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Synthesis of Chiral 1,4-Dihydropyridines by Diastereoface-selective Asymmetric Addition to Nicotinic Amides

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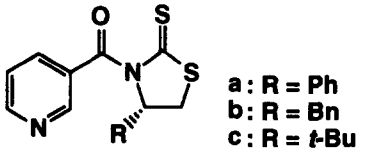
Abstract: Diastereoface-selective asymmetric addition of organometallic reagents to pyridinium salts of **1** and **2** was performed to give chiral 1,4-dihydropyridines in good regio- and stereoselectivities. The absolute configuration of the newly-produced chiral center was determined by X-ray analysis after derivation to menthyloxycarbamate **10**. Neighboring group participation of the thiocarbonyl group to the pyridinium nucleus was predicted by PM3 calculations of the intermediary pyridinium salts, which may play an important role in the generation of stereoselectivity.

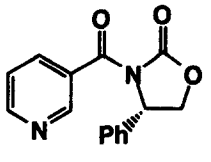
Key words: asymmetric synthesis; pyridine; pyridinium salts; neighboring group effects

Asymmetric synthesis of chiral dihydropyridines has received considerable attention because of their synthetic utility for various natural products and bioactive compounds. Diastereoface-selective addition of organometallic reagents to the 4-position of *N*-acylpyridinium salts is an effective method to produce chiral 1,4-dihydropyridines. To achieve the face-selective addition, chiral oxazoline[1], aminal[2] and $[\eta^5\text{-}C_5H_5)Fe(CO)(PPh_3)]$[3] groups at the 3-position of the pyridinium nucleus were proved to be effective chiral auxiliaries. In the course of our studies on the structure and selective reaction of the amides containing chiral 1,3-thiazolidine-2-thiones,[4] we were interested in the 1,5-remote asymmetric addition to nicotinic amides **1**. We now describe the asymmetric addition of organometallic reagents to the nicotinic amides **1** and **2** having chiral auxiliaries that are widely used in various asymmetric reactions.



a: R = Ph
b: R = Bn
c: R = *t*-Bu

1



2

As nicotinic amide derivatives, we used **1** and **2** which are readily prepared from chiral (*S*)-thiazolidine-2-thiones[4,5] and (*S*)-oxazolidinones[6] with nicotinic pivalic anhydride or nicotinoyl chloride, respectively. After the amides **1** and **2** were converted *in situ* into the corresponding pyridinium salts with acyl chlorides or chloroformates, the addition of nucleophiles to the pyridinium salts was performed as shown in Scheme 1. The results are listed in Table 1. The reaction of the pyridinium salts of **1** with Me_2CuLi gave a 93:7 mixture of 1,4-

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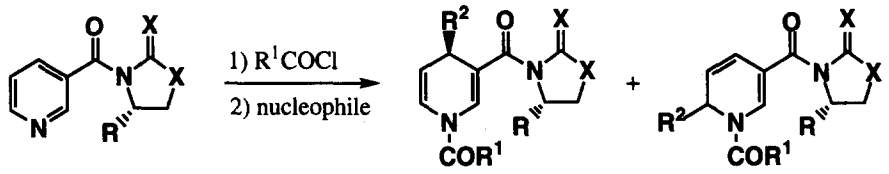
Scheme 1



1 or 2 | **3 : X = S, 5 : X = O** | **4 : X = S, 6 : X = O**

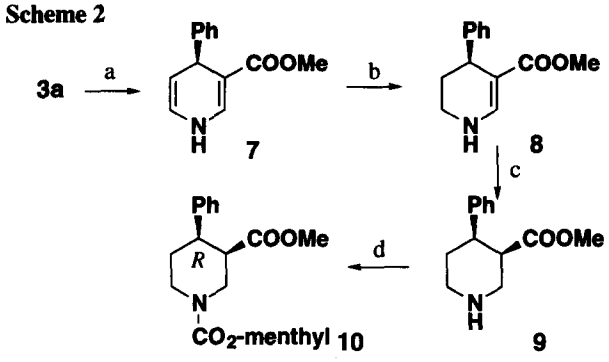
Table 1 Diastereoface-selective addition to amide **1** or **2**[a]

Entry	Amide	R^1	Nucleophile	Yield/%	**3 : 4** (**5 : 6**)	Diastereomer ratio of **3** or **5**
1	**1a**	OMe	Me_2CuLi	68[b](61)[c]	93 : 7	67 : 33
2	**1a**	OMe	Ph_2CuLi	70[b](46)[c]	95 : 5	84 : 16
3	**1a**	Ph	Ph_2CuLi	76[b](59)[c]	100 : 0	88 : 12
4	**1b**	Ph	Ph_2CuLi	59[b](48)[c]	100 : 0	88 : 12
5	**1c**	Ph	Ph_2CuLi	85[b](68)[c]	100 : 0	91 : 9
6	**1a**	OMe	$BnSnMe_3$[d]	72[c]	100 : 0	80 : 20
7	**1a**	OMe	$allylSnBu_3$[d]	85[c]	7 : 50(43)[e]	62 : 38
8	**2**	OMe	Ph_2CuLi	70[b](47)[c]	72 : 28	60 : 40
9	**2**	OMe	$BnSnMe_3$[d]	62[c]	100 : 0	66 : 34

[a] The reactions were conducted in THF at -70°C unless otherwise noted. [b] Conversion yield. [c] Isolated yield. [d] The reaction was conducted in CH_2Cl_2 at 0°C. [e] The ratio of 1,2-dihydropyridine is indicated in parentheses.

and 1,6-adducts **3** and **4**. The diastereomer ratio of **3** is 67:33 (entry 1). These regio- and stereoisomer ratios were determined by ^1H NMR spectroscopy. The preference in the 1,4-addition has been generally observed when using organocuprates.[7] Ph_2CuLi added to the pyridinium salts with higher stereoselectivity than Me_2CuLi (entry 2). When benzoyl chloride was employed instead of methyl chloroformate to generate an intermediary pyridinium salt, both regio- and stereoselectivities in the adducts were improved (entries 3-5), indicating the importance of the steric bulkiness around the N atom in the selectivities. Although the difference in the substituents at the chiral center of the thiazolidine-2-thione moiety did not have a significant effect on the stereoselectivity, amide **1c** having the most bulky t-butyl group slightly raised the selectivity (entry 5). Trimethylbenzyltin also works as a nucleophile[8] to give **3** in good regio- and stereoselectivities (entry 6). In contrast, allyltributyltin mainly provided 2- and 6-adducts with the ratio of 43:50, the result of which is almost in agreement with the reported observation[9] (entry 7). Amide **2**, which has an oxazolidinone moiety as a chiral auxiliary, also reacts with organocopper and organotin reagents to give **5** and **6** similar to the reaction of amide **1** (entries 8 and 9). However, the stereoselectivities are much lower than those obtained in the corresponding reactions of **1a** (entries 2 and 6).

Scheme 2



Reagents: a) NaOMe, MeOH; b) PtO_2, H_2, EtOH; c) PtO_2, H_2, EtOH, AcOH; d) (+)-$ClCO_2$menthyl, Et_3N, CH_2Cl_2

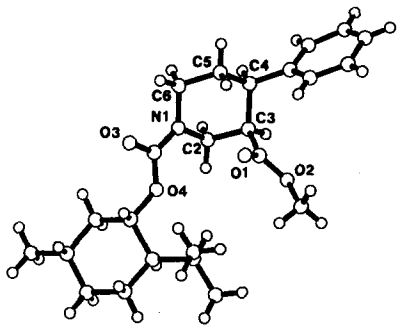
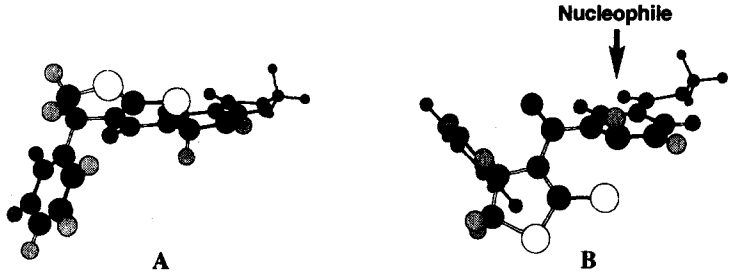


Figure 1 X-ray structure of **10**

The absolute configuration of the newly-produced asymmetric center of the major product could not be readily determined by X-ray analysis because of their instability. Therefore, after **3a**(R^1=Ph, R^2=Ph) was derived to **10**, the absolute configuration of the 4-position was determined by X-ray analysis (Scheme 2). Thus, the chiral auxiliary of the dihydropyridine **3a** was removed by treatment with NaOMe to produce a methyl ester **7**. Catalytic hydrogenation of **7** with PtO_2 in EtOH resulted in selectively reduced tetrahydropiperidine **8**, whereas in the presence of acetic acid the hydrogenation completed to give a 9:1 *cis* and *trans* mixture of **9**. After **9** was converted to menthyloxycarbamates **10**, several recrystallizations provided a pure analytical sample for X-ray crystallographic analysis.[10] The X-ray structure of **10** unequivocally showed that the 4-position possesses *R*-configuration (Figure 1); the absolute configuration of the 4-position of dihydropyridine **3a** was determined to be *S*-configuration.



ΔH_f = 136.46 kcal / mol

ΔH_f = 136.42 kcal / mol

Figure 2 Two stable conformers of the pyridinium salt of **1a**

To elucidate the mechanism of the 1,5-remote asymmetric induction, we studied the optimized structure of the intermediary pyridinium salt of **1a** by PM3 method.[11] Two stable conformers, the energies of which are similar in magnitude, were observed as shown in Figure 2. It is interesting to note that the neighboring group participation was predicted between the thiocarbonyl and pyridinium cation for both conformers; intramolecular distances between the S atom of thiocarbonyl and the 4-position of pyridinium nucleus for **A** and **B** are 1.870Å and 1.874Å, respectively. This seems to stabilize their conformations. Since nucleophiles attack the the pyridinium plane from the opposite side of the thiocarbonyl group, the less hindered conformer **B** will react

with the nucleophiles in preference to conformer **A** to give the dihydropyridines possessing *S*-configuration (R^2 = Ph) predominantly. Such intramolecular interaction was not predicted in the salt of amide **2** by the calculations; therefore, the difference in the stereoselectivities between amide **1** and **2** may also be ascribed to the neighboring group participation.

The intramolecular interaction was studied by ^{1}H NMR spectroscopy. The Δδ H values (difference of δH between the pyridinium salt and the corresponding pyridine) for **1a** are very different from those for standard *N,N*-dimethylnicotinamide,[12] which suggests that the thiazolidine-2-thione moiety influences on the electronic properties of the pyridinium nucleus. The details of the neighboring group participation have now been investigated by various spectroscopies and will be reported in due course.

Typical procedure for the synthesis of chiral dihydropyridines is as follows. To a solution of amide **1a** (130 mg) in dry THF (1.0 ml) was added benzoyl chloride (60 μl) at 0°C and the solution was stirred for 1 h. After the solution was cooled to -70°C, diphenylcuprate (1.2 eq) in THF was added to the solution. The solution was stirred for 2h and then allowed to warm to room temperature. The hydrolysis was done with saturated ammonium chloride solution by stirring for 1 h. The aqueous phase was extracted with ether to give a crude product, which was subjected to column chromatography on silica gel to give pure 1,4-dihydropyridine **4a**.

Acknowledgments

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9. Yamaguchi, R.; Moriyasu, M.; Yoshioka, M.; Kawanisi, M. *J. Org. Chem.*, **1985**, *50*, 287.
10. Crystal data for **10** : $C_{24}H_{35}NO_4$, M = 401.53, orthorhombic, space group $P2_12_12_1$ a = 17.372(3), b = 23.791(2), c = 5.549(3) Å, V = 2293.5(13) $Å^3$, Z = 4, ρ_{calcd} = 1.163 Mgm^{-3}, m = 0.623 mm^{-1}(Cu-$K\alpha$, λ = 1.54178 Å), $F(000)$ = 872, T = 293 K. A total of 1710 unique data for 2Θmax = 120° was collected of which 1710 were independent. The structure was solved by direct methods with SHELXS-86 and refined on F^2 using the SHELXL-93. Non-hydrogen atoms were refined anisotropically by full-matrix least squares method. All the H atoms were treated isotropic. The R and Rw factors after refinement of 263 parameters using 1708 observed reflections [$I > 2\sigma(I)$] were 0.0620 and 0.2441, respectively.
11. PM3 calculations were performed by using *CS MOPAC Pro* with MMOK empirical amide correction factor.
12. Δδ H (ppm) values of **1a**: H2; 0.20, H4; 0.20, H5; 0.04, H6; 0.08. Δδ H (ppm) values of *N,N*-dimethylnicotinamide: H2; 0.17, H4; 0.42, H5; 0.39, H6; 0.19.