

# 1,4-Asymmetric Induction in Palladium(II)-catalyzed Intramolecular *N*-Alkylation Reaction. Construction of 2-Functionalized 5-Hydroxypiperidine

Yoshiro Hirai,\* Kaori Shibuya, Yoko Fukuda, Hajime Yokoyama, and Seiji Yamaguchi  
Department of Chemistry, Faculty of Science, Toyama University, Gofuku 3190, Toyama 930

(Received November 11, 1996)

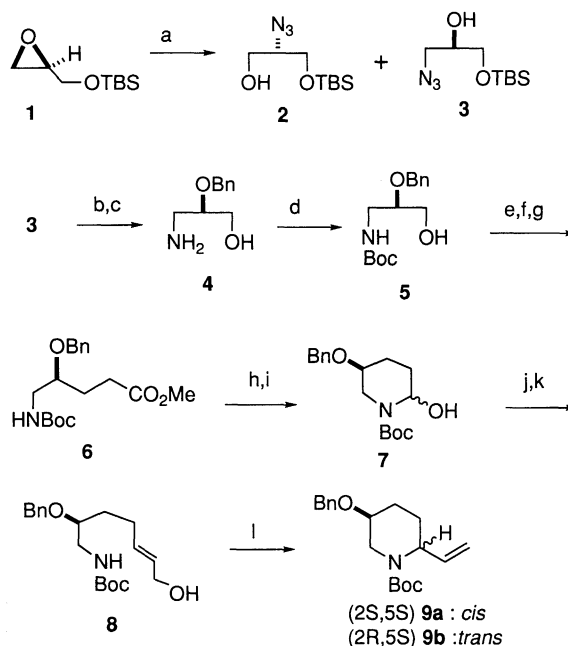
Palladium(II)-catalyzed cyclization of optically active urethanes containing an allylic alcohol moiety was examined. Efficient 1,4-asymmetric induction was found in this reaction. The cycloadducts were converted to pseudoconhydrine.

Intramolecular amino cyclization<sup>1</sup> is one of the most important methodologies for stereo-controlled construction of functionalized nitrogen heterocycles, which form the skeletons of a number of biologically active natural products and related compounds. We recently developed the intramolecular substitution of an allylic alcohol by a heteroatom using a palladium(II) catalyst<sup>2</sup> without activation of the allylic hydroxy group and reported its application to the synthesis of (-)-bulgecinine and (+)-coniine.<sup>3</sup> In connection with our current investigation of the synthetic utility of this palladium-catalyzed *N*-alkylation, we became interested in 1,4-asymmetric induction. We describe here the stereocontrolled construction of 2-functionalized 5-hydroxypiperidine by a palladium(II)-catalyzed intramolecular *N* →  $\pi$  cyclization and its application to the synthesis of pseudoconhydrine, one of the hemlock alkaloids.<sup>4</sup>

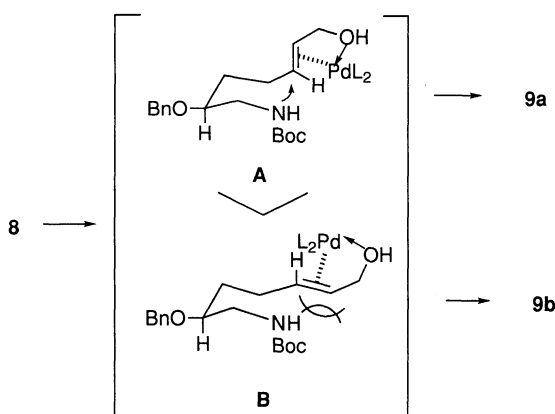
The substrate **8** for palladium(II)-catalyzed cyclization was prepared in a straightforward fashion from (*R*)-*O*-*t*-butylsilyl glycidol (**1**). Regio- and stereoselective cleavage of the oxirane ring was achieved by exposure of **1** to sodium azide in DMF in the presence of ammonium chloride to give the azide **3** in 45% yield, with the regio-isomer **2** (15% yield).<sup>5</sup> After protection of the secondary alcohol of **3** with benzyl bromide, the azide group was reduced with LiAlH<sub>4</sub> to give the amino-alcohol **4**, and its primary amino group was protected with di-*t*-butyl dicarbonate (Boc<sub>2</sub>O) to give the urethane **5**. The Swern oxidation of **5** and subsequent Wittig reaction gave the  $\alpha,\beta$ -unsaturated ester, which was subjected to catalytic hydrogenation to afford the ester **6** in 55% in 3 steps. Diisobutylaluminum hydride (DIBAL) reduction of **6** and subsequent Swern oxidation gave the cyclic alcohol **7**. Treatment of **7** with methyl (triphenylphosphoranylidene)acetate in benzene at 80 °C followed by reduction with DIBAL afforded the desired allyl alcohol **8** in 67% yield from **6**.

The intramolecular cyclization of **8** was effected by treatment with bis(acetonitrile)palladium(II) chloride (30 mol%) [PdCl<sub>2</sub>(CH<sub>3</sub>CN)<sub>2</sub>] in tetrahydrofuran (THF) to give a product consisting predominantly of the piperidine **9a** and its stereo-isomer **9b** in a ratio of 8:1. The stereoselective formation of **9a** could be explained by assuming the transition state **A**. The transition state **B**, which leads to **9b**, would be disadvantageous because of non-bonding interaction between the carbamate moiety and  $\pi$ -allyl-oxy palladium complex.

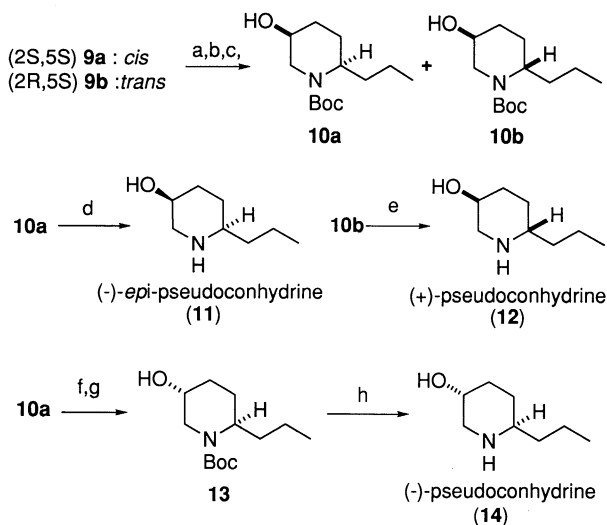
Next, we examined the conversion of **9a** and **9b** to (-)-*epi*-pseudoconhydrine (**11**) and (+)-pseudoconhydrine (**12**), respectively. Ozonolysis of **9** followed by Wittig reaction with (ethyl)triphenylphosphonium bromide and subsequent catalytic



**Scheme 1.** a) NaN<sub>3</sub>, NH<sub>4</sub>Cl, DMF (60%, 2:3=1:3); b) BnBr, NaH, Bu<sub>4</sub>NI, THF (94%); c) LAH, Et<sub>2</sub>O (76%); d) (Boc)<sub>2</sub>O, Et<sub>3</sub>N, CH<sub>2</sub>Cl<sub>2</sub> (70%); e) (COCl)<sub>2</sub>, DMSO, Et<sub>3</sub>N, CH<sub>2</sub>Cl<sub>2</sub>, (84%); f) Ph<sub>3</sub>P=CHCO<sub>2</sub>Me, CH<sub>2</sub>Cl<sub>2</sub> (68%); g) H<sub>2</sub>/Pd-C, AcOEt (97%); h) DIBAL, THF, -78 °C (79%); i) (COCl)<sub>2</sub>, DMSO, Et<sub>3</sub>N, CH<sub>2</sub>Cl<sub>2</sub> (98%); j) Ph<sub>3</sub>P=CHCO<sub>2</sub>Me, benzene, refl. (91%); k) DIBAL, THF, -78 °C (95%); l) 30 mol% PdCl<sub>2</sub>(CH<sub>3</sub>CN)<sub>2</sub>, THF (81%, **9a**:**9b**=8:1).



hydrogenation with Pd-C gave **10a**, [ $\alpha$ ]<sub>D</sub><sup>26</sup> -2.7° (CHCl<sub>3</sub>), and **10b**, [ $\alpha$ ]<sub>D</sub><sup>27</sup> +9.4° (CHCl<sub>3</sub>), in 42% and 6% yield, which were easily separated by silica gel column chromatography. The carbamate group of **10a** and **10b** was removed by treatment with



**Scheme 2.** a)  $O_3$  and then  $Me_2S$ ,  $CH_2Cl_2$  (85%); b)  $Ph_3P^+CH_2CH_3Br^-$ ,  $n-BuLi$ , THF (61%); c)  $H_2$ , Pd-C, MeOH (58%); d)  $CF_3CO_2H$ ,  $CH_2Cl_2$  (80%); e)  $CF_3CO_2H$ ,  $CH_2Cl_2$  (95%); f) diethyl azodicarboxylate,  $PhCO_2H$ ,  $Ph_3P$ , benzene (52%); g)  $K_2CO_3$ , MeOH (40%); h)  $CF_3CO_2H$ ,  $CH_2Cl_2$  (90%).

$CF_3CO_2H$  (TFA) to provide **11** and **12**, respectively.<sup>6</sup> The physical data for the synthetic product **12**,  $[\alpha]^{27}_D +10.5^\circ$  (c 0.1,  $CHCl_3$ ), were in accordance with those reported for natural pseudoconhydrine.<sup>4,6d</sup>

Compound **10a** was also converted to (-)-pseudoconhydrine (**14**). The inversion of the alcohol moiety of **10a** under Mitsunobu conditions followed by debenzoylation of the resulting benzoate with aq.  $K_2CO_3$  gave **13**, which was treated with TFA to furnish **14**.<sup>7</sup>

In conclusion, efficient 1,4-asymmetric induction was found in a palladium-catalyzed intramolecular *N*-alkylation reaction. The scope and limitations, as well as further applications, of the present methodology are under investigation.

We are grateful to Dr. Hiroki Takahata, Toyama Medical and Pharmaceutical University, for his kind gift of the spectral data for (+)-pseudoconhydrine and (-)-epi-pseudoconhydrine. We also thank DAISO Co., Ltd. for providing (*S*)-glycidol. This work was financially support in part by a Grant-in Aid for

Scientific Research (C) from the Ministry of Education, Science, Sports, and Culture of Japan.

## References and Notes

- a) Y. Saitoh, Y. Moriyama, H. Hirota, T. Takahashi, and Q. Khuong-Huu, *Bull. Chem. Soc. Jpn.*, **54**, 488 (1981); b) M. Hiram, T. Shigemoto, Y. Yamazaki, and S. Ito, *J. Am. Chem. Soc.*, **107**, 1797 (1985); c) Y. Tamaru, M. Hojo, and Z. Yoshida, *J. Org. Chem.*, **53**, 5731(1988); d) J. Kobayashi, K. Naitoh, Y. Doi, K. Deki, and M. Ishibashi, *J. Org. Chem.*, **60**, 6941(1995). e) S. Knapp, K. E. Rodriques, A. T. Levorse, and R. M. Orna, *Tetrahedron Lett.*, **26**, 1803 (1985). f) M. Kitamura, S. Tanaka, and Y. Tamaru, *J. Org. Chem.*, **60**, 3764 (1995) and references cited therein.
- For palladium(0)-promoted cyclization, see: a) B. M. Trost and D. L. Van Vranken, *Chem. Rev.*, **96**, 395 (1996). b) T. Bando, H. Harayama, Y. Fukazawa, M. Shiro, K. Fugami, S. Tanaka, and Y. Tamaru, *J. Org. Chem.*, **59**, 1465 (1994). c) H. Yoshizaki, H. Satoh, Y. Sato, S. Nukui, M. Sibasaki, and M. Mori, *J. Org. Chem.*, **60**, 2016 (1995). d) K. Takao, Y. Nigawara, E. Nishio, I. Takagi, K. Maeda, K. Tadano, and S. Ogawa, *Tetrahedron*, **50**, 5681 (1994).
- Y. Hirai, T. Terada, Y. Amemiya, and T. Momose, *Tetrahedron Lett.*, **33**, 7893 (1992); Y. Hirai and M. Nagatsu, *Chem. Lett.*, **1994**, 21.
- a) A. Ladenberg and G. Adams, *Ber.*, **24**, 1671 (1891); b) G. M. Strunz and J. A. Findlay, In *The Alkaloides*, ed by A. Brossi, Academic Press, San Diego (1986), Vol 26, p.89.
- C. H. Behrens and K. B. Sharpless, *J. Org. Chem.*, **26**, 5696 (1985).
- For syntheses of ( $\pm$ )-pseudoconhydrine, see: a) K. E. Harding and S. R. Burks, *J. Org. Chem.*, **49**, 40 (1984); b) T. Shono, Y. Matsumura, O. Onomura, T. Kanazawa, and M. Habuka, *Chem. Lett.*, **1984**, 1101; c) E. Brown, J. Lavoue, and R. Dahl, *Tetrahedron*, **29**, 455 (1973). For it's chiral synthesis: d) K. Tadano, Y. Iimura, and T. Suami, *J. Carbohydr. Chem.*, **4**, 129 (1985); e) H. Takahata, K. Inose, and T. Momose, *Heterocycles*, **38**, 269 (1994).
- Since (*R*)-glycidol is commercial available, this method also constitutes an enantioselective synthesis of (+)-pseudoconhydrine.