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NEW UTILIZATIONS OF OPTICALLY ACTIVE HOMOALLYLAMINES: HIGHLY STEREOSELECTIVE SYNTHESIS OF CYCLIC GUANIDINE AND THIOUREA

Reiko Yanada,[a] Akira Kaieda,[a] Kazuo Yanada,[b] and Yoshiji Takemoto*[a]

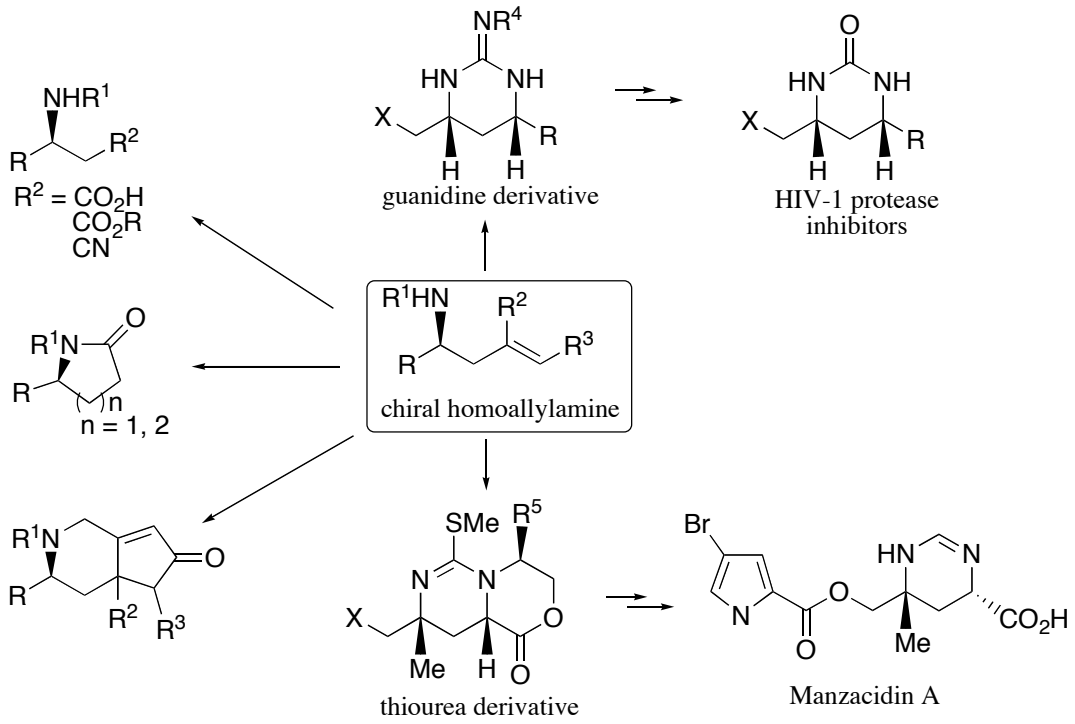
[a]Graduate School of Pharmaceutical Sciences, Kyoto University, Yoshida, Sakyo-ku, Kyoto 606-8501, Japan. e-mail: takemoto@pharm.kyoto-u.ac.jp
[b]Faculty of Pharmaceutical Sciences, Setsunan University, Nagaotoge-cho, Hirakata, Osaka 573-0101, Japan.

Abstract – Halocyclizations of optically active homoallylguanidine and homoallylthiourea were examined. These reactions proceeded stereoselectively to give six membered cyclic guanidines and thiourea. High 1,3-asymmetric induction by the homoallylic substituents is observed in these halocyclizations.

The allylation of imines, providing the corresponding homoallylamines, is an important synthetic transformation.[1] Therefore asymmetric allylation reactions of allylic metal compounds to carbon-nitrogen double bond of optically active imines have broadly been studied.[2] Recently we also reported diastereoselective samarium- or indium-mediated allylations of optically active aromatic imines containing a β-alkoxyamino group or a β-amino hydroxy group as a chiral auxiliary unit on the nitrogen of imines.[3, 4] So far, optically active homoallylamines have been transformed to β-amino acids,[5] β-aminoesters,[6] γ-lactams,[7] piperidines,[8] and nitrogen containing bicycles[9] (Scheme 1). As a new application method of optically active homoallylamine, we planned to build the second asymmetric position by the cyclization reaction and applied to the construction of polyfunctionalized cyclic compounds such as guanidine and thiourea derivatives which attract attentions for the synthesis of HIV-1 protease inhibitors,[10] bromopyrrole alkaloide Manzacidin A[11] and the ability as super bases.[12] Here we report the new synthetic application of optically active homoallylamines. The application contains the novel stereoselective halocyclization of optically active homoallyl guanidines (**4**, **9**) and homoallylthiourea (**11**) as a key step.

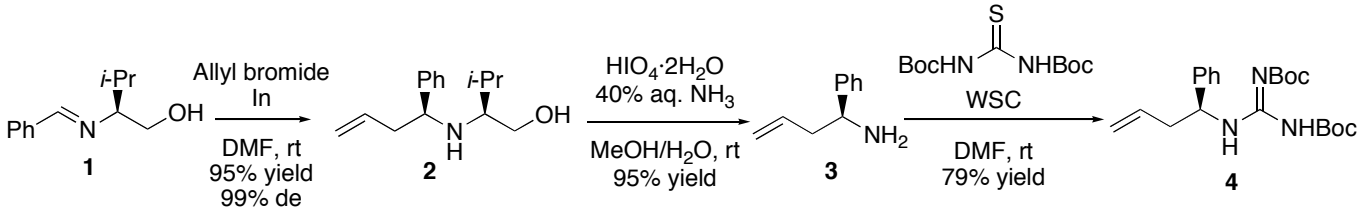
† This paper is dedicated to the memory of Professor Kenji Koga (1938–2004).

Scheme 1. Synthetic utilities of chiral homoallylamines.



According to our method,[4] we first synthesized optically active homoallylamine (**2**) from aromatic imine (**1**) in 95% yield and >99% de. By removing chiral auxiliary of **2** with HIO_4•$2H_2O$ and 40% aq. NH_3, optically active homoallylamine derivative (**3**) was obtained in 95% yield according to our method.[3b] Subsequent condensation of homoallylamine (**3**) with *N,N'*-bis-Boc-thiourea lead to homoallyl guanidine (**4**) in good yield.

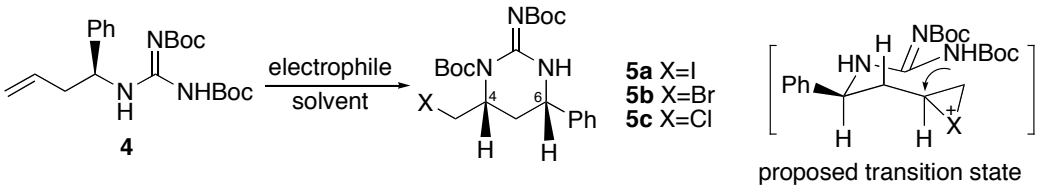
Scheme 2. Synthesis of optically active acyclic homoallyl guanidines.



With the requisite substrate in hand, we next turned our attention to the key halocyclization. Iodocyclization of guanidines bearing allyl, alkynyl or allenyl groups[12c,13] has already been reported. We investigated the cyclization reaction of guanidine bearing homoallyl group under variable conditions (Table 1). The cyclization of compound (**4**) was first examined with several electrophiles in dioxane (runs 1–4). The cyclization of **4** with NIS proceeded smoothly to give the desired product (**5a**) in moderate yield and stereoselectivity (run 1). Surprisingly when the same reaction was carried out with NCS, stereoselectivity was quite opposite, resulting in the major formation of *trans* isomer (run 3). This reason

is unclear at present. With pyridinium hydrobromide perbromide in dichloromethane, the rate acceleration was dramatically improved (run 5). The similar better result was obtained when THF was used as solvent (run 6). Use of pyridine, DMF and acetonitrile gave lower yields and stereoselectivities (runs 7–9). The relative *cis* stereochemistry was established on the basis of NMR spectroscopy. The NOE experiment of NMR spectrum (14.2%) between C4-hydrogen and C6-hydrogen in major stereoisomer (**5b**, X=Br) was observed, showing the *cis* relationship between the bromomethyl and phenyl groups. We propose the observed diastereoselectivity can be rationalized by considering a chair-like transition state for attack on the halonium ion, where the phenyl group and the halonium ion are both oriented in a pseudo-equatorial position. Similar models have been proposed to explain homoallylic induction for iodocyclization of thioimidates[13e] and isothioureas.[12c]

Table 1. Cyclization reaction of homoallylguanidine.

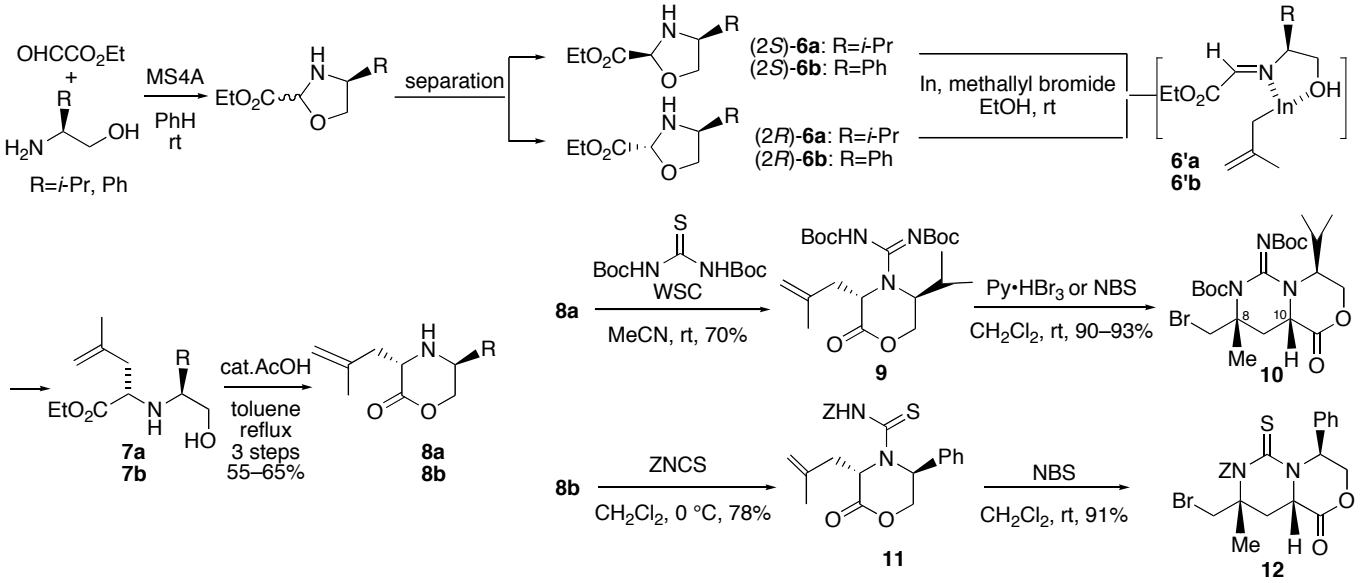


run	electrophile	X	solvent	time (h)	yield (%)	**5** (*cis*/*trans*)
1	NIS	I	Dioxane	10	68	**5a** (6 : 1)
2	NBS	Br	Dioxane	10	47	**5b** (3 : 1)
3	NCS	Cl	Dioxane	48	35	**5c** (1 : 3)
4	Py•HBr_3	Br	Dioxane	10	93	6 : 1
5	Py•HBr_3	Br	CH_2Cl_2	5	90	6 : 1
6	Py•HBr_3	Br	THF	5	87	6 : 1
7	Py•HBr_3	Br	Pyridine	10	52	2 : 1
8	Py•HBr_3	Br	DMF	10	69	5 : 1
9	Py•HBr_3	Br	MeCN	10	80	3 : 1

Then we applied the bromoguanidination method described above to the synthesis of multifunctionalized bicyclic compounds (**10**) and (**12**) (Scheme 3). Condensation of glyoxylic acid ethyl ester with (*S*)-2-amino-2-isopropylethanol or (*S*)-2-amino-2-phenylethanol gave oxazolidine (**6a**) or (**6b**) as a mixture of diatereomers, respectively. These diastereoisomers could be separated by column chromatography on basic silica gel to give (2*S*)-**6a** and (2*R*)-**6a** or (2*S*)-**6b** and (2*R*)-**6b**, then reacted respectively with methallylindium bromide. Surprisingly, the reaction gave only one diastereoisomer (**7a**) or (**7b**) in sharp contrast to 2-fluoroalkyl-1,3-oxazolidines bearing an electronwithdrawing trifluoromethyl group on the imine carbon atom, which also could be separated by column chromatography, to provide a mixture of the diastereomers *via* without formation of an imine intermediate.[14] Our results indicate that the allylation reaction of (2*S*)- and (2*R*)-oxazolidines (**6**) with In and methallyl bromide proceeded *via* the same imine intermediate (**6'a**) or (**6'b**). Then we transformed

compound (**7**) to morpholinone (**8**) in the presence of a catalytic amount of acetic acid in toluene. Guanidination of compound (**8a**) with *N*-Boc-thiourea gave compound (**9**). Fortunatelly, the bromoguanidination according to our method with Py•HBr_3 or NBS in CH_2Cl_2 gave only one diastereomer (**10**)[15] in excellent yield. The *cis* stereostructure between C10-hydrogen and C8-methyl group was also determined by NOE experiment of NMR spectroscopy (37%). On the other hand, the treatment of morpholinone derivative (**8b**) with benzyloxycarbonyl isothiocyanate (ZNCS) gave thiourea (**11**). Then treatment of **11** with NBS also proceeded stereoselectively to furnish bicyclic compound (**12**)[16] in excellent yield. The stereostructure of compound (**12**) was also elucidated as 1,3-*cis* by NOE measurement. The bromocyclization of compounds (**9**) and (**11**) could proceed in stereoselective manners to give bicyclic guanidine (**10**) and bicyclic thiourea (**12**), respectively. They are interested in versatile synthetic intermediates of several biologically active compounds.

Scheme 3. Synthesis of multifunctionalized bicyclic compounds.



In summary, we accomplished the novel utilization as chiral source of optically active homoallylamines. This method contained the stereoselective cyclization reaction of optically active homoallylguanidine and thiourea with some electrophiles. In this reaction, the complete 1,3-*cis*-stereoselectivity was observed. In this manner, 1,3-*cis* six-membered monocyclic compounds and multifunctionalized bicyclic compounds were synthesized easily. The construction of polyfunctionalized cyclic compounds was established using highly stereoselective allylations with indium and halocyclizations. These compounds are useful as diverse precursors for pharmaceutically active compounds, super bases and the intermediate for Manzacidin A.

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15. Compound (**10**): ^{1}H-NMR ($CDC1_3$, 500 MHz) δ 1.07 (d, *J* = 6.7 Hz, 6H), 1.46 (s, 9H), l.46 (s, 9H), 1.80 (s, 3H), 1.93 (m, 1H), 2.12 (dd, *J* = 12.5, 13.1 Hz, 1H), 2.51 (dd, *J* = 1.5, 13.1 Hz, 1H), 3.67 (d, *J* = 10.4 Hz, 1H), 4.17 (d, *J* = 10.4 Hz, 1H), 4.30 (dd, *J* = 1.5, 12.5 Hz, 1H), 4.41 (dd, *J* = 2.4, 12.2 Hz, 1H), 4.57 (dd, *J* = 1.5, 12.2 Hz, 1H), 4.58 (m, 1H); ^{13}C-NMR ($CDC1_3$, 126 MHz) δ 19.1, 19.2, 22.6, 28.0, 28.4, 28.3, 40.6, 45.3, 51.6, 54.2, 60.5, 67.9, 79.3, 83.7, 151.3, 151.4, 158.6, 167.0; IR ($CHCl_3$) ν 3028, 2980, 2934, 1735, 1666, 1578 cm^{-1}; MS (CI) *m/z* 518 (MH^+); HRMS (CI) calcd. for $C_{22}H_{37}N_3O_6Br$ (MH^+) 518.1866, found 518.1872; $[\alpha]^{31}_D$ –90.7° (*c* 0.69, $CHC1_3$).
16. Compound (**12**): ^{1}H-NMR ($CDC1_3$, 500 MHz) δ 1.58 (s, Me, 3H), 2.31 (dd, *J* = 12.2, 14.0 Hz, 1H), 2.69 (dd, *J* = 4.0, 14.0 Hz, 1H), 3.52 (d, *J* = 11.3 Hz, 1H), 3.54 (d, *J* = 11.3 Hz, 1H), 4.36 (dd, *J* = 4.0, 12.2 Hz, 1H), 4.70 (dd, *J* = 3.7, 12.2 Hz, 1H), 4.86 (dd, *J* = 3.4, 12.2 Hz, 1H), 5.10 (d, *J* = 12.2 Hz, 1H), 5.14 (d, *J* = 12.2 Hz, 1H), 6.42 (dd, *J* = 3.4, 3.7 Hz, 1H), 7.27–7.39 (m, 10H); ^{13}C-NMR ($CDC1_3$, 126 MHz) δ 25.8, 38.9, 42.4, 45.7, 53.9, 54.3, 67.7, 68.6, 126.6, 128.0, 128.2, 128.4, 128.6 129.3, 134.3, 136.2, 160.8, 163.5, 166.4; IR ($CHCl_3$) ν 3031, 3011, 2961, 1749, 1667, 1496 cm^{-1}; MS (CI) *m/z* 503 (MH^+); HRMS (CI) calcd. for $C_{23}H_{24}N_2O_4BrS$ (MH^+) 503.0641, found 503.0627; $[\alpha]^{24}_D$ +21.1° (*c* 1.05, $CHC1_3$).