Transition Metal-Mediated Stereocontrolled Cyclization of Urethanes Leading to Versatile Fused Piperidines and Its Application to the Synthesis of (+)-Prosopinine and (+)-Palustrine

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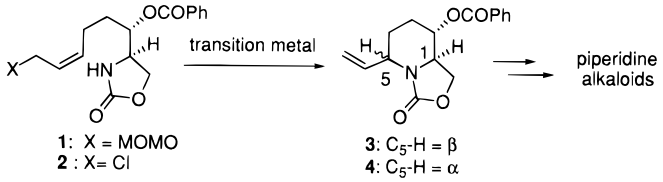
Stereoselective amino cycloaddition[1] of alkenylamines is one of the most important approaches for the stereoselective construction of nitrogen heteroalicycles, which form the skeletons of several biologically active natural products and related compounds. Palladium(0)-catalyzed allylic substitution in particular provides efficient stereoselective C−N bond formation.[2] Esters and carbamates of allylic alcohols have frequently been used as substrates in such reactions because of the low reactivity of the parent alcohol as a leaving group. We recently developed the intramolecular substitution of an allylic alcohol by a heteroatom using a palladium(II) catalyst without activation of the allylic alcohol.[3] As a continuation of that work, we have focused on the asymmetric construction of bicyclic oxazolidinone derivatives (**3** and **4**, Scheme 1), which provide a path to piperidine alkaloids.[4,5] The stereoselective construction of different stereoisomers, such as **3** and **4**, from similar precursors by changing transition metals is an especially challenging problem. We report here the facile preparation of optically active bicyclic oxazolidinones **3** and **4** by the stereocontrolled cyclization of urethanes **1** and **2** using palladium(II) catalyst and silver(I) salt, as well as the conversion of these bicyclic oxazolidinones to (+)-prosopinine and a synthetic intermediate of (+)-palustrine.

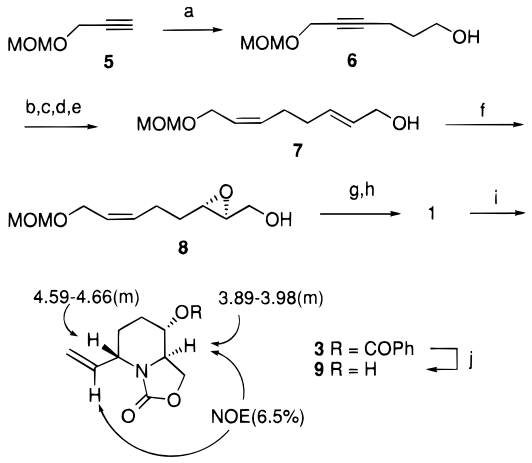
First, the substrate **1** for palladium-catalyzed cyclization was prepared from propargyl alcohol via the Katsuki−Sharpless asymmetric epoxidation. 3-[(Methoxymethyl)oxy]-2-propyne (**5**) was reacted with BuLi, BF_3·OEt_2, and oxetane to give an alcohol **6**, which was converted to the allylic alcohol **7** in a four-step process (catalytic hydrogenation, Swern oxidation, Wittig reaction, DIBALH reduction; overall yield of 56%) (Scheme 2). The asymmetric epoxidation of **7** under Katsuki−Sharpless conditions[6] gave the optically active epoxide **8**, $[\alpha]_D$ −11.3° ($CHCl_3$), in 80% yield. Treatment of the epoxide **8** with benzoyl isocyanate, followed by cyclization with migration of the *N*-benzoyl group over K_2CO_3 in acetonitrile, gave the 2-oxazolidinone **1** in 96% yield (94% ee).[7] The intramolecular cyclization of **1** was achieved by treatment with bis(acetonitrile)palladium(II) chloride (20 mol %) [$PdCl_2(CH_3CN)_2$] in THF at room temperature to give a bicyclic oxazolidinone **3** in 72% yield as a single diastereoisomer. The structure of **3** was confirmed by the spectral data and by an NOE experiment that indicated that the proton at the 1-position and the vinyl group at the 5-position are in a *cis* relation.

Next, we examined the silver(I) salt-promoted cyclization[8] of the chloride (**2**), which was easily obtained from **1**. Cyclization of **2** using silver trifluoroacetate[9] in the presence of NaH in THF gave a bicyclic oxazolidinone **10** in 72% yield as a single diastereoisomer (Scheme 3). The structure of **10** was confirmed by comparison of its spectral data to those of the alcohol (**9**), which was

Scheme 1

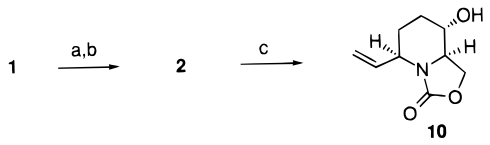


Scheme 2[a]



[a] Reagents and conditions: (a) *n*-BuLi, BF_3·OEt_2, oxetane, THF, −78 °C (58%); (b) H_2, Lindlar catalyst, AcOEt (84%); (c) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, −78 °C (81%); (d) $Ph_3P{=}CHCO_2Me$, CH_2Cl_2 (88%); (e) DIBALH, THF (94%); (f) Ti(*i*-PrO)$_4$, L-DIPT, *t*-BuOOH, CH_2Cl_2, −23 °C (80%); (g) benzoyl isocyanate, THF, rt; (h) K_2CO_3, $(C_8H_{17})_3NMeCl$ (cat.), CH_3CN (96% from **8**); (i) $PdCl_2(CH_3CN)_2$ (20 mol %), THF, rt (77%); (j) K_2CO_3 (aq), MeOH, rt (95%).

Scheme 3[a]



[a] Reagents and conditions: (a) concd HCl, MeOH, 60 °C (94%); (b) MsCl, DMAP, CH_2Cl_2, rt (75%); (c) $AgOCOCF_3$, NaH, THF, rt (72%).

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(4) Fodor, G. B.; Colasanti, B. In *Alkaloids: Chemical and Biological Perspectives*; Pelletier, S. W., Ed.; Wiley; New York, 1985; Vol. 3, pp 1−90.

(5) Some of these alkaloids possess local anesthetic activity: Bourrinet, P.; Quevauviller, A. *Comput. Rend. Soc. Biol.* **1968**, *162*, 1138; *Ann. Pharm, Fr.* **1968**, *26*, 787.

(6) Katsuki, T.; Sharpless, K. B. *J. Am. Chem. Soc.* **1980**, *102*, 5974.

(7) The optical purity of the 2-oxazolidinone **1**, $[\alpha]_D$ −31.2° ($CHCl_3$), was determined by HPLC using a chiral column (Daicel AS, Daicel Chemical Industries, Ltd.).

(8) Kimura, M.; Tanaka, S.; Tamaru, Y. *Bull. Chem. Soc. Jpn.* **1995**, *68*, 1689.

(9) Though the cyclization reaction using other silver salts was examined, silver trifluoroacetate provided the best results.

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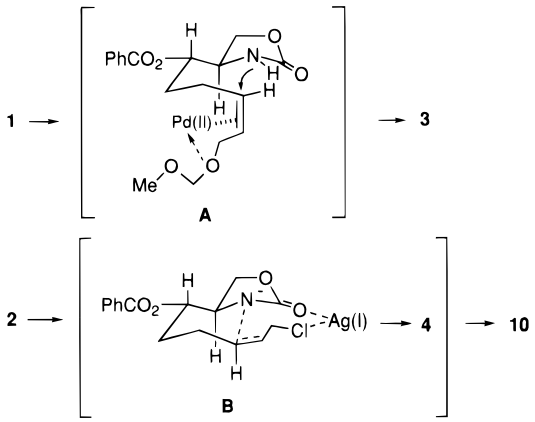
Scheme 4



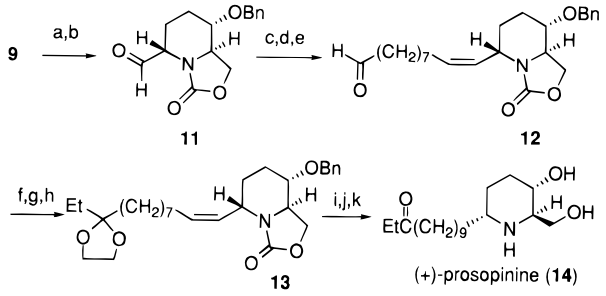
obtained from **3** by alkaline hydrolysis of the benzoate (Scheme 2).[10]

This high stereoselectivity of the palladium(II)-catalyzed allylic substitution reaction can be explained by assuming the involvement of a transition state **A**, which minimizes nonbonding interaction between the oxa-π-allylpalladium complex and the oxazolidinone ring (Scheme 4). The initial formation of an oxa-π-allylpalladium intermediate **A**, followed by backside N-nucleophilic attack upon the remote Pd-coordinated alkene, usually results in palladium-oxygen elimination to give the *trans*-2,6-disubstituted piperidine system **3** stereoselectively. On the other hand, the high stereoselectivity of silver(I)-promoted cyclization can be explained by assuming a transition state **B**, which gives the *cis*-2,6-disubstituted piperidine system **10** via **4**.

The resulting oxazolidinones **9** and **10** are useful chiral building blocks for the preparation of nitrogen-containing natural products, and their versatility has been demonstrated by their transformation into (+)-prosopinine[11,12] and a synthetic intermediate of (+)-palustrine,[13,14] respectively. Benzylation of **9** followed by ozonolysis gave the aldehyde **11**, which was subjected to a Wittig reaction, hydrolysis of the acetate moiety, and Swern oxidation to give the aldehyde **12** in 22% overall yield (Scheme 5). Grignard reaction of **12** with ethylmagnesium bromide in THF and the subsequent treatment of the resulting alcohol with PCC gave the ketone, which was converted to the ketal **13**. Finally, the conversion of **13** to **14** was achieved in three steps: debenzylation and hydrogenation of the olefin moiety, cleavage of the oxazolidinone ring, and deketalization. The physical data for the synthetic product, including the specific rotation, were identical to those reported for natural (+)-prosopinine.[10]

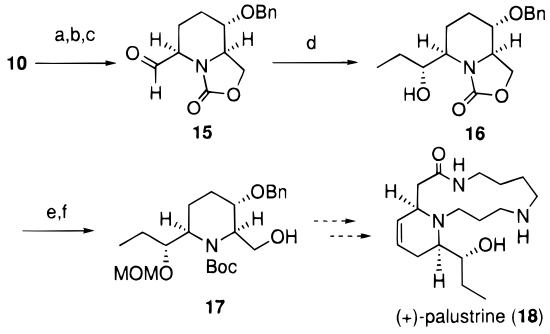
Furthermore, the conversion of **10** to a synthetic intermediate of (+)-palustrine (**18**) was also examined (Scheme 6). Benzylation of **9** followed by oxidative cleavage of the olefin moiety gave the aldehyde **15**, which

Scheme 5[a]



[a] Reagents and conditions: (a) BnBr, NaH, Bu_4NI, THF (97%); (b) O_3, Me_2S, CH_2Cl_2 (70%); (c) NaH, DMSO, $Ph_3P^+(CH_2)_9OAc\ Br^-$, THF (65%); (d) satd $NaHCO_3$ (aq), MeOH (70%); (e) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2 (72%); (f) EtMgBr, THF (65%); (g) PCC, CH_2Cl_2 (91%); (h) ethylene glycol, *p*-TsOH, benzene (73%); (i) H_2, 10% Pd−C, MeOH (89%); (j) 8 N KOH, MeOH (45%); (k) 10% aqueous HCl, 2 h (80%).

Scheme 6[a]



[a] Reagents and conditions: (a) BnBr, NaH, Bu_4NI, THF (93%); (b) OsO_4, NMO, 1,4-dioxane; (c) $NaIO_4$ (aq) (two steps 82%); (d) EtMgBr, $MgBr_2$, THF, −20 °C (57%); (e) MOMCl, Et_2NMe, CH_2Cl_2, rt (75%); (f) 8 N KOH, MeOH and then $(Boc)_2O$ (40%).

was subjected to a Grignard reaction with ethylmagnesium bromide in the presence of $MgBr_2$ to give the alcohol **16** stereoselectively in 57% yield. Protection of the alcohol moiety and cleavage of the oxazolidinone ring of **16** furnished **17**, which is a prospective intermediate for the synthesis of (+)-palustrine.[14]

In conclusion, a highly efficient method was established for constructing both the *trans*-2,6-disubstituted and the *cis*-2,6-disubstituted piperidine ring from the same precursor via transition metal-catalyzed intramolecular N-alkylation. Further application of the approach described here to the synthesis of other natural products is in progress.

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Supporting Information Available: Experimental procedures, characterization data, and ^1H NMR spectra for new compounds (42 pages).

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(10) The signal of an allylic methine proton of **10**, which was situated in an equatorial position in PMR, was observed at a lower field (4.40−4.47 ppm, m) than that of **9**, and no NOE was observed between the proton at the 1-position and the vinyl proton at the 11-position of **10**.

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