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Face-Selective Addition to a Cation−π Complex of a Pyridinium Salt: Synthesis of Chiral 1,4-Dihydropyridines

Shinji Yamada* and Chisako Morita

Department of Chemistry, Faculty of Science, Ochanomizu University, Bunkyo-ku, Tokyo 112-8610, Japan

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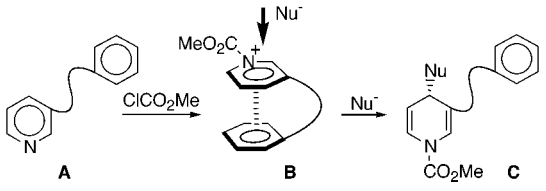
An intramolecular $\pi-\pi$ interaction is recognized as a powerful conformation-controlling tool in various face-selective addition reactions such as aldol reactions, conjugate additions, Diels−Alder reactions, and [3 + 2] and [2 + 2] cycloadditions.[1] In contrast, although a cation−π interaction[2]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

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,[6] we focused on a cation−π interaction between a pyridinium and a phenyl ring[7] as a conformation-controlling tool. Since chiral 1,4-dihydropyridines continue to be of great interest in relation with calcium agonists,[8] NADH models,[9] and intermediates for alkaloid syntheses,[10] the stereoselective synthesis of these compounds has attracted the attention of researchers.[6,11] Here we report a new synthetic method of chiral 1,4-dihydropyridines by way of a face-selective addition to a cation−π 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−π 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.

Scheme 1



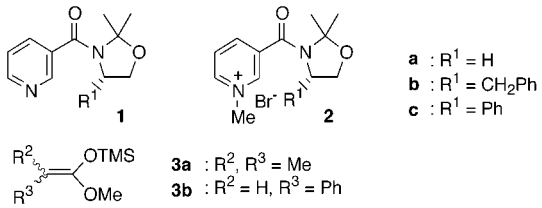
We prepared nicotinic amide derivatives **1b** and **1c** having chiral 2,2-dimethyloxazolidines[12,13] and their *N*-methyl salts **2b** and **2c** for the geometrical studies. Achiral **1a** and **2a** were used as the standard compounds. Although intramolecular $\pi-\pi$ interactions are postulated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

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 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.

Table 1. ^{1}H NMR Chemical Shifts (ppm)[a] for **1a**, **1b**, **2a** and **2b**, and $\Delta\delta$ Values[b]

	δ1a	δ1b	$\Delta\delta$1b	δ2a	δ2b	$\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

[a] Measured at 270 MHz in 2.5 mM solution of $CDCl_3$. [b] The $\Delta\delta$ values were calculated using the equations, $\Delta\delta 1b = \delta 1b - \delta 1a$, $\Delta\delta 2b = \delta 2b - \delta 2a$.



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 ^{1}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−π interaction governs the conformation of **2b**. Similar intramolecular $Py^+-\pi$ interactions have been postulated in some reaction intermediates.[15] Although charge transfer is considered to be a major attractive force in several $Py^+-\pi$ complexes,[16] no charge-transfer absorption was observed in the present complex.

The cation−π 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,[11] ketene silyl acetals have scarcely been employed for the face-selective addition reactions except for our previous report.[6c] Addition of ketene silyl acetals **3a** to **1b** and **1c** in the presence of methyl chloroformate in CH_2Cl_2 gave 1,4-adducts **4b** and **4c** as a major product with a small amount of 1,6-adducts, respectively, as shown

* Corresponding author. E-mail: yamada@cc.ocha.ac.jp, Fax: 81-3-5978-5715.

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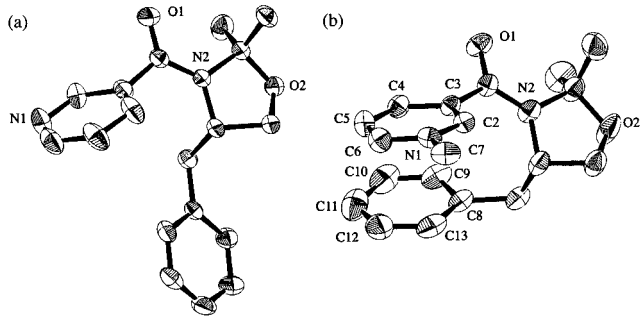
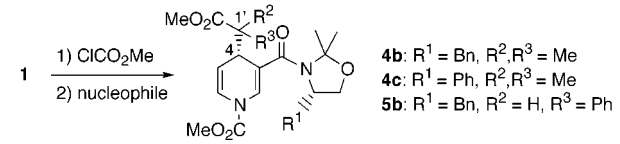


Figure 1. X-ray structures for **1b** (a) and **2b** (b). The thermal ellipsoids are set at the 30% probability level for each. The hydrogen atoms and a counterion are omitted for clarity. Selected interatomic distances for **2b** (Å): C3···C8 3.323, C3···C13 3.491, C4···C8 3.551, C4···C9 3.557, C4···C10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



entry	compd	acetal	solv	yield/%[a]	(1,4-: 1,6-)[b]	de/% of **4** or **5**[b]
1	**1b**	**3a**	CH_2Cl_2	94	86:14	>99
2	**1c**	**3a**	CH_2Cl_2	60(94)	78:22	12
3	**1b**	**3a**	$CHCl_3$	90	93:7	>99
4	**1b**	**3a**	THF	56(99)	87:13	>99
5	**1b**	**3a**	toluene	70(99)	97:3	>99
6	**1b**	**3b**[c]	CH_3CN	80	>99:1	>99(93:7)[d]
7	**1b**	**3b**	CH_2Cl_2	61(99)	93:7	>99(94:6)[d]

[a] Isolated yields. Conversion yield is indicated in parentheses. [b] Determined by ^{1}H NMR spectroscopy. [c] Eight equivalents were used. [d] *syn/anti* diastereomer ratio.

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 $CHCl_3$, THF, toluene, and CH_3CN 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 ^{1}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 δ 4.41 for the major isomer, and 7.6 Hz and δ 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.[17] 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 aldehyde 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 (4*R*,1′*S*). This indicates that the cation−π 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

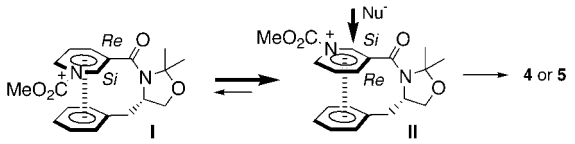


Figure 2. Working model for nucleophilic addition to a cation−π complex.

supported by structural optimization of the intermediary pyridinium cation by *ab initio* calculations at the RHF/3-21G* level,[17] 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 nonshielded side to give a chiral dihydropyridine in good stereoselectivity.

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