

## Face-Selective Addition to a Cation $-\pi$ Complex of a Pyridinium Salt: Synthesis of Chiral 1,4-Dihydropyridines

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An intramolecular  $\pi - \pi$  interaction is recognized as a powerful conformation-controlling tool in various face-selective addition reactions such as aldol reactions, conjugate additions, Diels-Alder reactions, and [3 + 2] and [2 + 2] cycloadditions.<sup>1</sup> In contrast, although a cation- $\pi$  interaction<sup>2</sup> has a stronger interactive force, little is known about its application to synthetic reactions except for stereoselective  $\beta$ -galactosylation in the presence of calixarene,<sup>3</sup> selective photoisomerization of diphenylcyclopropane,<sup>4</sup> and chemoselective hydroperoxidation of alkenylarenes in zeolite.<sup>5</sup>

As part of our research program on the development of a new synthetic method of chiral 1,4-dihydropyridines by face-selective nucleophilic addition to pyridinium salts,<sup>6</sup> we focused on a cation– $\pi$  interaction between a pyridinium and a phenyl ring<sup>7</sup> as a conformation-controlling tool. Since chiral 1,4-dihydropyridines continue to be of great interest in relation with calcium agonists,<sup>8</sup> NADH models,<sup>9</sup> and intermediates for alkaloid syntheses,<sup>10</sup> the stereose-lective synthesis of these compounds has attracted the attention of researchers.<sup>6,11</sup> Here we report a new synthetic method of chiral 1,4-dihydropyridines by way of a face-selective addition to a cation– $\pi$  complex.

Our strategy for the stereoselective synthesis of 1,4-dihydropyridines is outlined in Scheme 1: (a) conversion of compound **A** containing both a pyridine and a phenyl moiety into a pyridinium salt gives rise to an attractive force between the two entities to form a cation  $-\pi$  complex **B**; (b) the selective shielding of one side of the pyridinium face by the phenyl ring enables nucleophiles to attack the complex only from the nonshielded side, which will result in 1,4-dihydropyridine **C** stereoselectively.



We prepared nicotinic amide derivatives **1b** and **1c** having chiral 2,2-dimethyloxazolidines<sup>12,13</sup> and their *N*-methyl salts **2b** and **2c** for the geometrical studies. Achiral **1a** and **2a** were used as the standard compounds. Although intramolecular  $\pi - \pi$  interactions are postulated in some benzyloxazolidinone derivatives during asymmetric addition reactions,<sup>14</sup> our previous studies indicated that the oxazolidinones are a less effective chiral auxiliary for the present purpose.<sup>6c</sup>

Table 1 lists the chemical shifts for the pyridine and pyridinium protons of 1 and 2, and the  $\Delta\delta$  value that is the changes in the chemical shifts compared to those for standards 1a and 2a. It is

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Table 1.	<sup>1</sup> H NMR	Chemical	Shifts	(ppm) <sup>a</sup>	for	1a,	1b,	2a	and	2b,
and $\Delta\delta$ V	′alues <sup>b</sup>									

	$\delta$ 1a	$\delta$ 1b	$\Delta\delta$ 1b	δ2a	$\delta 2b$	$\Delta\delta$ 2b
2H	8.76	8.66	-0.10	9.17	9.10	-0.07
4H	7.82	7.67	-0.15	8.47	7.73	-0.74
5H	7.36	7.36	0.00	8.11	7.67	-0.44
6H	8.67	8.70	0.03	9.15	8.93	-0.22

<sup>*a*</sup> Measured at 270 MHz in 2.5 mM solution of CDCl<sub>3</sub>. <sup>*b*</sup> The  $\Delta\delta$  values were calculated using the equations,  $\Delta\delta$ 1b =  $\delta$ 1b -  $\delta$ 1a,  $\Delta\delta$ 2b =  $\delta$ 2b -  $\delta$ 2a.



obvious that the  $\Delta\delta 2b$  values are negatively larger than the  $\Delta\delta 1b$  values, suggesting a considerable conformational difference between **1b** and **2b**; the pyridine and the phenyl ring of **1b** would be apart from each other, whereas the phenyl ring of **2b** would be so close to shield the pyridinium protons. On the other hand, the differences between  $\Delta\delta 1c$  and  $\Delta\delta 2c$  were very small.

X-ray analyses clarified significant geometrical differences between **1b** and **2b** (Figure 1). The most striking structural feature in **2b** is that the pyridinium and the phenyl rings lie parallel to each other and the two rings are arranged face-to-face, the distance between which is about 3.4 Å. On the other hand, the pyridine and the phenyl moieties of **1b** are apart from each other. These geometrical difference can reasonably explain the small  $\Delta\delta$ 1b and negatively larger  $\Delta\delta$ 2b in the <sup>1</sup>H NMR studies described above. The fact that the geometry largely depends on whether the pyridine nucleus has a cationic charge unambiguously evidences that a cation- $\pi$  interaction governs the conformation of **2b**. Similar intramolecular Py<sup>+</sup>- $\pi$  interactions have been postulated in some reaction intermediates.<sup>15</sup> Although charge transfer is considered to be a major attractive force in several Py<sup>+</sup>- $\pi$  complexes,<sup>16</sup> no charge-transfer absorption was observed in the present complex.

The cation  $-\pi$  complex formation in **2b** prompted us to study the face-selective addition of nucleophiles to **1b** and **1c**. For nucleophiles, we employed ketene silyl acetals **3a** and **3b**. Since most face-selective nucleophilic 1,4-addition to pyridinium salts has been performed under chelation-controlling conditions,<sup>11</sup> ketene silyl acetals have scarcely been employed for the face-selective addition reactions except for our previous report.<sup>6c</sup> Addition of ketene silyl acetals **3a** to **1b** and **1c** in the presence of methyl chloroformate in CH<sub>2</sub>Cl<sub>2</sub> gave 1,4-adducts **4b** and **4c** as a major product with a small amount of 1,6-adducts, respectively, as shown



*Figure 1.* X-ray structures for **1b** (a) and **2b** (b). The thermal ellipsoids are set at the 30% probability level for each. The hydrogen atoms and a counterion are omitted for clarity. Selected interatomic distances for **2b** (Å): C3···C8 3.323, C3···C13 3.491, C4···C8 3.551, C4···C9 3.557, C4···C10 3.530, C4···C11 3.511, C4···C12 3.441, C4···C13 3.454, C5···C12 3.354.

Table 2.	Addition	of Ketene	Silyl	Acetals t	to	•
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in Table 2 (entries 1 and 2). Remarkable is the significant difference in the stereoselectivities depending on the chiral auxiliaries; addition to 1b gave excellent selectivity (entry 1), whereas the selectivity in the case of 1c was very low (entry 2). This would be attributable to the geometrical differences between the intermediary pyridinium salts; the benzyl group much more effectively shields one side of the pyridinium face than does the phenyl group. Various solvents, such as CHCl<sub>3</sub>, THF, toluene, and CH<sub>3</sub>CN are available in these reactions (entries 3-6). Ketene silyl acetal 3b also serves as a good nucleophile to give 1,4-adduct 5b in excellent regio- and stereoselectivities with good syn selectivities about the newly produced two chiral centers (entries 6 and 7). The <sup>1</sup>H NMR spectrum for the major isomer shows a smaller coupling constant between 4H and 1'H and a significant downfield shift of 1'H due to a deshielding effect of the dihydropyridine moiety (4.9 Hz and  $\delta$  4.41 for the major isomer, and 7.6 Hz and  $\delta$  3.78 for the minor isomer), which suggest 1'H being syn to the 4H on the basis of the optimized structures obtained by ab initio calculations at the RHF/3-21G\* level.<sup>17</sup> It is worthwhile to note that the chiral auxiliary of adduct **4b** can be removed with  $Cp_2Zr(H)Cl^{18}$  to give the corresponding aldehvde without reduction of the other functionaries.

The absolute configuration of the stereogenic center for **4b** was clarified to be *S* by X-ray analysis. Analogously, the two chiral centers for the major isomer of **5b** are assigned to be (4R, 1'S). This indicates that the cation $-\pi$  interaction will occur with the *re* face of the pyridinium ring, and the nucleophiles attack from the *si* face of the complex **II** as shown in Figure 2. This working model was



*Figure 2.* Working model for nucleophilic addition to a cation  $-\pi$  complex.

supported by structural optimization of the intermediary pyridinium cation by *ab initio* calculations at the RHF/3-21G\* level,<sup>17</sup> where conformer **II** is 2.1 kcal/mol more stable than conformer **I**. Therefore, the equilibrium between conformers **I** and **II** favors **II**; as a result, a nucleophile will attack the conformer **II** from the non-shielded side to give a chiral dihydropyridine in good stereoselectivity.

In summary, we have shown the first evidence for the existence of an intramolecular cation $-\pi$  interaction between a pyridinium cation and a benzyl moiety. Moreover, the utility of the intramolecular cation $-\pi$  interaction was demonstrated by the synthesis of chiral 1,4-dihydropyridines with excellent stereoselectivity. Since the cation $-\pi$  interaction generally has a stronger interactive force than the  $\pi-\pi$  interaction, it will be a promising conformationcontrolling tool for a variety of synthetic reactions.

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Supporting Information Available: Crystallographic data for 1b, 2b and 4b, synthetic procedures and spectral data for 1a-1c, 2a, 2b, 4b and 5b, and optimized structures for two isomers of 5b with their stereochemical assignment (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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