S*)-MTPA ester of (*S*)-**2b** : $\delta$ 6.12 (dd. 1H, J=7.1 and 4.7 Hz).

**1-(4-Methoxyphenyl)-2-(2-pyridylseleno)ethanol (2c)**: $^1$H NMR $\delta$ 3.39 (dd. 1H, J=13.8 and 7.2 Hz), 3.46 (dd. 1H, J=13.8 and 3.6 Hz), 3.80 (s. 3H), 5.13 (dd.

1H, J=7.2 and 3.6 Hz), 6.39 (s. 1H), 6.89 (d. 2H, J = 8.6 Hz), 7.0–7.2 (m. 1H), 7.37 (d. 2H, J=8.6 Hz), 7.3–7.6 (m. 2H), and 8.4–8.5 (m. 1H).

**(*R*)-1-(4-Methoxyphenyl)-2-(2-pyridylseleno)ethyl (*S*)-2,2,2-trifluoro-1-methoxy-1-phenylpropanoate [(*S*)-MTPA ester of (*R*)-2c]**: $^1$H NMR $\delta$ 3.45 (q. 3H, J=1.2 Hz), 3.60 (dd. 1H, J=12.9 and 8.2 Hz), 3.69 (dd. 1H, J=12.9 and 5.7 Hz), 3.80 (s. 3H), 6.22 (dd. 1H, J=8.2 and 5.7 Hz), 6.7–7.6 (m. 12H), and 8.3–8.5 (m. 1H). Proton geminal to oxyten in (*S*)-MTPA ester of (*S*)-**2c**: $\delta$ 6.12 (dd. 1H, J=8.5 and 5.1 Hz).

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