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

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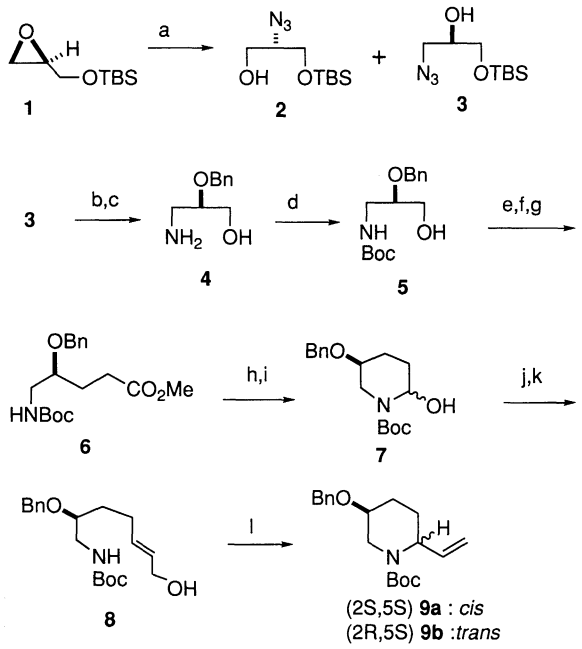
Palladium(II)-catalyzed cyclization of optically active urethanes containing an allylic alcohol moiety was examined. Efficient 1,4-asymmetric induction was found in this reaction. The cycloadducts were converted to pseudoconhydrine.

Intramolecular amino cyclization[1] 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[2] without activation of the allylic hydroxy group and reported its application to the synthesis of (-)-bulgecinine and (+)-coniine.[3] 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 intramolecullar $N \rightarrow \pi$ cyclization and its application to the synthesis of pseudoconhydrine, one of the hemlock alkaloids.[4]

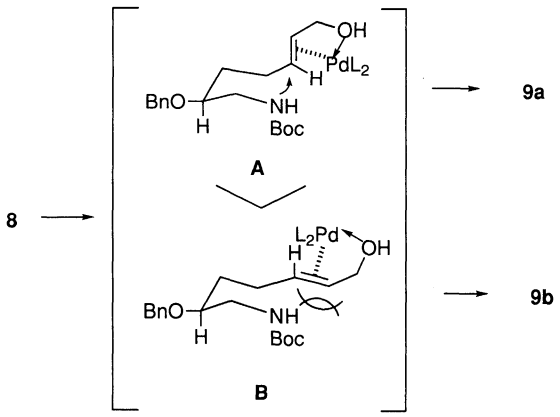
The substrate **8** for palladium(II)-catalyzed cyclization was prepared in a straightforward fashion from (*R*)-O-*t*-butylsilylglycidol (**1**). Regio- and stereoselective cleavage of the oxirane ring was achieved by exposure of **1** to sodium azide in DMF in the presence of ammonium chloride to give the azide **3** in 45% yield, with the regio-isomer **2** (15% yield).[5] After protection of the secondary alcohol of **3** with benzyl bromide, the azide group was reduced with $LiAlH_4$ to give the amino-alcohol **4**, and it's primary amino group was protected with di-*t*-butyl dicarbonate (Boc_2O) to give the urethane **5**. The Swern oxidation of **5** and subsequent Wittig reaction gave the α,β-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%) [$PdCl_2(CH_3CN)_2$] 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 π-allyl-oxy palladium complex.

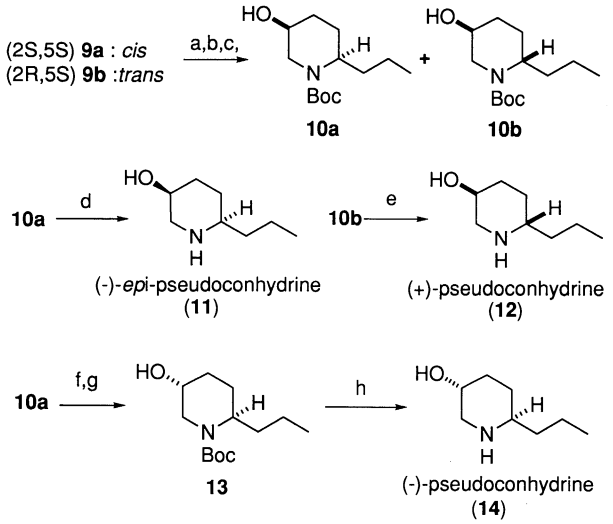
Next, we examined the conversion of **9a** and **9b** to (-)-*epi*-pseudoconhydrine (**11**) and (+)-pseudoconhydrine (**12**), respectively. Ozonolysis of **9** followed by Wittig reaction with (ethyl)triphenylphosphonium bromide and subsequent catalytic



Scheme 1. a) NaN_3, NH_4Cl, DMF (60%, **2**:**3**=1:3); b) BnBr, NaH, Bu_4NI, THF (94%); c) LAH, Et_2O (76%); d) $(Boc)_2O$, Et_3N, CH_2Cl_2 (70%); e) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, (84%); f) $Ph_3P{=}CHCO_2Me$, CH_2Cl_2 (68%); g) H_2/Pd-C, AcOEt (97%); h) DIBAL, THF, -78°C (79%); i) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2 (98%); j) $Ph_3P{=}CHCO_2Me$, benzene, refl. (91%); k) DIBAL, THF, -78°C (95%); l) 30 mol%-$PdCl_2(CH_3CN)_2$, THF (81%, **9a**:**9b**=8:1).



hydrogenation with Pd-C gave **10a**, $[\alpha]^{26}_D$ -2.7° ($CHCl_3$), and **10b** , $[\alpha]^{27}_D$ +9.4° ($CHCl_3$), 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.[6] The physical data for the synthetic product **12**, $[\alpha]^{27}_D$ +10.5° (c 0.1, $CHCl_3$), were in accordance with those reported for natural pseudoconhydrine.[4,6d]

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

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.

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7 Since (*R*)-glycidol is commercial avaiable, this method also constitutes an enantioselective synthesis of (+)-pseudoconhydrine.