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Electronic and Chelation Effects on the Unusual C2-Methylation of *N*-(*para*-Substituted)Phenylaziridines with Lithium Organocuprates

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Abstract: Density functional theory calculations with the B3LYP functional were performed for the title ring-opening reaction to understand the intrinsic activating and directing effects of the *N*-substituents, as well as the electron donating effect of the para-substituted (Y = Cl, H, Me) phenyl group at the more hindered benzylic C2 atom. The *N*-tosyl group (i.e., *N*-Tos) or the *N*-(2-pyridyl)sulfonyl group (i.e., *N*-Py) was introduced to activate the ring nitrogen atom (N1) and the para-substituted (Y = Cl, H, Me) phenyl group for the activation of the C2 atom. Conformational searches and geometry optimizations were performed for the *N*-(*para*-substituted)phenylaziridines (**1**∼**6**). Calculations indicate that the aziridine **6** (i.e., Py/Me) has the most elongated C2—N1 bond intrinsically due to the electronic activating effects, implying the aziridine **6** to be the most potent candidate for the more-hindered C2 opening. Transition states (TSs) were investigated for the prospective ring-opening paths (I∼IV), considering the types of intermolecular push–pull interactions between the *N*-activated phenylaziridines and the cuprate. The *N*-Py group provides an unique C2-favored TS along the path IV, which the *N*-Tos group cannot afford, due to the less charge transfer from the nucleophilic $CH_3^{\delta-}$ of the cuprate into the electrophilic C2 atom. Furthermore, the e-donating effect of the para-substituents (Y = Cl, H, Me) enhances the C2 opening for the path IV. This study enables us to understand the unusual ring-opening phenomena in terms of electronic and directing effects and hence may serve as a tool to design substrates for highly regioselective ring openings.

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Key words: ring-opening reactions; DFT calculations; aziridine ring opening; reaction mechanism; cuprate catalyst

Introduction

Aziridines, the nitrogenous analog and a cousin of epoxides,[1] are widely distributed in nature as biologically active species[2] and have been utilized in synthetic organic chemistry as versatile building blocks.[3–8] It is well known that the ring-opening reactions of most three-membered heterocycles (e.g., oxiranes, aziridines, and thiiranes) usually lead to both the more hindered C2 opening (*minor*) and the less hindered C3 opening (*major*). The regioselective C2-opening reactions have been achieved depending on the following conditions: C2 aromatic activations,[9–11] heteroatom activations (e.g., N-activating groups or aziridinium salts),[12–15] catalysts (e.g., Lewis acids, metal–ligand complexes, metal oxides, and organic/inorganic catalysts),[16–32] unique nucleophiles,[33–38] and C2-driecting effects of nucleophiles.[39–42] Despite previous theoretical studies on the ring-opening mechanism,[43–56] little have been explored in regard to the favored opening at the more-hindered C2 atom,[57–61] especially at the benzylic C2 atom.[62,63] Moreover, to the best of our knowledge, there are no theoretical works on the preferential methylation at the benzylic C2 atom of three-membered heterocycles, which especially have no substituents on the C3 atom.

We have already reported the regioselective C2 opening experiments at the more hindered benzylic position of the N-activated phenylaziridines with a lithium organocuparte, $(CH_3)_2$Cu-Li•LiI,[64] and theoretical investigation on the preferential aziridination by 2-pyridylsulfonyl moieties.[65] However, the regioselective

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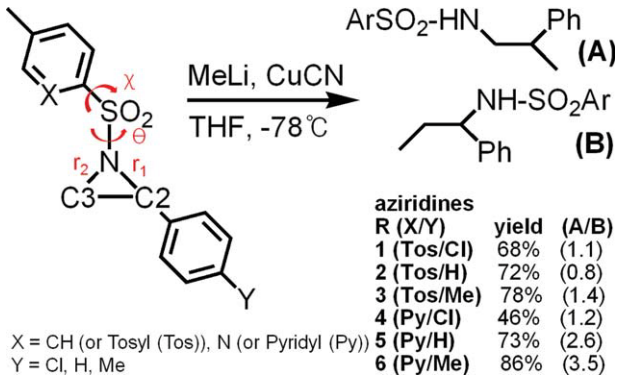


aziridines

R (X/Y)	yield	(A/B)
1 (Tos/Cl)	68%	(1.1)
2 (Tos/H)	72%	(0.8)
3 (Tos/Me)	78%	(1.4)
4 (Py/Cl)	46%	(1.2)
5 (Py/H)	73%	(2.6)
6 (Py/Me)	86%	(3.5)

Scheme 1. Unusual C2-opening experiment. *N*-Tos and *N*-Py refer to abbreviations of the *N*-tosyl and the *N*-(2-pyridyl)sulfonyl groups when X is CH and N, respectively. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

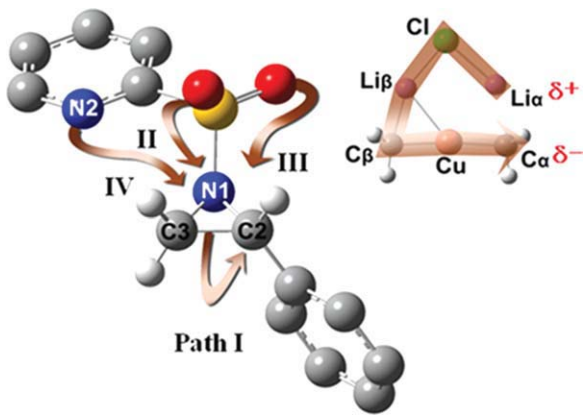
ring-opening mechanisms have not been elucidated. Herein we report a new experimental data (Scheme 1) and a theoretical study (Scheme 2) on the regioselective C2 opening of the N-activated phenylaziridines considering the activating and directing effects of the N-substituents and the e-donating effect of the para-substituted (Y = Cl, H, Me) phenyl group at the more hindered benzylic C2 atom. The hard nucleophiles such as a CH_3^- generally have been known to favor the less-hindered C3 attack. The steric and electronic shielding effects of the C2-phenyl group against the incoming CH_3^- group neutralize its C2-activating effect. However, the energetically C2-favored TS of three-membered phenylheterocycles by the CH_3^- nucleophile have not been identified by calculations. In this study, a tosyl group or a 2-pyridylsulfonyl group, abbreviated as *N*-Tos and *N*-Py respectively, is used to activate the ring nitrogen atom N1 and to direct the regioselective C2-methylation of the N-activated phenylaziridines by the cuprate. These N-substituents differentiate aziridines from their cousins (i.e., oxiranes and thiiranes) by the presence of an additional valency on the ring heteroatom N1. The N-substituents afford some advantages on the ring-opening process because of the kinetic activation and polarization effects of C—N1 bonds and the thermodynamic stabilization effect of the resultant amine anion, mainly owing to their e-withdrawing inductive effects.[1] Moreover, the para-substituents (Y = Cl, H, Me) are expected to give an additional activation effect to the C2-phenyl group due to the electronic effect.[9,10,43,50]

The cuprate, a methyl source and catalyst, has been known to catalyze 1,4-addition to α,β-unsaturated ketones[66] and C2-attack at the benzylic position.[11,38] It was reported that the cuprate has different structures depending on the dielectric properties of solvents.[67] For instance, an open cluster form of the cuprate was found in polar solvents such as THF, where the electrostatic bond between Li_α and C_α weakens due to the solvation of the Li_α by the solvent molecules, and the partial positive and negative charges are developed on the Li_α and C_α atoms, respectively, (Scheme 2). Angles and lengths of the cuprate framework are the key factors for its push–pull behaviors in TS, which determines both the span and the position of the cuprate chain toward the electrophilic C2 and C3 atoms. The S_N2-like push–pull behavior of the cuprate in the nucleophilic addition (or substitution) reactions has been extensively elucidated by Nakamura and coworkers in recent years.[67–70] In this study, on the basis of the epoxide-opening work of Mori et al. using the cuprate $(CH_3)_2CuLi{\cdot}LiCl$,[71] we suggest the energetically lower C2-opening TS along the path IV driven by the C2-activating and -directing effects of the *N*-Py group.

Computational Model and Method

The *N*-(*para*-substituted)phenylaziridines have rotational degrees of freedom on the *N*-Tos and the *N*-Py groups along the dihedral angles χ and θ (Scheme 1). To screen the promising conformers relevant to our C2-regioselective ring-opening experiment, the conformational searches were performed using the two dihedral angles (χ, θ) followed by the geometry optimizations. Bond lengths, charges, and σ-antibonding molecular orbital (MO) energy levels concerning the reaction centers C2 and C3 were analyzed to narrow the scope of target molecules for TS calculations, because these factors are closely related to the intrinsic activation of the breaking C—N1 bonds in the ring opening process.[10,55–56] The para-methyl group of the *N*-Tos and the *N*-Py groups was replaced by the H atom to alleviate the computational convergence problem and the high cost involved in the methyl rotation during optimization.

Transition state (TS) searches via S_N2- rather than S_N1-type mechanism (Scheme 2) were performed for the prospective ring-opening paths (I∼IV), depending on the types of electrostatic interactions between the cuprate and any electronegative atoms (e.g., N2, O1, and O2) of the *N*-substituents and the ring nitrogen atom (N1). For the S_N1-type reactions, the N-substituents



Scheme 2. Prospective ring-opening paths (I∼IV). The one (e.g., Li_α) of the lithium atoms in the cuprate cluster sticks to any electronegative atoms (N1, N2, and two oxygen atoms). The arrow on the cuprate symbolizes the shape of the open cluster where the beginning and the end correspond to the opened lithium atom ($Li_\alpha^{\delta+}$) and the liberated methyl group ($C_\alpha H_3^{\delta-}$). Each path responsible for the C2 and C3 openings is depicted with the cuprate arrow. All hydrogen atoms except those around the C2 and C3 atoms were hidden for clear view. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

should undergo large structural changes to form an intermediate carbocation, which means kinetically unfavorable processes. Moreover, the S_N2-type attack is favored by the N-activating groups, temperatures to subzero (e.g., −78°C),[38,50] and the push–pull behavior of the cuprate.[72] Although this type of S_N2 mechanism is often found to accompany a secondary TS of the reductive elimination from Cu(III) intermediate according to Mori et al.,[71] we treat only the first rate-determining TS because we focus on kinetics rather than thermodynamics.

Concerning the cuprate, we used the model Cl atom for TS calculations as in the work of Mori et al.[71] instead of the CN group used in our experiments. The reason is just not a problem of computational cost but reaction mechanism. As seen in theoretical work of Nakamura et al.,[68] the CN moiety may induce two ring-opening mechanisms via the major and minor species of the cyanocuprate, respectively, whereas the halogen atoms (e.g., Cl, Br, I) afford only the one reaction mechanism. The reaction mechanism by the major species of the cyanocuprate is equal to that of the the cuparte with the Cl atom as in the theoretical work of Mori et al. for epoxide ring-opening reactions.[71] Here, we focus on the ring-opening mechanism by the major species of the cyanocuprate and model the TS using the Cl atom instead of the CN group. In addition, similar stereoselectivity was observed for aziridines with the CuI catalyst.[64] The other mechanisms using CuCN including those by the minor species may be investigated in the future work.

All calculations were performed using Gaussian 03[73] with the B3LYP hybrid functional[74,75] and differing basis sets, the Ahlrichs all-electron SVP[76] for the Cu atom and 6-31G(d) for the rest in geometry optimizations and 3-21G(d) for conformational searches. The vibrational analysis was carried out to evaluate zero-point energy and activation free energy barriers ($\Delta G^{\ddagger}$) at 195.15 K/1.0 atm, as well as to identify ground states (no imaginary frequency) and TS (one imaginary frequency: see S4 in Supporting Information). TS were further verified by intrinsic reaction coordinates (IRC) calculations.[77–79] Natural population analysis charges[80] and σ-antibonding MO energy levels of the two breaking C—N1 bonds, which were localized ones as used in the work of Jin Kak Lee et al.,[55] were investigated using NBO 5.G implemented in G03. Polarized continuum model (PCM) calculations were performed to investigate the bulk solvation effect on the TS structures obtained for the gas phase.[81,82] Finally, we have partially considered explicit solvation effect on the TS energy and shape.

Results and Discussion

Reactants

The potential energy surface maps on the rotation of the N-substituents were depicted with the dihedral angles (θ, χ) for the representative aziridines **2** and **5** (Fig. 1). There are two local minima within 1 kcal/mol for each case displayed with blue color. The two points A and B in the blue color regions denote, respectively, *anti*-conformers (2A, 5A) and *syn*-conformers (2B, 5B) for both the aziridine **2** and **5**. The *anti*- and *syn*-conformations are defined as the relative position of the C2-phenyl group

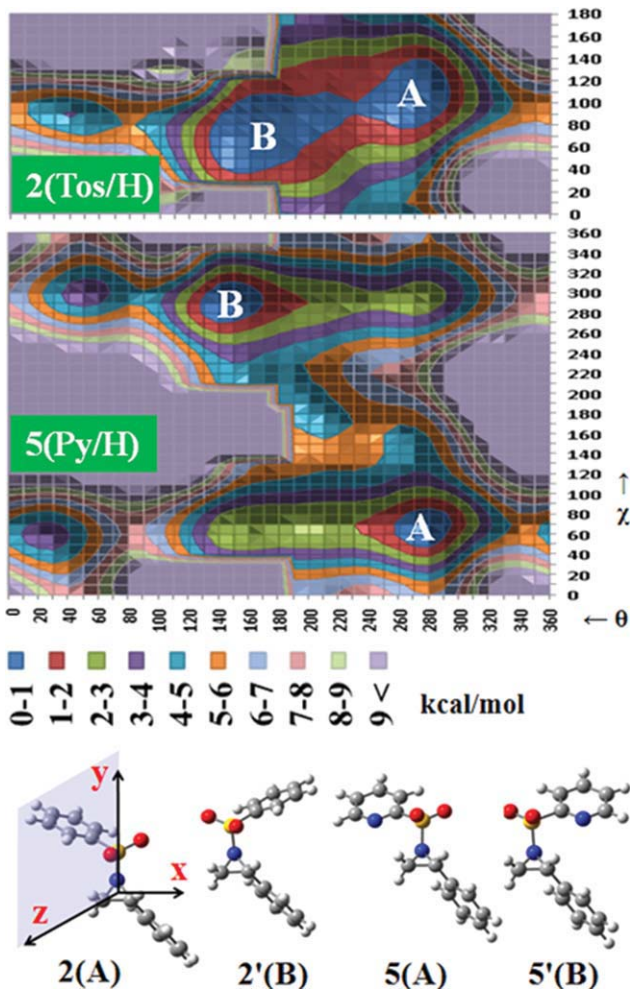


Figure 1. Potential energy surfaces (PES) of the aziridines **2** and **5** through conformational searches along the dihedral angles (θ, χ). Respective two minima (A and B) in each case are displayed with blue color. The optimized structures of the two minima are depicted for each aziridine **2** and **5**. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

to the N-substituents against the vertical *yz*-plane bisecting the aziridine ring. Subsequent optimizations of the aziridines **2** and **5** separately yield similar energies (<0.06 kcal/mol) for their *anti*- and *syn*-conformers. Although both *anti*- and *syn*-conformers could be responsible for the ring opening process, we opt to screen the candidate reactants based on the intrinsic bond activation effect prior to the heavy TS calculations.[10,55–56] Bond lengths and charges were compared for the two conformers to investigate the C—N1 bond activation effect (Table 1). Compared with the *syn*-conformers, the *anti*-conformers have more elongated C2—N1 bond over C3—N1 bond denoted as r_1 and r_2, respectively. Considering the Y substituents having the e-donating effect (Cl < H < Me), the r_1 distance is more elongated for *anti*-conformers than for *syn*-conformers. In contrast, the *syn*-conformers increase both r_1 and r_2 leading to less C2 activation, which is not in agreement with the experimental data. These computational results are also in agreement with the

Table 1. Bond Lengths and Natural Population Analysis Charges of the *N*-Substituted Phenylaziridine Reactants.

Aziridines: R (X/Y)	r_1	r_2	$\Delta(r_1 - r_2)$	C2	C3	Δ(C2−C3)
0 (H/H)[a]	1.473	1.466	0.006	−0.096	−0.270	0.174
1 (Tos/Cl)	1.480	1.470	0.010	−0.081	−0.258	0.177
2 (Tos/H)	1.482	1.471	0.011	−0.079	−0.259	0.180
3 (Tos/Me)	1.483	1.471	0.012	−0.077	−0.260	0.182
4 (Py/Cl)	1.484	1.472	0.012	−0.084	−0.249	0.165
5 (Py/H)	1.486	1.472	0.014	−0.081	−0.249	0.168
6 (Py/Me)	1.487	1.472	0.015	−0.080	−0.251	0.170
2′ (Tos/H)[a]	1.481	1.472	0.009	−0.086	−0.253	0.167
5′ (Py/H)[a]	1.484	1.475	0.009	−0.080	−0.256	0.176

[a]For comparisons, values of the phenylaziridine **0** and the *syn*-conformers **2′** and **5′** were presented.

experimental X-ray crystallography structure (see S1 in Supporting Information) for one of the aziridines prepared according to our developed method.[64] The single crystal of the aziridine used in the X-ray crystallographic analysis was obtained by recrystallization in CH_2Cl_2/hexane. Therefore, we focus on the *anti*-conformers of the N-substituted phenylaziridines.

The N-substituent effect on r_1 and r_2 are shown in Table 1. The phenylaziridine **0** has asymmetric C—N1 bonds due to the activation effect by the C2-phenyl group where the r_1 distance is slightly longer than the r_2 distance by 0.006 Å. When the *N*-Tos or the *N*-Py is introduced for N-activation, both r_1 and r_2 are elongated. However, the *N*-Py than the *N*-Tos causes a larger effect on the r_1 distance, whereas both of them give similar effect on the r_2 distance. For example, the aziridine **5** has longer r_1 distance (1.486 Å) than the aziridine **2** does (1.482 Å) while they have similar r_2 distances (∼1.472 Å). Because of the different N-activation effects, the relative elongation of r_1 to r_2 increases as much as 0.006, 0.011, and 0.014 Å in the aziridines **0**, **2**, and **5** respectively. Furthermore, the e-donating effect of the Y substituents on the C2 atom systematically increases the r_1 distances from 1.480 to 1.487 Å, but almost does not change the r_2 distances (∼1.472 Å) due to the weak interaction with the remote C3 atom. The bond length differences between r_1 and r_2 in the presence of e-donating effect of the Y substituents gradually increase from 0.010 to 0.015 Å for the *N*-Py but not so much for the *N*-Tos. It is reported that the small changes in bond lengths and charges can lead to profound changes in binding energy (e.g., even small charge difference of 0.013 is up to about 11 kcal/mol in energy)[83] or in TS energy.[84] Hence, the aziridine **6** (Py/Me) is most likely involved in the C2 favored opening in view of bond activation. Details are discussed below in terms of charge, σ-antibonding MO energy, and TS energy.

The phenylaziridine **0** has more positive charge on the C2 atom (−0.096) than on the C3 atom (−0.270) due to the C2-activation effect, which makes the C2 atom more electrophilic than the C3 atom. The e-withdrawing *N*-substituents additionally increase the C2 and C3 charges toward the positive: −0.079 on C2 and −0.259 on C3 for the aziridine **2** and −0.081 on C2 and −0.249 on C3 for the aziridine **5**. However, the activating effect is larger for the *N*-Tos group than for the *N*-Py group even in the presence of e-donating effect of Y, which implies inconsistency with the experiment. Therefore, σ-antibonding MO rather than charge is recommended for the analysis of the aziridine reactants especially when considering S_N2-type reactions.

As shown in Figure 2, the *N*-Tos-phenylaziridines (**1**∼**3**) have small energy gaps (∼2.5 kcal/mol) between the two σ-antibonding MO of breaking C—N1 bonds denoted as $\sigma^*_{(1)}$ and $\sigma^*_{(2)}$, respectively, whereas the *N*-Py-phenylaziridines (**4**∼**6**) have large energy gaps (∼6.3 kcal/mol). Accordingly, the nucleophile $CH_3^{\delta-}$ distinguishes the *N*-Py-phenylaziridines better than the *N*-Tos-phenylaziridines for the regioselective ring-opening. The e-donating effect of the Y substituents is also reflected in the relative energy gaps of σ-antibonding MOs. Hence, the concerted activation between the e-withdrawing *N*-substituents and the e-donating/withdrawing para-substituted phenyl groups elongates the r_1 distance rather than the r_2 distance, making the aziridine **6** (Py/Me) be the most potent candidate for the regioselective C2 opening.

Transition States

A preliminary study was performed for the TS of the simple phenylaziridine (**TS0**) to understand the activating role of the C2-aromatic group and the push–pull behavior of the cuparte involved in the ring-opening reactions (Fig. 3). As shown in Scheme 2, the aziridine **0** has only the path I leading to C2 and C3 openings because the interaction site between the cuprate and the ring nitrogen atom (N1) is unique. The C3 opening has lower activation barrier (39.4 kcal/mol) than the C2 opening (48.2 kcal/mol) by 8.8 kcal/mol (Table 2). In the C2 opening, the Li_α atom of the cuprate sticks to the ring nitrogen atom N1, generating the intermolecular complex (**IMC0-I-C2**) with the partially anionic methyl group ($CH_3^{\delta-}$). Then, the $CH_3^{\delta-}$ attacks the C2 atom above the aziridine ring plane via flipping of the

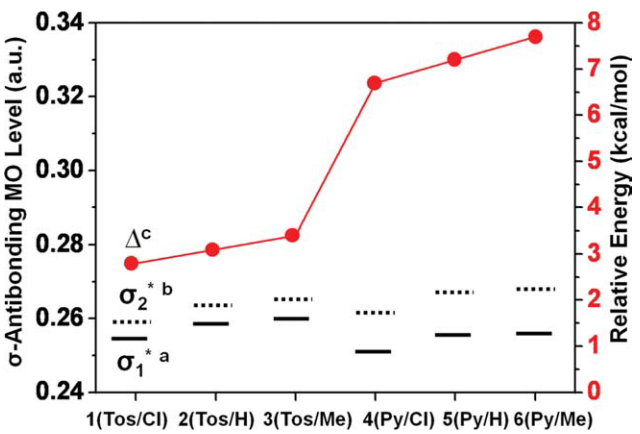


Figure 2. σ-antibonding molecular orbital (MO) energy diagram of the breaking C2—N1 (r_1) and C3—N1 (r_2) bonds of the *N*-substituted phenylaziridines. A and B refer to the σ-antibonding MO energy levels of r_1 and r_2, respectively. C refers to the energy difference between the two σ-antibonding MO energy levels (σ_1^* and σ_2^*). [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

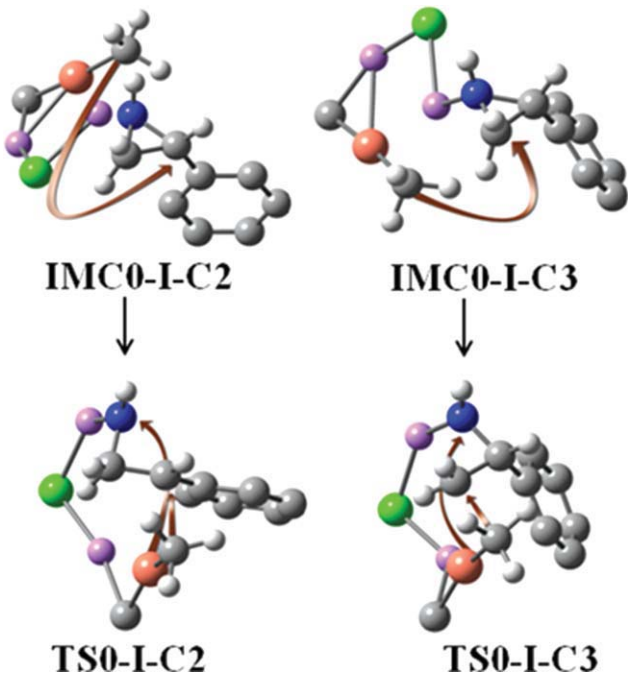


Figure 3. Transition state structures of the phenylaziridine **0** (H/H), **TS0**. Arrows depict the behavior of the nucleophilic methyl group (CH_3^-) from IMC to TS and from TS to P. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

cuprate ring (**TS0-I-C2**). Afterward, the positively charged Cu atom of the remaining part of the cuprate binds to the negatively charged N1 below the aziridine ring plane. In the C3-opening, the cuparte has open character due to the interaction with a vicinal hydrogen atom of the C3 atom (**IMC0-I-C3**). Accordingly, it was confirmed by the IRC calculation that the liberated $CH_3^{\delta-}$ group of the cuprate directly attacks the C3 atom without any ring flipping (**TS0-I-C3**). In the product formation, the remaining Cu atom heads to N1 below the aziridine ring plane. In TS, the almost linear nucleophilic CH_3^-—Cu—$CH_3^{\delta-}$ moiety of the cuprate has a position perpendicular to the direction of the $CH_3^{\delta-}$ attack on the electrophilic C2 and C3 atoms due to the limited span of the cuprate bridge and avoids steric hindrance from the C2-phenyl π-electrons.

The **TS2** (Fig. 4), a representative example of ring opening of the *N*-Tos-phenylaziridines (**1**∼**3**), can have three paths (I, II, and III) due to the additional interaction between the cuprate and either oxygen atom of the *N*-Tos group as shown in Scheme 2. For the path I, the C2 and C3 openings have the same IMC structure (**IMC2-I-C2/C3**) resembling the **IMC0-I-C3**, because the **IMC0-I-C2**-like structure cannot exist in the aziridine **2** due to the steric hindrance of the electron-rich SO_2 moiety of the *N*-Tos group. Owing to the activation effect of the *N*-Tos group, the path I reduces the barriers to 32.1 kcal/mol for the C2 opening and to 26.0 kcal/mol for the C3 opening compared with the aziridine **0** (Table 2). The relative TS energy of the C2 opening to the C3 opening is lowered to 6.1 kcal/mol compared with the azididine **0** (8.8 kcal/mol), but the decrease is not much sensitive (6.3→6.1→6.0 kcal/mol) to the e-donating effect of the Y

Table 2. Energetics of Ring-Opening Reactions along the Prospective Paths (**I**∼**IV**) in kcal/mol.

Aziridines: R (X/Y)	R + cuprate	path	IMC-C2	IMC-C3	TS-C2	TS-C3	Δ	P-C2	P-C3
0 (H/H)	−2560.3500[a]	I	−11.9[b]	−11.5[b]	36.3[b] (48.2)[c]	27.9[b] (39.4)[c]	8.3[b] (8.8)[c]	−42.9[b]	−46.1[b]
1 (Tos/Cl)	−3799.4854	I	0.0	←[d]	32.0 (31.9)	25.7 (25.6)	6.3	−33.0	−58.5
2 (Tos/H)	−3339.8821		−0.9	←	31.2 (32.1)	25.1 (26.0)	6.1	−34.5	−59.8
3 (Tos/Me)	−3379.1735		−1.7	←	30.5 (32.3)	24.5 (26.2)	6.0	−35.0	−60.2
1 (Tos/Cl)	−3799.4854	II	NA	2.6	NA	17.6 (15.1)	NA	NA	−38.7
2 (Tos/H)	−3339.8821		NA	2.2	NA	17.5 (15.3)	NA	NA	−38.3
3 (Tos/Me)	−3379.1735		NA	2.0	NA	17.3 (15.4)	NA	NA	−38.7
1 (Tos/Cl)	−3799.4854	III	−12.1	←	12.4 (24.5)	16.8 (28.9)	−4.4	−39.0	−38.7
2 (Tos/H)	−3339.8821		−12.3	←	12.5 (24.9)	16.9 (29.2)	−4.3	−39.2	−38.3
3 (Tos/Me)	−3379.1735		−12.9	←	11.7 (24.6)	16.7 (29.6)	−5.0	−39.3	−38.7
4 (Py/Cl)	−3815.5308	I	−8.5	−3.8	19.4 (27.9)	14.5 (18.3)	4.9 (9.5)	−68.5	−57.6
5 (Py/H)	−3355.9274		−9.5	−4.4	18.8 (28.3)	14.6 (19.0)	4.2 (9.3)	−68.8	−59.5
6 (Py/Me)	−3395.2189		−9.8	−4.8	17.8 (27.6)	14.3 (19.1)	3.5 (8.5)	−68.8	−59.9
4 (Py/Cl)	−3815.5308	III	−12.6	←	12.4 (25.0)	17.0 (29.6)	−4.6	−40.4	−39.4
5 (Py/H)	−3355.9274		−13.1	←	12.3 (25.4)	17.3 (30.4)	−5.0	−40.6	−38.9
6 (Py/Me)	−3395.2189		−13.0	←	11.5 (24.6)	17.1 (30.2)	−5.6	−40.6	−38.5
4 (Py/Cl)	−3815.5308	IV	−12.8	←	6.3 (19.1)	9.9 (22.6)	−3.6	−55.8	−57.3
5 (Py/H)	−3355.9274		−13.1	←	6.1 (19.2)	9.8 (22.9)	−3.7	−55.7	−56.7
6 (Py/Me)	−3395.2189		−13.2	←	5.2 (18.4)	9.9 (23.1)	−4.7	−55.5	−56.9

IMC, TS, and P stand for an intermolecular complex, a transition state, and a product respectively. For example, the C2 opening TS of aziridine **5** along the path **IV** abbreviated as **TS5-IV-C2** has an activation barrier of 6.1kcal/mol.

[a]Sum of free energies of the separated aziridine and the cuprate for each path (in hartrees).

[b,c]Relative energies calculated from the separated species (aziridine + cuparte) and IMC**s**, respectively.

[d]Values are the same to what the arrows point to.

Δ, Energy differences between C2 and C3 activation barriers.

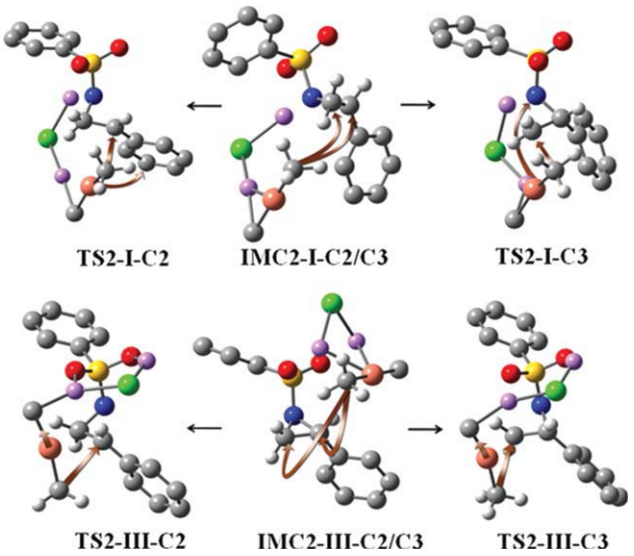


Figure 4. Transition state structures of the *N*-Tos-phenylaziridine **2** (Tos/H), **TS2**. Arrows depict the behavior of the nucleophilic methyl group (CH_3^-) from IMC to TS and from TS to P. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

substituents. The path II, where the lithium atom (Li_α) of the cuprate migrates from its initial position in Scheme 2 into between the two oxygen atoms of the *N*-Tos group, does not provide the C2 opening TS. Thus, the path II should not be discussed any more because the experimental data (C2/C3 ratio = 0.8) still support the existence of the C2 opening. The path III remarkably lowers the ring-opening barriers, where the two lithium atoms (Li_α and Li_β) of the cuprate interact with the two oxygen atoms of the *N*-Tos group in a pentagonal shape. However, **TS2-III** is similar to **TS5-III** in terms of structure and ring-opening barrier, which is not in agreement with the experimental data. Thus, the path III will not be discussed from now on. Concerning the product formation of the C2 opening of the aziridine **2** along the path I (**TS2-I-C2**), the positively charged Cu atom does not go directly toward the ring nitrogen atom N1 but stays around the π-electrons of the C2-phenyl group. Overall, the ring opening of the *N*-Tos-phenylaziridines proceeds along the path I but does not exhibit *N*-activation effect large enough to give the preferential C2 opening.

The **TS5** (Fig. 5), a representative example of the ring opening of the *N*-Py-phenylaziridines (**4**∼**6**), has four possible paths (I, II, III, and IV) as depicted in Scheme 2. The path I has two different IMCs for the C2 and C3 openings. The latter **IMC5-I-C3** resembles the **IMC2-I-C2/C3** of the aziridine **2**, whereas the former **IMC5-I-C2** has a different structure owing to the additional coordination effect from the 2-pyridyl nitrogen atom N2 of the *N*-Py group. The *N*-Py group of the aziridine **5** having stronger activation effect than the *N*-Tos of the aziridine **2** lowers the ring-opening barriers, but still the activation is not enough to favor the C2 opening (Fig. 6a). Most importantly, the *N*-Py group generates an additional unique path IV guiding the nucleophilic group ($CH_3—Cu—CH_3^{\delta-}$) to the preferential position around the C2 atom, which is not available for the *N*-Tos group. This path originates from the simultaneous interaction of the Li_α atom of the cuprate with the 2-pyridyl nitrogen atom N2 and the oxygen atom at the front of the SO_2 moiety. The path IV greatly lowers the ring-opening barriers to 19.2 kcal/mol for the C2 opening and to 22.9 kcal/mol for the C3 opening leading to the C2-favored opening (Fig. 6a), where the relative TS energy of C2 to C3 opening is reversed to −3.7 kcal/mol. In product formation along with the path IV, the Cu atom does not go directly toward the N1 atom but goes toward the oxygen atom at the back of the SO_2 moiety (Fig. 5). Considering the e-donating effect of the Y substituents (Cl < H < Me) for the path IV, the relative TS energy of C2 to C3 opening is gradually reversed to −3.6→−3.7→−4.7 kcal/mol. Therefore, the ring-opening path IV of the *N*-Py-phenylaziridines exhibits N-activation effect large enough to get the preferential C2 opening, especially in the presence of the e-donating effect by the para-substituents (Y = Cl, H, Me) of the C2-phenyl group.

Bond distances and charges involved in the bond breaking (C2/C3—N1: r_1 and r_2) and forming (CH_3—C2/C3 and Cu—C2/C3) in TS are listed in Table 3. For the path I, the aziridine **5** (**TS5-I**) has less changes in the bond lengths (e.g., r_1, r_2)

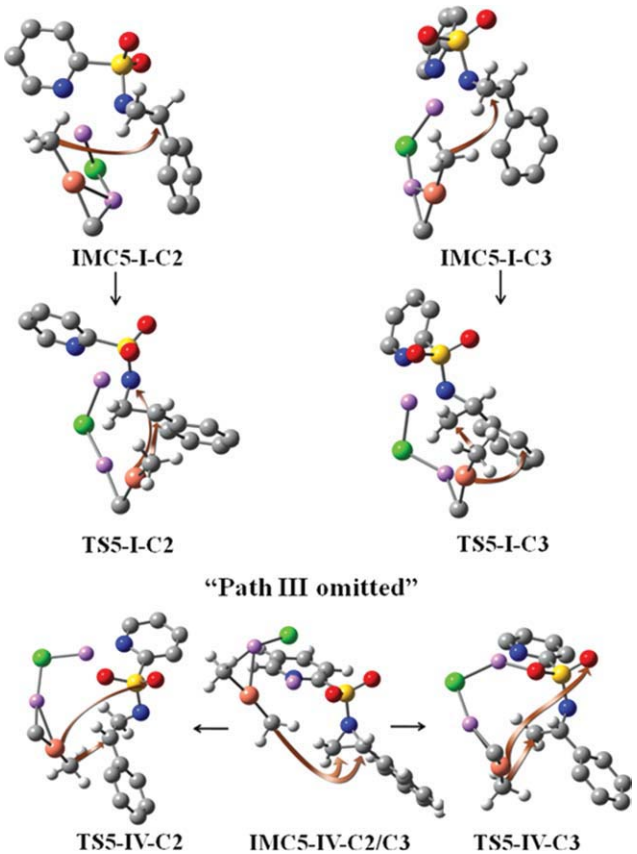


Figure 5. Transition state structures of the *N*-Py-phenylaziridine **5** (Py/H), **TS5**. Arrows depict the behavior of the nucleophilic methyl group (CH_3^-) from IMC to TS and from TS to P. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

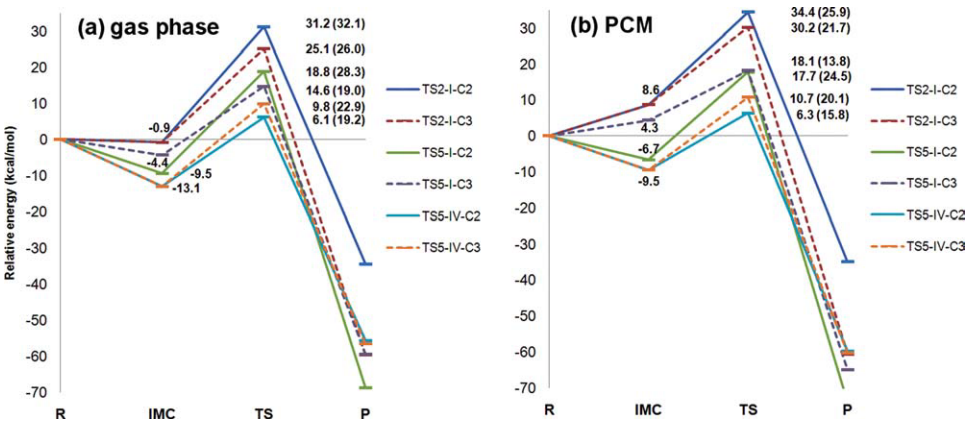


Figure 6. Energy profiles of the ring opening of the aziridines **2** (Tos/H) and **5** (Py/H) along the path I and IV calculated in gas phase (a) and in solution with PCM method (b). Values in parenthesis refer to activation barriers calculated from IMCs. Solid and dashed lines indicate the C2 and C3 openings, respectively. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

and in the N1 charge for both the C2 and C3 opening than the aziridine **2** (**TS2-I**) does but still shows less changes for the C3 opening than for the C2 opening which imply the C3 favored opening through an early TS. Compared with the **TS5-I**, the **TS5-IV** has an additional decrease in the r_1 distance for the C2 opening (30.8→29.3%) while an increase in the r_2 distance for the C3 opening (23.7→28.3%), leading to less N1 charge variation for the C2 opening (13.8%) than for the C3 opening (15.9%). These phenomena can be explained additionally in terms of the Cu and $CH_3^{\delta-}$ positions relative to the electrophilic C2 and C3 atoms as well as the charge transfer from the nucleophilic $CH_3^{\delta-}$ into the electrophilic carbons. For the C2 opening, the Cu atom is closer to the C2 atom in the **TS5-IV** (2.766 Å) than in the **TS5-I** (3.012 Å), making the $CH_3^{\delta-}$ nucleophile be farther away from the C2 atom in the **TS5-IV** (3.297 Å) than in the **TS5-I** (2.949 Å), which would induce less charge transfer from the $CH_3^{\delta-}$ nuclophile into the C2 atom in the **TS5-IV** (−16.2%) than in the **TS5-I** (−18.9%). Therefore, the *N*-Py group in the

Table 3. Bond Distances and Charges of Aziridines (Upper) and Cupartes (Lower) in TS.

Transition states of R (X/Y)	Path	r_1[a] (%)[c]	r_2[b] (%)	N1[a] (%)	N1[b] (%)
TS1 (Tos/Cl)	I	1.959 (+32.4)	1.868 (+27.1)	−0.989 (+37.9)	−0.984 (+37.3)
TS2 (Tos/H)		1.954 (+31.8)	1.861 (+26.5)	−0.983 (+37.1)	−0.986 (+37.6)
TS3 (Tos/Me)		2.003 (+35.1)	1.863 (+26.7)	−1.009 (+40.6)	−0.986 (+37.3)
TS4 (Py/Cl)	I	1.942 (+30.8)	1.834 (+24.6)	−0.964 (+34.3)	−0.956 (+33.3)
TS5 (Py/H)		1.943 (+30.8)	1.820 (+23.7)	−0.982 (+36.8)	−0.943 (+31.4)
TS6 (Py/Me)		1.985 (+33.5)	1.822 (+23.8)	−0.989 (+37.7)	−0.956 (+33.0)
TS4 (Py/Cl)	IV	1.917 (+29.1)	1.885 (+28.1)	−0.813 (+13.3)	−0.825 (+14.9)
TS5 (Py/H)		1.921 (+29.3)	1.888 (+28.3)	−0.817 (+13.8)	−0.832 (+15.9)
TS6 (Py/Me)		1.924 (+29.4)	1.888 (+28.2)	−0.820 (+14.2)	−0.830 (+15.5)

Transition states of R (X/Y)	Path	r^a (Cu−C2)	r^b (Cu−C3)	r^a (CH_3^-−C2)	r^b (CH_3^-−C3)	CH_3[a]	CH_3[b]
TS1 (Tos/Cl)	I	3.003	2.549	2.932	2.800	(−18.5)	(−23.7)
TS2 (Tos/H)		2.983	2.540	2.949	2.828	(−18.4)	(−23.6)
TS3 (Tos/Me)		3.106	2.543	2.968	2.820	(−17.9)	(−23.5)
TS4 (Py/Cl)	I	3.010	2.592	2.950	2.763	(−16.3)	(−22.7)
TS5 (Py/H)		3.012	2.579	2.949	2.789	(−18.9)	(−20.7)
TS6 (Py/Me)		3.111	2.583	3.003	2.786	(−16.8)	(−20.4)
TS4 (Py/Cl)	IV	2.758	2.443	3.298	2.888	(−16.0)	(−24.6)
TS5 (Py/H)		2.766	2.432	3.297	2.886	(−16.2)	(−24.2)
TS6 (Py/Me)		2.805	2.430	3.331	2.896	(−15.4)	(−24.6)

[a,b]Stand for the C2 and the C3 opening, respectively.
[c]Percent values in the parenthesis are variations of bond distances and charges in TS relative to those of the reactants.

Table 4. Energetics of Bulk Solvation Effect on Aziridine Ring-Opening Reactions Calculated with PCM Method.

Aziridines: R (X/Y)	R + cuprate[a]	Path	IMC-C2	IMC-C3	TS-C2	TS-C3	Δ	P-C2	P-C3
1 (Tos/Cl)	−3799.764391	I	9.2[b]	←[d]	35.3[b] (26.1)[c]	32.4[b] (23.2)[c]	2.9[b]	−32.5[b]	−58.9[b]
2 (Tos/H)	−3340.171762		8.6	←	34.4 (25.9)	30.2 (21.7)	4.2	−35.0	−60.7
3 (Tos/Me)	−3379.485594		8.4	←	33.6 (25.2)	30.6 (22.2)	3.0	−34.4	−60.5
4 (Py/Cl)	−3815.800078	I	−4.5	5.2	18.9 (23.5)	20.7 (15.6)	−1.8 (7.9)[c]	−73.2	−62.8
5 (Py/H)	−3356.207516		−6.7	4.3	17.7 (24.5)	18.1 (13.8)	−0.4 (10.7)	−73.9	−65.0
6 (Py/Me)	−3395.521345		−6.4	4.3	16.7 (23.1)	18.5 (14.2)	−1.8 (8.9)	−73.5	−65.8
4 (Py/Cl)	−3815.800078	IV	−9.9	←	6.6 (16.5)	10.5 (20.4)	−3.9	−60.2	−60.8
5 (Py/H)	−3356.207516		−9.5	←	6.3 (15.8)	10.7 (20.1)	−4.4	−59.8	−60.3
6 (Py/Me)	−3395.521345		−9.5	←	5.2 (14.7)	11.0 (20.5)	−5.8	−59.5	−60.2

IMC, TS, and P stand for an intermolecular complex, a transition state, and a product respectively.
[a]Sum of free energies of the separated aziridine and the cuprate for each path (in hartrees).
[b,c]Relative energies calculated from the separated species (aziridine + cuparte) and IMCs, respectively.
[d]Values are the same to what the arrows point to.
Δ, Energy differences between C2 and C3 activation barriers.

aziridine **5** induces the C2 favored opening along the path IV owing to the less charge transfer from the $CH_3^{\delta-}$ nucleophile into the C2 atom by the cooperative role of the Cu atom.

Solvation Effect

The implicit solvation effect on the ring-opening barriers of the N-activated phenylaziridines was calculated by the PCM method (Table 4), and the reaction energy profiles of the aziridines **2** and **5** along the paths I and IV are shown in Figure 6b. Compared with the gas phase results, the solvation effect reduces the ring opening barriers while destabilizing both of the IMC and TS energy. For the aziridine **2** along the path I, the reduction of the activation barriers results from mainly the IMC species destabilized in the solution phase (8.6 kcal/mol) rather than in the gas phase (−0.9 kcal/mol). As the barrier of the C3 opening is lower (13.8 kcal/mol) than that of the C2 opening (24.5 kcal/mol), the C3 opening is favored by 10.7 kcal/mol. For the aziridine **5** along the path I, the IMC energies are remarkably destabilized for the C3 opening (4.3 kcal/mol) than for the C2 opening (−6.7 kcal/mol), whereas the TS energies are similar for the C2 and C3 openings, which also leads to the C3 favored opening. However, in the path IV, the TS energy is lower for the C2 opening (6.3 kcal/mol) than for the C3 opening (10.7 kcal/mol), whereas the IMC energies are the same (−9.5 kcal/mol). The activation barrier is lower for the C2 opening (15.8 kcal/mol) than the C3 opening (20.1 kcal/mol). Overall, the results of the solution phase calculations are in good agreement with those of the gas phase, showing the same trend but lowering the activation barriers.

The explicit solvation might give various TSs according to the number, position, and orientation of solvent molecules interacting with lithium atoms of the cuprate. In reality, one cannot know the exact shape of complicated explicit solvation. As a test, we investigated explicit solvation effect on TSs of the aziridines **2** and **5** via the path III using Me_2O instead of THF (*see* S2 in Supporting Information). The coordination shape between the two Li atoms and the two O atoms of the N-substituents resembles those of the gas phase. Furthermore, their relative TS energies of C2 to C3 opening are similar to those of the gas phase. This test suggests that we have identified the intrinsic C2-favored TS, which might be valid under solvation.

Conclusions

We have postulated the TS models of the prospective paths (I∼IV) considering the interactions between the N-activating groups and the cuprate, kinetics rather than thermodynamics, first TS rather than second TS, and S_N2-type rather than S_N1-type mechanism. This assumption led us to explain our unusual C2-methylation reactions of the *N*-(*para*-substituted)phenylaziridines with the cuprate in terms of the intrinsic activating and directing effects of the N-substituents as well as the e-donating effect of the para-substituted C2-phenyl group (Cl < H < Me). The *N*-activating effect of the *N*-(2-pyridyl)sulfonyl group (i.e., *N*-Py) is larger than that of the *N*-tosyl group (i.e., *N*-Tos) especially in conjuction with the e-donating effect of the para-substituted phenyl group at the more hindered C2 atom, which makes the aziridine **6** (Py/Me) be the most potent substrate for the C2 opening. In TSs, the *N*-Py group lowers the aziridine ring-opening barriers along the path IV due to the C2-directing effect which the *N*-Tos group cannot afford. The 2-pyridyl nitrogen atom N2 of the *N*-Py group interacting with the Li_α atom of the cuprate directs the nucleophilic $CH_3^{\delta-}$ group of the cuprate to an energetically favorable position of the C2-benzylic site leading to an early TS for the C2 opening. This phenomenon is supported by the less charge transfer from the $CH_3^{\delta-}$ group into the benzylic C2 atom due to the cooperative charge transfer from the Cu atom in the cuprate. The results of the implicit and explicit solvation calculations are in good agreement with those of the gas phase calculations. In the future work, the ring opening mechanisms using the CN group instead of the Cl atom for the cuprate behavior may be investigated as in the work of Nakamura et al.[68]

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