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Enantioselective cyclopropanation reaction using a conformationally fixed pyridinium ylide through a cation–π interaction

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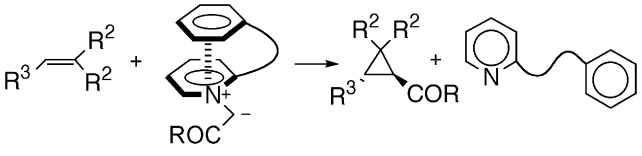
Abstract—Using a chiral pyridinium ylide with a fixed conformation through a cation–π interaction performs enantioselective cyclopropanation of electron-deficient olefins. ^{1}H NMR, X-ray structural analysis and DFT calculations elucidated the self-complexation and the face-to-face arrangement between the pyridinium and the phenyl rings. The absolute configuration of the product was determined after conversion into a bicyclic cyclopropane derivative.

Cyclopropanes constitute various natural products, biologically active compounds, and synthetic intermediates,[1] and, therefore, cyclopropane synthesis has continued to be an attractive subject.[2] There have been various methods known for the stereoselective cyclopropanation of unsaturated compounds such as the Simmons–Smith reaction,[3] addition of carbene complexes,[4] biomimetic approach,[5] and addition–elimination reaction of ylides.[6–8] Recently, sulfonium[6] and ammonium[7] ylide-based enantioselective cyclopropanation has extensively been explored; however, little is reported on an enantioselective approach using a pyridinium ylide.[8]

Continuing our research program on the synthetic application of pyridine compounds,[9] we focused on a pyridinium ylide-based enantioselective cyclopropanation reaction. In the previous studies, we have reported a face-selective addition reaction of a nucleophile toward a pyridinium–π complex to give chiral dihydropyridines,[9] where the phenyl ring selectively blocks one face of the pyridinium ring. This face-selective process prompted us to use a pyridinium–π complex for cyclopropanation reactions using a pyridinium ylide. In this Letter, we describe a new method for the pyridinium ylide-based enantioselective cyclopropanation.

Scheme 1 outlined our strategy: (1) An ylide produced from a pyridinium salt bearing a chiral auxiliary would form a self-complex with shielding of one of the pyridinium faces. (2) This ylide attacks an electron-deficient olefin at the unblocked side to form a betaine, which makes a cyclopropane with recovery of the framework picolinic amide.

Picolinic amides **1a** and **1b** were prepared by a coupling reaction of picolinic acid and 1,3-oxazolidine derivatives. This was converted to pyridinium salts **2a**–**2e** with the corresponding bromides at 40 °C without a solvent. The cyclopropanation reaction of benzyliden malononitril **3a** with pyridinium salt **2a** was carried out in the presence of Et_3N at rt to yield *trans*-cyclopropane **4a** in good enantiomer ratio with recovery of the chiral auxiliary **1b** (Table 1, entry 1). The enantioselectivity is determined by HPLC analysis using a chiral stationary phase. X-ray structural analysis of compound **6** clarified



Scheme 1. Strategy of enantioselective cyclopropanation.

Keywords: Cyclopropanation; Pyridinium ylide; Cation–π interaction; Pyridinium–π interaction; Enantioselective reaction.
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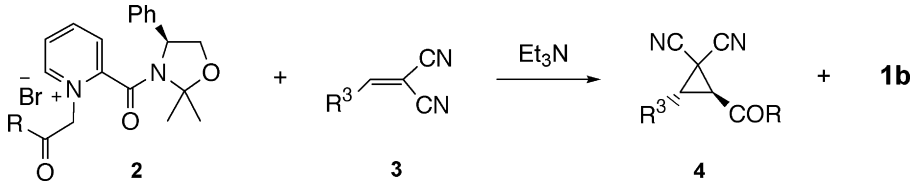
Table 1. Enantioselective cyclopropanation by way of pyridinium ylide

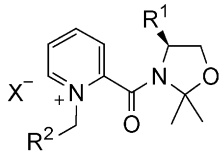


Entry	Pyridinium salt	Alkene	Solv	Product	Yield[a] (%)	er[b] (%)
1	**2a**	**3a**	CH_2Cl_2	**4a**	78	83:17
2	**2a**	**3a**	THF	**4a**	87	62:38
3	**2a**	**3a**	CH_3CN	**4a**	84	70:30
4	**2a**	**3a**	Toluene	**4a**	46	78:22
5	**2a**	**3b**	CH_2Cl_2	**4b**	82	81:19
6	**2a**	**3c**	CH_2Cl_2	**4c**	80	84:16
7	**2a**	**3d**	CH_2Cl_2	**4d**	81	89:11
8	**2b**	**3e**	CH_2Cl_2	**4e**	49	96:4
9	**2c**	**3e**	CH_2Cl_2	**4f**	82	91:9
10	**2c**	**3f**	CH_2Cl_2	**4g**	89	91:9
11	**2c**	**3g**	CH_2Cl_2	**4h**	90	64:36

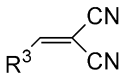
[a] Isolated yield.
[b] Enantiomer ratio was determined by HPLC with CHIRALCEL OD.

the *trans*-selectivity described later, which is in agreement with that reported in the literature of pyridinium ylide-based cyclopropanation reactions.[8]

1a: R^1 = H
1b: R^1 = Ph



2a: R^1 = Ph, R^2 = CO_2Et, X = Br
2b: R^1 = Ph, R^2 = CO_2Bn, X = Br
2c: R^1 = Ph, R^2 = COPh, X = Br
2d: R^1 = H, R^2 = CO_2Et, X = Br
2e: R^1 = Ph, R^2 = H, X = I

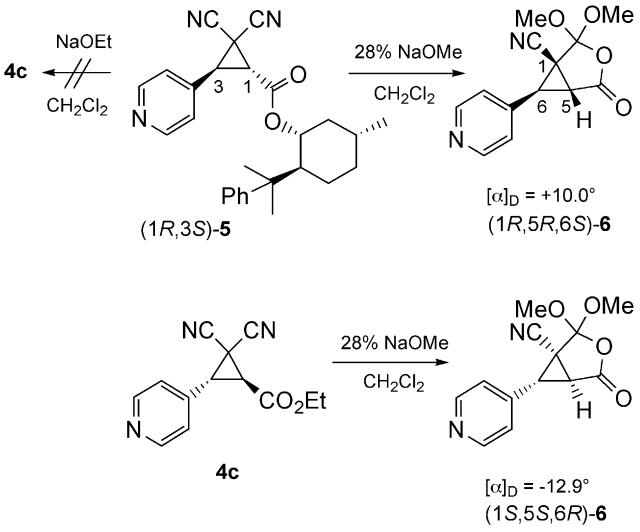


3a: R^3 = Ph
3b: R^3 = *o*-MeO-C_6H_4
3c: R^3 = pyridyl
3d: R^3 = 1-naphthyl
3e: R^3 = *t*-Bu
3f: R^3 = cyclohexyl
3g: R^3 = Et

Among the solvents we investigated, CH_2Cl_2 is the most effective to give an 83:17 mixture of enantiomers of **4a** (entries 1–4). Cyclopropanation of various alkenes bearing *o*-methoxyphenyl, pyridyl, and naphthyl substituents is performed in a good yield with a high selectivity (entries 5–7). The alkenes having an alkyl substituent are also available for this reaction. The reaction of **3e** having the bulkiest substituent resulted in the highest enantioselectivity regardless of the N-substituent of the pyridinium salt (entries 8 and 9). A cyclohexyl group is also an effective substituent, however, an ethyl group is less effective to give lower selectivity, suggesting the importance in the steric bulkiness to attain a high stereoselectivity (entries 10 and 11).

To determine the absolute configuration of the product cyclopropanes, we attempted to prepare authentic **4c** from reported chiral compound (1*R*,3*S*)-**5**[8a,c] by an ester exchange reaction (Scheme 2). Treatment of **5** with sodium ethoxide resulted in a complex mixture and no ethyl ester **4c** was obtained despite exerting much effort. When the ester exchange reaction was carried out using 28% NaOMe in CH_2Cl_2 at rt for 5 min, unusual bicyclic acetal (1*R*,5*R*,6*S*)-**6** was obtained instead of corresponding methyl ester in 31% yield, the structure of which was determined by X-ray crystallographic analysis[10] as shown in Figure 1.[11]

Compound **6** has a γ-lactone framework with an orthoester moiety. This may be produced via hydrolysis of an ester with contaminating hydroxide ion, successive



Scheme 2. Unusual formation of bicyclic compound **6** and determination of absolute configuration.

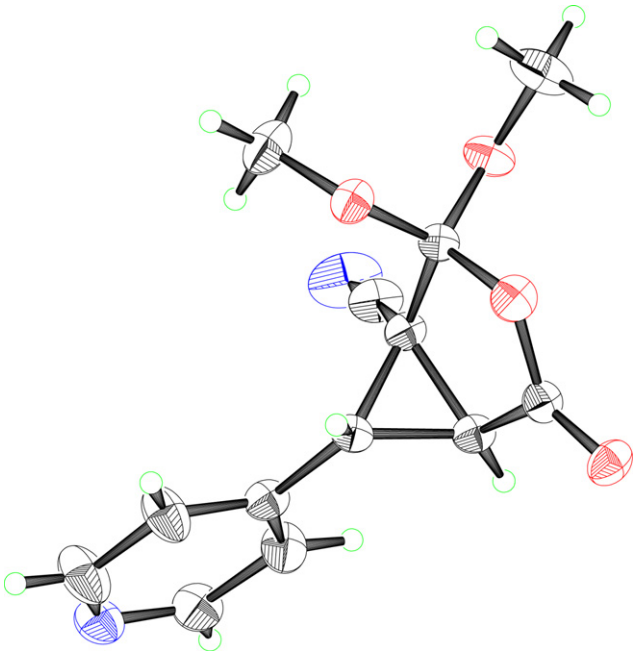


Figure 1. ORTEP drawing of **6** at the 30% probability level. Chloroform molecule was omitted for clarity.

cyclization of the resulting carboxylate anion with a cyano group, and acetalization with MeOH. Similar transformation of **4c** into **6** and comparison of the specific rotation with that of authentic (1*R*,5*R*,6*S*)-**6** clarified that the absolute configuration of **6** is opposite to that of authentic **6**; therefore, the configuration of **4c** is 1*S*,3*R*.

In order to gain evidence for the self-complexation of **2a** through cation–π interaction, comparison of the ^{1}H NMR spectra between **2a** and **2d** was performed. The spectrum of **2a** showed significant broadening of the pyridinium proton, whereas all protons of **2d** clearly appeared. Remarkable difference was observed in the chemical shifts of the methylene protons next to the carbonyl group; while both methylene protons of **2d** appeared as a singlet (δ 5.96), each methylene proton of **2a** was separated with higher field shift (δ 5.58 and 5.90). In addition, H3 of the pyridinium ring for **2d** was significantly shifted to upper field; the δ values of **2a** and **2d** are 8.08 and 7.15, respectively. These features in the ^{1}H NMR studies strongly suggest that the phenyl ring is close to the methylene moiety and prevents the rotation of the CH_2CO_2Et moiety.

X-ray structural analysis of pyridinium **2e** elucidated the existence of the pyridinium–π interaction.[12] Since **2a**–**2c** were oily compounds, the corresponding *N*-methyl pyridinium salt **2e** was used as a model compound. Figure 2 clearly shows that the pyridinium and the phenyl rings of **2e** are very close to each other with face-to-face arrangement. The phenyl ring blocks around the N atom, and the distances between the centroid of the phenyl group and N and C7 are 3.678 and 3.677 Å, respectively, suggesting an intramolecular cation–π interaction between the pyridinium and the phenyl rings.

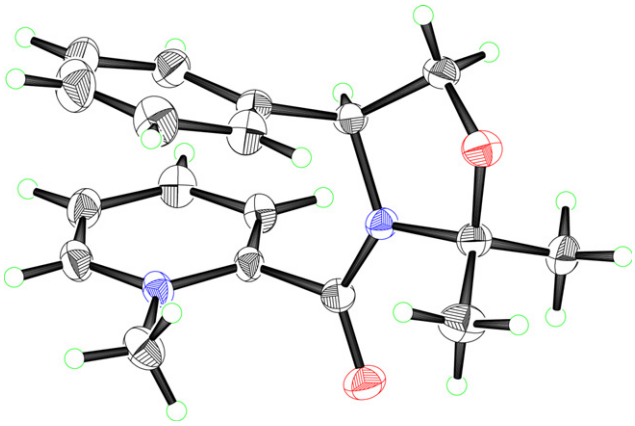


Figure 2. ORTEP drawing of **2e** at the 30% probability level. Iodo anion was omitted for clarity.

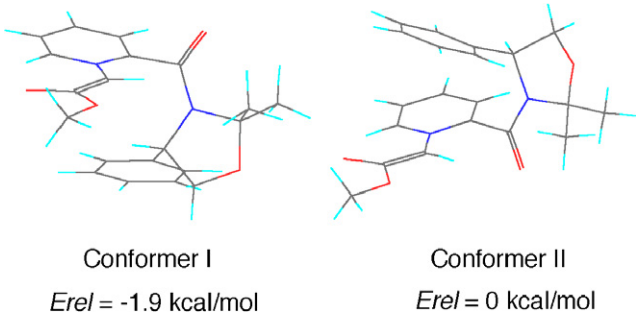


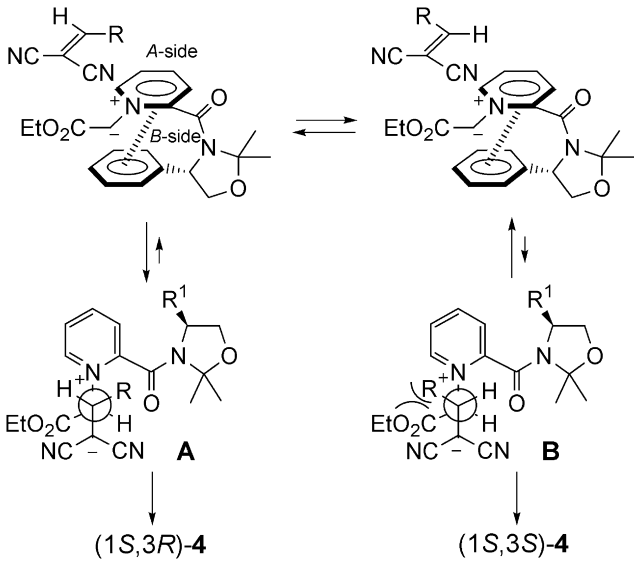
Figure 3. Optimized geometries for a model ylide.

The significant high-field shift for one of the CH_2CO_2Et protons described above can also be explained by this geometry.

DFT calculations of an intermediate pyridinium ylide[13] at B3LYP/6-31G* level predicted three stable conformers I–III.[14] The pyridinium and the phenyl rings of I and II arrange in a face-to-face manner and the pyridinium rings are blocked opposite side each other by the phenyl rings, whereas the two rings of conformer III having the highest energy are apart from each other. Conformers I and II are shown in Figure 3. Since conformer I is much more stable than II, I would be the major conformer.

These studies led to a working model for the stereoselective formation of cyclopropanes outlined in Scheme 3. An electron-deficient olefin will approach conformer I from the less-hindered A-side. Two intermediates **A** and **B** would be produced depending on whether the ylide attacks *Re* or *Si* face of the olefin. The equilibrium between **A** and **B** would shift to **A** so as to avoid severe steric repulsion between the CO_2Et and the R groups in **B**; consequently, (1*S*,3*R*)-**4** was produced as a major product.

In summary, enantioselective cyclopropanation of electron-deficient olefins was performed by the reaction with a pyridinium ylide, the conformation of which is fixed



Scheme 3. Plausible mechanism for the selective formation of (1*S*,3*R*)-**4**.

through a cation–π interaction. The key feature in this process is that the cation–π interaction allows producing a chiral environment around the active site, which enables to distinguish the *Re* and *Si* faces of olefins, although the chiral center is apart from it.

Acknowledgment

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10. Racemic **6** was used for X-ray crystallographic analysis.
11. X-ray crystal data for **6**: $C_{13}H_{12}N_2O_2{\cdot}CHCl_3$, $M = 379.63$, monoclinic, $P2_1/c$, $\mu = 4.945\ mm^{-1}$, $a = 11.633(3)$ Å, $b = 17.615(4)$ Å, $c = 8.7459(15)$ Å, $\beta = 103.342(15)°$, $V = 1743.8(6)\ A^3$, $T = 230$ K, $Z = 4$, $D_c = 1.446\ g\ cm^{-1}$. A total of 3216 reflections were collected and 3194 are unique ($R_{int} = 0.051$). R_1 and wR_2 are 0.0835 [$I > 2\sigma(I)$] and 0.2661 (all data), respectively. See CCDC 619224.
12. X-ray crystal data for **2e**: $C_{18}H_{21}N_2O_2I$, $M = 424.28$, triclinic, $P\text{-}1$, $\mu = 13.946\ mm^{-1}$, $a = 7.134(3)$ Å, $b = 9.4702(10)$ Å, $c = 13.9853(10)$ Å, $\alpha = 86.096(16)°$, $\beta = 103.302(15)°$, $\gamma = 99.103(10)°$, $V = 907.4(4)\ A^3$, $T = 298$ K, $Z = 2$, $D_c = 1.553\ g\ cm^{-1}$. A total of 4403 reflections were collected and 3170 are unique ($R_{int} = 0.069$). R_1 and wR_2 are 0.0866 [$I > 2\sigma(I)$] and 0.2013 (all data), respectively. See CCDC 619223.
13. Instead of ylide of **2a**, corresponding methyl ester was used for the DFT calculations as a model ylide to reduce conformational freedom.
14. The optimized energies for conformers I–III are −744019.268, −744017.366, and −744016.064 kcal/mol, respectively.