Pergamon

Tetrahedron Letters, Vol. 35, No. 33, pp. 6119-6122, 1994
Elsevier Science Ltd
Printed in Great Britain
0040-4039/94 $7.00+0.00

0040-4039(94)01238-5

Asymmetric Synthesis of 2-Substituted Pyrrolidines and Piperidines by Nucleophilic Addition to *N*-Acyliminium Ions Bearing Pyrrolidine Chiral Auxiliaries

Hideaki Suzuki, Sakae Aoyagi, and Chihiro Kibayashi*

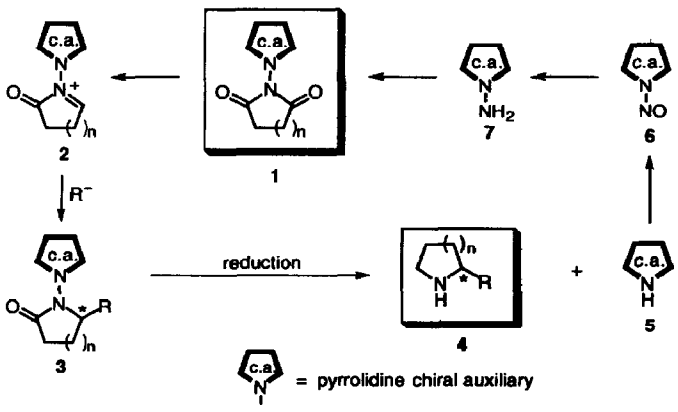
Tokyo College of Pharmacy, Horinouchi, Hachioji, Tokyo 192-03, Japan

Abstract: Addition of carbon nucleophiles to cyclic *N*-acyliminium salts chirally modified by various optically active pyrrolidines leads to highly enantioselective synthesis of 2-substituted pyrrolidines and piperidines.

Nucleophilic addition to *N*-acyliminium salts is a useful organic reaction,[1] which could be exploited if it were rendered enantioselective. From this point of view a number of chiral auxiliaries such as camphonic acid,[2] diphenylhydroxyethylamine,[3] 1-phenylethylamine,[4] and phenylglycinol[5] have been employed to do such, with some considerable success. Whereas optically active pyrrolidines have been used extensively as versatile chiral auxiliaries for substrate-controlled asymmetric synthesis,[6] no attention has been paid to their use in enantioselective alkylation via nucleophilic addition to *N*-acyliminium salts. In this communication we describe addition of carbon nucleophiles to *N*-acyliminium salts chirally modified by various optically active pyrrolidines, leading to highly enantioselective synthesis of 2-substituted pyrrolidines and piperidines.

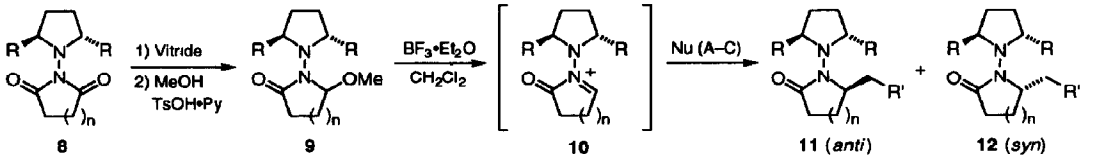
Our strategy for the asymmetric synthesis of the 2-substituted saturated heterocycles **4** employs the cyclic imides **1** bearing a variety of the pyrrolidine chiral auxiliaries as summarized in Scheme 1. Conversion to cyclic *N*-acyliminium ions **2** followed by nucleophilic addition leads to asymmetric amidoalkylation to give **3**. Subsequent reduction involving N–N bond cleavage results in the formation of the optically active heterocycles **4** as well as recovery of the chiral auxiliaries **5**, the latter of which can be recycled via N-nitrosation (*t*-BuONO) and reduction ($LiAlH_4$) to afford **1**.

Scheme 1

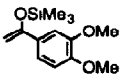


Thus, we first investigated utilizing chiral pyrrolidines having C_2 symmetry attached at nitrogen of the cyclic *N*-acyliminium ions **10**. Installation of the chiral auxiliaries could be readily achieved according to Scheme 1 (**7** → **1**) by the reaction of the chiral *trans*-2,5-disubstituted 1-aminopyrrolidines[7] with the corresponding cyclic acid anhydrides (Ac_2O, NaOAc) to give the cyclic *N*-(pyrrolidinyl)imides **8**, which was converted to the *N*-acyliminium intermediates **10** via the methoxy lactams **9** by treatment with Lewis acid (BF_3•Et_2O) in CH_2Cl_2 at room temperature. Subsequent nucleophilic addition of the silyl enol ethers and allyltrimethylsilane to **10** led to amidoalkylation to afford a chromatographically separable mixture of the *anti*- and *syn*-hydrazides **11** and **12** in favor of the *anti* isomer **11**; however, as shown in Table 1, the diastereoselectivities obtained were modest to low.

Table 1. Asymmetric amidoalkylation of cyclic *N*-(2,5-disubstituted-pyrrolidin-1-yl)imides **8**.



	compound (**8**)				products (**11** and **12**)			
entry		R	n	nucleophile[a]		R'[b]	**11**:**12** ratio[c]	yield, %[d]
1	**a**	Me	1	A	**a**	COAr	83:17	82
2	**b**	CH_2OBn	1	A	**b**	COAr	78:22	80
3	**b**	CH_2OBn	1	B	**c**	COPr	71:29	93
4	**b**	CH_2OBn	1	C	**d**	$CH{=}CH_2$	66:34	81
5	**c**	CH_2OBn	2	C	**e**	$CH{=}CH_2$	58:42	64

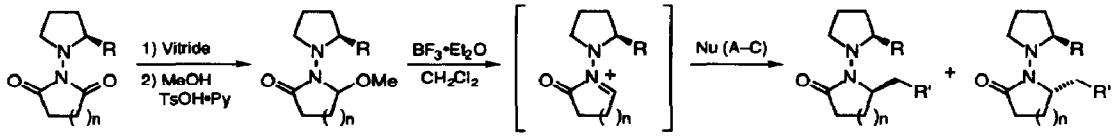
[a] A =  B =  C =  [b] Ar = C_6H_3-3,4-$(OMe)_2$. [c] Determined by ^1H NMR.

[d] Isolated yield of diastereomeric mixture from **9**.

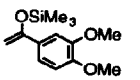
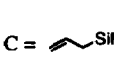
On the other hand, when the corresponding reactions were performed with the cyclic imides **13** under the same conditions employed above by using the various 2-substituted pyrrolidines as chiral auxiliaries, the remarkable enhancement of the diastereoselectivities for the *syn*-hydrazides **16** was observed (Table 2), wherein the sense of induction (*anti* vs. *syn*) was opposite to that observed for the cyclic imides **8** having the 2,5-disubstituted pyrrolidine auxiliaries. As can be seen in entries 7–13, when the six-membered ring imides **13e–g** were employed, the syn selectivity was higher than that obtained in the five-membered ring imides **13a–d** (entries 1–6). In particular, almost complete syn selectivities were obtained for the six-membered ring imide **13f** possessing the isopropyl group (entries 9, 10).

The absolute configurations of the newly induced asymmetric centers of the lactams **11** and **16** were determined by their chemical transformation into a natural alkaloid and an amino acid as outlined in Scheme 2. Thus, **11e** and **16l** were both converted to (+)-coniine (**19**) with borane[9] via a simultaneous process involving reduction of the lactam carbonyl group and cleavage of the chiral auxiliaries **20**. Alternatively,

Table 2. Asymmetric amidoalkylation of cyclic *N*-(2-substituted-pyrrolidin-1-yl)imides **13**.



entry	compound (13)			products (16 and 17)				
		R	n	nucleophile[a]		R'[b]	16:17 ratio[c]	yield, %[d]
1	a	Me	1	A	a	COAr	89:11	88
2	b	*i*-Pr	1	A	b	COAr	96:4	90
3	c	CH_2OBn	1	C	c	$CH{=}CH_2$	84:16	94
4	c	CH_2OBn	1	A	d	COAr	85:15	95
5	d	$CHPh_2$	1	A	e	COAr	80:20	89
6	d	$CHPh_2$	1	C	f	$CH{=}CH_2$	81:19	90
7	e	Me	2	A	g	COAr	95:5	70
8	e	Me	2	B	h	COPh	93:7	63
9	f	*i*-Pr	2	A	i	COAr	>99:1	69
10	f	*i*-Pr	2	B	j	COPh	>99:1	65
11	g	CH_2OBn	2	A	k	COAr	99:1	70
12	g	CH_2OBn	2	C	l	$CH{=}CH_2$	99:1	64
13	g	CH_2OBn	2	B	m	COPh	96:4	68

[a] A =  B =  C =  [b] Ar = C_6H_3-3,4-$(OMe)_2$. [c] Determined by ^1H NMR.

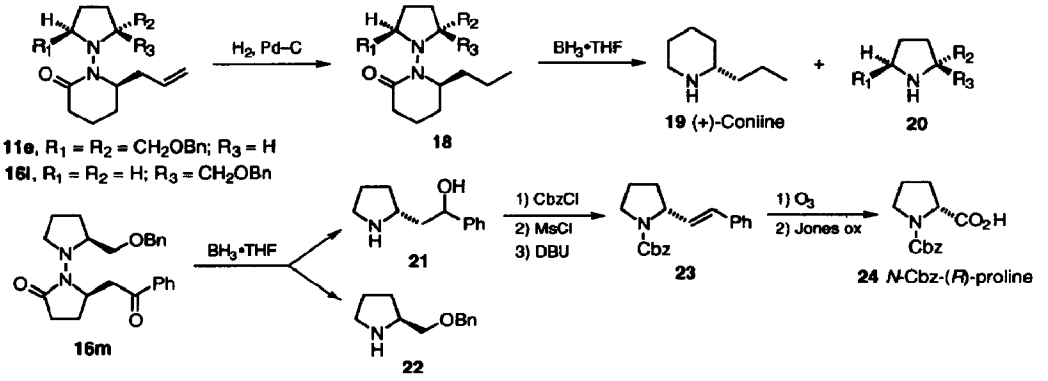
[d] Isolated yield of diastereomeric mixture from **14**.

treatment of **16m** with borane provided the amino alcohol **21** as well as the chiral auxiliary **22**, the former of which was then converted to *N*-Cbz-(*R*)-proline (**24**). The auxiliaries **20** and **22** recovered in these transformations without racemization can be recycled by the sequence outlined in Scheme 1.

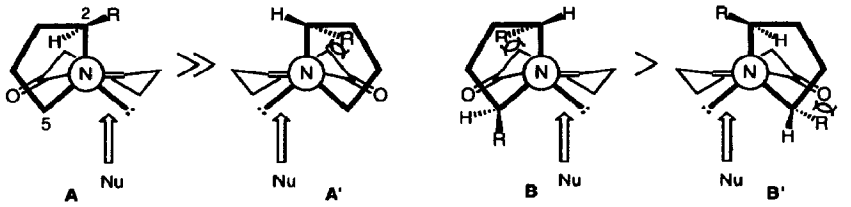
The C_2 symmetric pyrrolidines have proved to be advantageous and useful chiral auxiliaries in substrate-controlled asymmetric synthesis.[6b] In the present cases, however, higher levels of diastereoselectivity were recognized using the monosubstituted pyrrolidines rather than the C_2 symmetric disubstituted pyrrolidines. The difference in the degree of diastereoselectivity and the inversion of the chirality induction (*anti* to *syn*), both arising from the chiral auxiliaries employed, lead to a rationalization for the observed asymmetric inductions as follows.

High syn stereoselectivities leading to **16** during nucleophilic addition to the acyliminium ions **15** containing the chiral monosubstituted pyrrolidines may be ascribed to the preferred transition conformer **A** (represented by a six-membered ring acyliminium ion), where the largest N-substituent (C-2) adopts a perpendicular position to the plane of the C=N double bond due to a destabilizing $A^{1,3}$ type interaction, and the ring methylene group (C-5) is placed syn to the sterically less demanding amide carbonyl group. Thus, in the conformer **A** the pyrrolidine nitrogen atom possesses the pyramidal stability and may constitute an asymmetric center. The antiperiplanar approach of the nucleophile then should preferentially occur from the

Scheme 2



α-face of **A**, providing the *syn* isomers **16**. The alternative conformer **A'** (leading to the *anti* isomers **17**), which arises from pyramidal inversion in the trivalent pyrrolidine nitrogen, however, should suffer from nonbonding interaction between the C-2 substituent (R) and the ring methylene group. On the other hand, in the case of the acyliminium ions **10** possessing the C_2-symmetric pyrrolidines, the observed anti stereoselectivity is consistent with the conformer **B**, which, however, has destabilizing steric interaction due to the α-oriented R group on the pyrrolidine ring. Accordingly, the difference in the stability between **B** and **B'** (leading to the *syn* isomers **12**) is insufficient to induce high stereoselectivity.



Further application of this asymmetric amidoalkylation to enantioselective chiral synthesis of natural alkaloids is under study.

References and Notes

1. Hiemstra, H.; Speckamp, W. N. In *The Alkaloids*: Brossi, A., Ed.; Academic Press: New York, 1988; Vol. 32, Chap. 4.
2. Wanner, K. Th.; Kärtner, A. *Arch. Pharm.* **1987**, *320*, 1253.
3. Williams, R. M.; Sinclair, P. J.; Zhai, D.; Chen, D. *J. Am. Chem. Soc.* **1988**, *110*, 1547.
4. (a) Polniaszeck, R. P.; Belmont, S. E.; Alvarez, R. *J. Org. Chem.* **1990**, *55*, 215. (b) Kiguchi, T.; Nakazono, Y.; Kotera, S.; Ninomiya, I.; Naito, T. *Heterocycles* **1990**, *31*, 1525.
5. Laurence, E. B.; Meyers, A. I. *J. Am. Chem. Soc.* **1991**, *113*, 9858.
6. (a) Enders, S. In *Asymmetric Synthesis*: Morrison, J. D., Ed.; Academic Press: New York, 1983; Vol. 3, Chap. 4. (b) Whitesell, J. K. *Chem. Rev.* **1989**, *89*, 1581. (c) Schultz, A. G. *Acc. Chem. Res.* **1990**, *23*, 207. (d) Fuji, K. *Chem. Rev.* **1993**, *93*, 2037.
7. Conveniently prepared by the reaction of (2*S*,5*S*)-1,6-bis(benzyloxy)-2,5-bis(methylsulfonyloxy)hexane[8] and hydrazine (60 °C, 36 h).
8. Machinaga, N.; Kibayashi, C. *Synthesis* **1992**, 989.
9. Feuer, H.; Brown, F., Jr. *J. Org. Chem.* **1970**, *35*, 1468.

(*Received in Japan* 25 *February* 1994; *accepted* 9 *May* 1994)