

SYNTHESIS OF PYRROLIDINE DERIVATIVES BY IMPROVED AMINOSELENATION
VIA ADDITION OF BORON TRIFLUORIDE COMPLEX OF DIHOMOALLYLCUPRATE TO
ALDIMINES CONTAINING α -HYDROGEN

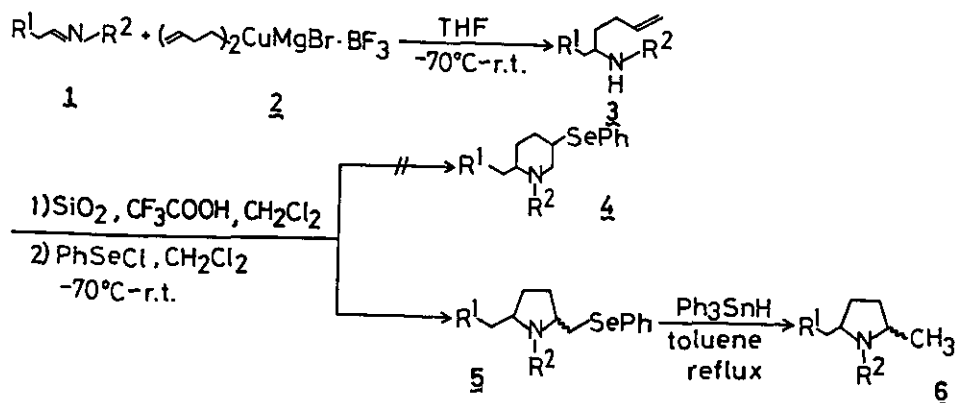
Makoto Wada, Hideki Aiura, and Kin-ya Akiba*

Department of Chemistry, Faculty of Science, Hiroshima University,
Higashisenda-machi, Hiroshima 730, Japan

Abstract— Boron trifluoride complex of magnesium dihomomallyl-
cuprate, $(\text{CH}_2=\text{CHCH}_2\text{CH}_2)_2\text{CuMgBr}\cdot\text{BF}_3$, reacted with aldimines
containing α -hydrogen to afford the corresponding addition
products in good yields. The addition products were converted
to pyrrolidine derivatives by treatment with phenylselenenyl
chloride in the presence of trifluoroacetic acid and silica
gel.

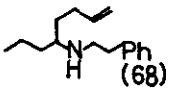
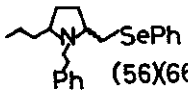
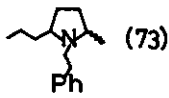
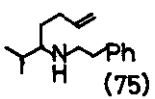
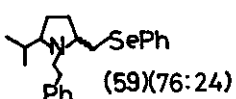
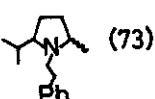
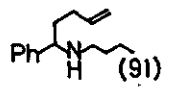
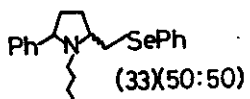
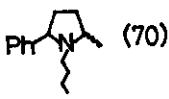
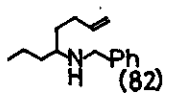
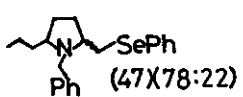
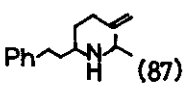
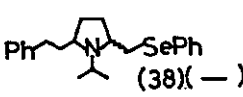
In the previous papers, we reported that $\text{RCu}\cdot\text{BF}_3$ or $\text{R}_2\text{CuMgX}\cdot\text{BF}_3$ ($\text{R}=\text{alkyl}$),
generated in situ from Grignard reagents, CuI , and $\text{BF}_3\cdot\text{OEt}_2$, added to aldimines
(1) without deprotonation of α -hydrogen to afford secondary amines in good
yields.¹⁾ As a further application on addition of $\text{R}_2\text{CuMgX}\cdot\text{BF}_3$, we found that
boron trifluoride complex of magnesium dihomomallylcuprate, $(\text{CH}_2=\text{CHCH}_2\text{CH}_2)_2\text{CuMg}$
 $\text{Br}\cdot\text{BF}_3$ (2), reacted with aldimines in good yields to give the corresponding
addition products (3) which can be a precursor for pyrrolidine synthesis.

Scheme 1



Some of the results are summarized in Table 1.

Table 1 Synthesis of Pyrrolidine Derivatives (5 and 6) from Imines (1)^{a)}

Aldimines(<u>1</u>)	Secondary Amines(<u>3</u>) ^{b)} (%,yield)	<u>5</u> (%,yield) (ratio,cis:trans) ^{c)}	<u>6</u> (%,yield)
<u>a</u> 	 (68)	 (56)(66:34)	 (73)
<u>b</u> 	 (75)	 (59)(76:24)	 (73)
<u>c</u> 	 (91)	 (33)(50:50)	 (70)
<u>d</u> 	 (82)	 (47)(78:22)	—
<u>e</u> 	 (87)	 (38)(—)	—

a) A standard procedure for preparation of 5 is as follows. Secondary amines (3) were prepared by our $(\text{CH}_2=\text{CHCH}_2\text{CH}_2)_2\text{CuMgBr}\cdot\text{BF}_3$ procedure.¹⁾ To a suspension of 0.3g of oven-dried silica gel (Merck Art 7730, 60 GF₂₅₄) and 1 mmol of 3 in 5 ml of dry CH_2Cl_2 was added 1.05 mmol of CF_3COOH at -70°C under argon atmosphere, and the reaction mixture was stirred for 30 min at that temperature. Then, 1.10 mmol of PhSeCl in 5 ml of dry CH_2Cl_2 was added and the mixture was allowed to warm to room temperature. After stirring for 4 h, the reaction mixture was quenched with 10 ml of 10% aqueous NaOH followed by extraction with CH_2Cl_2 . After drying the CH_2Cl_2 layer over anhydrous MgSO_4 , the solvent was evaporated *in vacuo*. The crude product was purified by TLC on silica gel (Merck Art 9385, dichloromethane : hexane=1 : 1).

b) Satisfactory IR, ^1H NMR, and MS data were obtained for these compounds. All 3 are hygroscopic, and 3d gave correct elemental analyses, but 3a, 3b, 3c,

and 3e gave correct result only when ca. 0.05-0.1 equivalent of water is assumed to be contained.

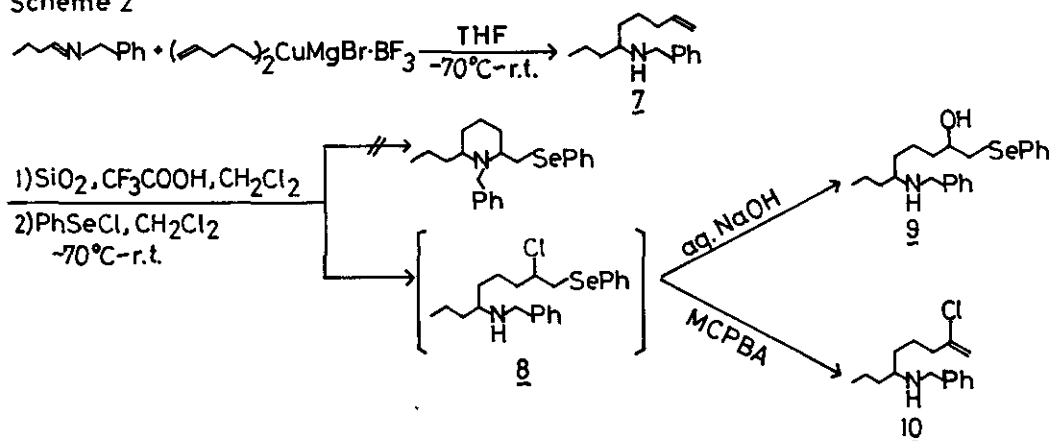
- c) The ratio was determined by silica gel TLC separation. It was estimated that the material having high R_f value on TLC was cis isomer and the other was trans isomer, based on ^1H NMR of 5c and 6c (see references 13 and 14). We did not investigate whether the ratio was controlled thermodynamically or kinetically.

In the next, we tried the ring closure to nitrogen heterocycles from secondary amines (3) utilizing phenylselenenyl halides,²⁾ and such a reaction is desirable due to the general importance of alkaloid synthesis. Phenylselenenyl halides are well known to effect a number of intramolecular oxyselenations to give cyclic ethers³⁾ and lactones,⁴⁾ but there are only a few reports concerning intramolecular aminoselenation such as on 1-aza-4-cyclooctene,⁵⁾ N-alkenyl-uretanes,⁶⁾ and N-alkenylamides.^{7),8)}

We treated 3 with PhSeCl under the same conditions that had worked well for preparing nitrogen heterocycles described above, but desired transformation did not proceed at all, presumably due to the reaction of PhSeCl on the nitrogen. This rationalization is supported by the literature that in the case of aliphatic amines, PhSeCl reacted on nitrogen in all examples which had been examined.⁹⁾ We discovered, however, that 3 did undergo the desired transformation to afford pyrrolidine derivatives (5), formal product by 5-exo closure,¹⁰⁾ when the reaction was carried out in the presence of CF_3COOH ¹¹⁾ using silica gel,¹²⁾ where piperidine derivatives, formal product by 6-endo closure,¹⁰⁾ were not formed at all. The reactions were then routinely run to afford 5 in this fashion and some of the results are summarized in Table 1. The final stage for the synthesis of pyrrolidine derivatives (6) is the elimination of the selenyl group. This was carried out by refluxing 5 in toluene with triphenyltin hydride.⁶⁾ 5 was a mixture of cis and trans isomers which were separable by silica gel TLC. The stereochemistry of 5¹³⁾ could be deduced from ^1H NMR measurement although the spectra were very complicated, and finally could be confirmed by ^1H NMR spectra and inspection of Dreiding models of 6.¹⁴⁾ Undoubtedly, there was no cis-trans isomerization during the conversion of 5 to 6.⁶⁾

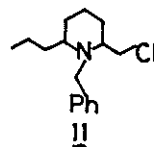
The ring closure of the addition product (7; 94% yield) prepared from $(\text{CH}_2=\text{CHCH}_2\text{CH}_2\text{CH}_2)_2\text{CuMgBr}\cdot\text{BF}_3$ and $\text{CH}_3\text{CH}_2\text{CH}_2\text{CH}=\text{NCH}_2\text{Ph}$ to the piperidine derivative did not take place even in the presence of CF_3COOH , but PhSeCl added to the double bond, and the corresponding hydroxyl compound (9)¹⁵ was obtained in 47% yield after aqueous workup. On the other hand, when PhSeCl addition compound (8) was treated with *m*-chloroperbenzoic acid before aqueous workup, a vinyl chloride (10)¹⁶ was obtained in 33% yield.

Scheme 2



Intramolecular aminomercuration utilizing HgCl_2 also did not afford the desired piperidine derivative under the standard conditions^{2a)} or even acidic conditions, but 7 was recovered, while a piperidine derivative (11)¹⁷ was obtained in 38% yield when 7 was treated with $\text{PdCl}_2(\text{PhCN})_2$ in the presence of CuCl_2 in PrCN .

Finally, intramolecular aminoselenation on *N*-alkenylamines such as 3 and 7 was difficult, different from *N*-alkenylurethanes⁶⁾ and *N*-alkenylamides.⁷⁾ Noteworthy is the fact that pyrrolidine derivatives (5) were obtained by treatment of 3 with PhSeCl in the presence of CF_3COOH .



REFERENCES AND NOTES

1. a) M. Wada, Y. Sakurai, and K-y. Akiba, Tetrahedron Lett., 1984, 25, 1079.
 b) M.-Wada, Y. Sakurai, and K-y. Akiba, Nippon Kagaku Kaishi, 1985, 295. See also: M. Wada, Y. Sakurai, and K-y. Akiba, Tetrahedron Lett., 1984, 25, 1083.
2. Mercuric ion is a conventional reagent for this approach^{a)} and a palladium-based methodology which provides a good route to indoles has been reported.^{b)}
 a) J. J. Perie, J. P. Laval, J. Roussel, and A. Lattes, Tetrahedron, 1972, 28, 675. b) L. S. Hegedus, G. F. Allen, J. J. Bozell, E. L. Waterman, J. Am. Chem. Soc., 1978, 100, 5800.
3. a) K. C. Nicolaou and Z. Lysenko, Tetrahedron Lett., 1977, 1257. b) D. L. J. Clive, G. Chittattu, and C. K. Wong, Can. J. Chem., 1977, 55, 3894.
4. a) D. L. J. Clive and G. Chittattu, J. Chem. Soc. Chem. Commun., 1977, 484.
 b) K. C. Nicolaou, S. P. Seitz, W. J. Sipio, and J. F. Blount, J. Am. Chem. Soc., 1979, 101, 3884.
5. S. R. Wilson and R. A. Sawicki, J. Org. Chem., 1979, 44, 287.
6. D. L. J. Clive, V. Farina, A. Singh, C. K. Wong, W. A. Kiel, and S. M. Menchen, J. Org. Chem., 1980, 45, 2120.
7. A. Toshimitsu, K. Terao, and S. Uemura, J. Org. Chem., 1986, 51, 1724.
8. Intramolecular aminoselenation utilizing N-phenylselenophthalimide was recently reported. S. Danishefsky, E. M. Berman, M. Ciufolini, S. J. Etheredge, and B. E. Segmuller, J. Am. Chem. Soc., 1985, 107, 3891.
9. H. J. Reich and J. M. Renga, J. Org. Chem., 1975, 40, 3313.
10. J. E. Baldwin, J. Chem. Soc. Chem. Commun., 1976, 734.
11. Recently, we encountered that oxymercuration of the olefin having amino group took place smoothly by the use of HBF_4 , while standard oxymercuration did not afford the desired alcohol at all. M. Wada, Y. Nishihara, and K-y. Akiba, Tetrahedron Lett., 1985, 26, 3267.
 Kametani and co-workers reported that ω -unsaturated amines were converted into pyrrolidine and piperidine derivatives by treatment of their hydrochlorides with benzenesulfonyl chloride followed by base-induced ring closure. T. Ohsawa, M. Ihara, K. Fukumoto, and T. Kametani, J. Org. Chem., 1983, 48, 3644.
12. Silica gel was necessary to increase the yield. See references 5 and 6.
13. Satisfactory IR, ^1H NMR, and MS data were obtained for 5. Satisfactory

elemental analyses data were obtained for 5a, 5b, and 5d. The ^1H NMR signal due to the methylene proton carrying the phenylseleno group usually appeared as a broad-doublet for cis isomer and two double-doublets for trans isomer. These results could be deduced from inspection of Dréiding models. Selected ^1H NMR signals of cis 5c: δ 2.90-3.23 (m, 1H, PhSe-C- $\underline{\text{CH}}$ -N-), 3.13 (bd, 2H, PhSe- $\underline{\text{CH}}_2$ -), 3.46-3.78 (m, 1H, Ph- $\underline{\text{CH}}$ -N-). Selected ^1H NMR signals of trans 5c: δ 2.82 (dd, $J=12$, 11Hz, 1H, PhSe- $\underline{\text{CH}}_a$ -), 3.23 (dd, $J=12$, 4Hz, 1H, PhSe- $\underline{\text{CH}}_b$ -), 3.36-3.74 (m, 1H, PhSe-C- $\underline{\text{CH}}$ -N-), 3.85 (dd, $J=8$, 5Hz, 1H, Ph- $\underline{\text{CH}}$ -N-).

14. Satisfactory IR, ^1H NMR, and MS data were obtained for 6. Selected ^1H NMR signals of cis 6c: δ 1.17 (d, $J=7\text{Hz}$, 3H, $\underline{\text{CH}}_3$ -C-N-), 2.76 (ddq, $J=7$, 7, 7Hz, 1H, $\underline{\text{CH}}_3$ - $\underline{\text{CH}}$ -N-), 3.58 (dd, $J=7$, 7Hz, 1H, Ph- $\underline{\text{CH}}$ -N-). Selected ^1H NMR signals of trans 6c: δ 0.95 (d, $J=7\text{Hz}$, 3H, $\underline{\text{CH}}_3$ -C-N-), 3.49 (dq, $J=7$, 4Hz, 1H, $\underline{\text{CH}}_3$ - $\underline{\text{CH}}$ -N-), 3.67 (dd, $J=9$, 7Hz, 1H, Ph- $\underline{\text{CH}}$ -N-). The determination of cis and trans isomer was confirmed by the difference of chemical shift of $\underline{\text{CH}}_3$ -C-N- and $\underline{\text{CH}}_3$ - $\underline{\text{CH}}$ -N- due to magnetic anisotropic effect of the phenyl group and also the coupling constants of the methine proton carrying the methyl group.

15. Satisfactory IR, ^1H NMR, and MS data were obtained for 9. Selected ^1H NMR signals of 9: δ 2.10 (bs, 2H, - $\underline{\text{NH}}$ -, $\underline{\text{HO}}$ -), 2.36-2.65 (m, 1H, $\text{CH}_3(\text{CH}_2)_2$ - $\underline{\text{CH}}$ -N-), 2.85 (dd, $J=13$, 9Hz, 1H, PhSe- $\underline{\text{CH}}_a$ -), 3.10 (dd, $J=13$, 5Hz, 1H, PhSe- $\underline{\text{CH}}_b$ -), 3.45-3.80 (m, 1H, $\text{HO}-\underline{\text{CH}}$ -), 3.72 (s, 2H, Ph $\underline{\text{CH}}_2$ -). MS(m/e): 404(M^+).

16. Satisfactory IR, ^1H NMR, and MS data were obtained for 10. Selected ^1H NMR signals of 10: δ 2.20-2.41 (bs, 1H, - $\underline{\text{NH}}$ -), 2.42-2.65 (m, 1H, $\text{CH}_3(\text{CH}_2)_2$ - $\underline{\text{CH}}$ -N-), 3.70 (s, 1H, Ph $\underline{\text{CH}}_2$ -), 5.00-5.14 (m, 2H, $\underline{\text{H}}_2\text{C}=\text{C}$ -). MS(m/e): 265(M^+), 267(M^++2).

17. Satisfactory IR, ^1H NMR, MS, and elemental analyses data were obtained for 11. Selected ^1H NMR signals of 11: δ 2.57-3.14 (m, 2H, $\text{CH}_3(\text{CH}_2)_2$ - $\underline{\text{CH}}$ -N-, Cl-C- $\underline{\text{CH}}$ -N-), 3.61 (d, $J=7\text{Hz}$, 2H, Cl- $\underline{\text{CH}}_2$ -), 3.73 (s, 2H, Ph $\underline{\text{CH}}_2$ -). MS(m/e): 265(M^+), 267(M^++2). Anal. Calcd for $\text{C}_{16}\text{H}_{24}\text{NCl}$: C, 72.29; H, 9.10; N, 5.27. Found: C, 72.42; H, 9.31; N, 4.97.

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