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Kinetics and Mechanism of the Pyridinolysis of (2*R*,4*R*,5*S*)-(+)-2-Chloro-3,4-dimethyl-5-phenyl-1,3,2-oxazaphospholidine 2-Sulfide in Acetonitrile†

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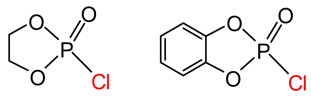
The nucleophilic substitution reactions of (2*R*,4*R*,5*S*)-(+)-2-chloro-3,4-dimethyl-5-phenyl-1,3,2-oxazaphospholidine 2-sulfide with X-pyridines are investigated kinetically in acetonitrile at 5.0 °C. The free energy relationships for substituent X variations in the nucleophiles exhibit biphasic concave upwards with a break point at X = 3-Ac. Unusual positive ρ_X (= +4.73) and negative β_X (= –0.75) values are obtained with the weakly basic pyridines, and rationalized by the isokinetic relationship with isokinetic temperature at $t_{ISOKINETIC}$ = 39.3 °C. A concerted mechanism involving a change of nucleophilic attacking direction from a frontside attack with the strongly basic pyridines to a backside attack with the weakly basic pyridines is proposed on the basis of greater magnitudes of selectivity parameters (ρ_X = –6.15 and β_X = 1.11) with the strongly basic pyridines compared to those (ρ_X = 4.73 and β_X = –0.75) with the weakly basic pyridines.

Key Words : Thiophosphoryl transfer reaction, Pyridinolysis, (2*R*,4*R*,5*S*)-(+)-2-Chloro-3,4-dimethyl-5-phenyl-1,3,2-oxazaphospholidine 2-sulfide, Biphasic concave upward free energy relationship, Isokinetic relationship

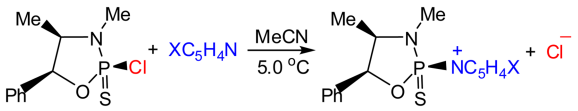
Introduction

The authors reported that the pyridinolysis and anilinolysis rates of cyclic five-membered rings of ethylene (**1**) and 1,2-phenylene (**2**) phosphorochloridates[1] are exceptionally faster than their acyclic counterparts of diethyl [$(EtO)_2P(=O)Cl$] and phenyl ethyl [(PhO)(EtO)P(=O)Cl] chlorophosphates in acetonitrile (MeCN).[2]



1 **2**

To extend the kinetic studies on the aminolyses of cyclic five-membered rings, the kinetic studies on the reactions of (2*R*,4*R*,5*S*)-(+)-2-chloro-3,4-dimethyl-5-phenyl-1,3,2-oxazaphospholidine 2-sulfide (**3**) with substituted pyridines (XC_5H_4N) have been carried out in MeCN at 5.0 ± 0.1 °C (Scheme 1), followed by the anilinolysis of **3** in MeCN at 5.0 °C.[3] The purpose of this work is to gain further information into the reactivity, solvent effect, and mechanism of the aminolyses of cyclic five-membered rings, as well as to compare with the relevant aminolyses of **1** and **2**.



X = 4-MeO, 4-Me, 3-Me, H, 3-Ph, 3-MeO, 3-Cl, 3-Ac, 4-Ac, 3-CN, 4-CN

Scheme 1. The pyridinolysis of (2*R*,4*R*,5*S*)-(+)-2-chloro-3,4-dimethyl-5-phenyl-1,3,2-oxazaphospholidine 2-sulfide (**3**) in MeCN at 5.0 °C.

†This paper is to commemorate Professor Kook Joe Shin's honourable retirement.

Results and Discussion

The reactions were carried out under pseudo-first-order conditions with a large excess of pyridine. The observed pseudo-first-order rate constants (k_{obsd}) for all the reactions obeyed Eq. (1) with negligible k_0 (≈ 0) in MeCN. The second-order rate constants (k_{Pyr}) were determined with at least five pyridine concentrations. The linear plots of Eq. (1) suggest a lack of any base-catalysis or side reaction, and the overall reaction is described by Scheme 1.

$$k_{obsd} = k_0 + k_{Pyr}[XC_5H_4N] \quad (1)$$

The second-order rate constants [k_{Pyr} (M^{-1} s^{-1})] are summarized in Table 1. The Brönsted β_X value was calculated by correlating log k_{Pyr}(MeCN) with pK_a(H_2O), which was justified theoretically and experimentally.[4] The substituent effects of the nucleophiles upon the pyridinolysis rates do not correlate with those for a typical nucleophilic substitution reaction: (i) for more basic pyridines (X = 4-MeO, 4-Me, 3-Me, H, 3-Ph, 3-MeO, 3-Cl, 3-Ac), the stronger nucleophile leads to a faster rate in line with a typical nucleophilic substitution reaction, resulting in negative ρ_X (= –6.15) and positive β_X (= +1.11) values; (ii) for less basic pyridines (X = 3-Ac, 4-Ac, 3-CN, 4-CN), on the contrary, the weaker nucleophile leads to a faster rate, resulting in unusual positive ρ_X (= +4.73) and negative β_X (= –0.75) values. Thus, both the Hammett (Fig. 1; log k_{Pyr} *vs* σ_X) and Brönsted [Fig. 2; log k_{Pyr} *vs* pK_a(X)] plots are biphasic concave upwards with a break point at X = 3-Ac, giving minimum second-order rate constant at a break point.

Table 1. Second-Order Rate Constants (k_{Pyr} × 10^2/M^{-1} s^{-1}) of the Reactions of (2*R*,4*R*,5*S*)-(+)-2-Chloro-3,4-dimethyl-5-phenyl-1,3,2-oxazaphospholidine 2-Sulfide (**3**) with XC_5H_4N in MeCN at 5.0 °C

X	4-MeO	4-Me	3-Me	H	3-Ph	3-MeO	3-Cl	3-Ac	4-Ac	3-CN	4-CN
k_{Pyr} × 10^2	569 ± 2	119 ± 1	30.3 ± 0.1	11.7 ± 0.1	2.96 ± 0.01	1.91 ± 0.01	0.0744 ± 0.0002	0.0457 ± 0.0003	0.155 ± 0.001	0.335 ± 0.002	0.939 ± 0.007

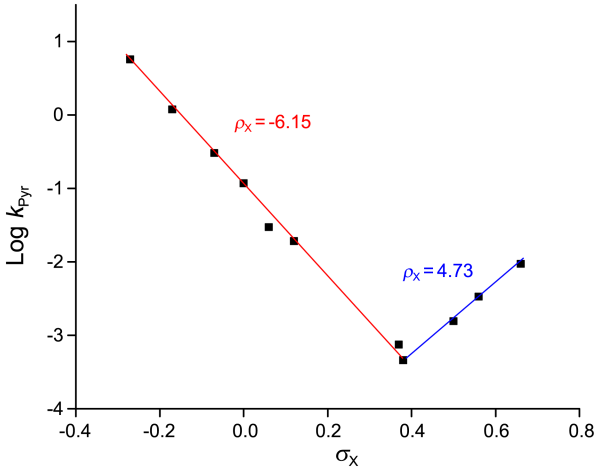


Figure 1. The Hammett plot (log k_{Pyr} *vs* σ_X) of the reactions of (2*R*,4*R*,5*S*)-(+)-2-chloro-3,4-dimethyl-5-phenyl-1,3,2-oxazaphospholidine 2-sulfide (**3**) with X-pyridines in MeCN at 5.0 °C.

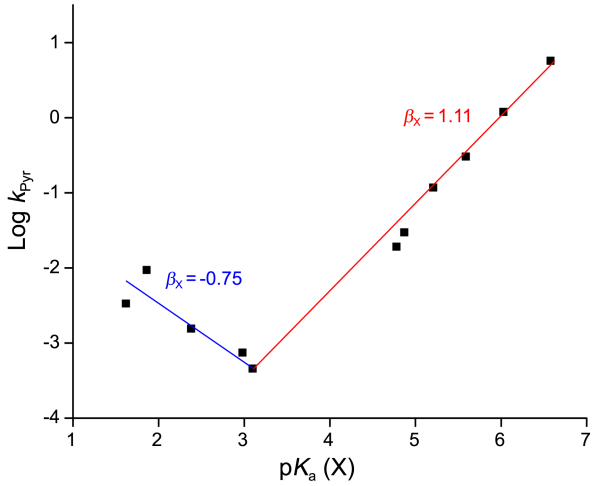


Figure 2. The Brönsted plot [log k_{Pyr} *vs* pK_a(X)] of the reactions of (2*R*,4*R*,5*S*)-(+)-2-chloro-3,4-dimethyl-5-phenyl-1,3,2-oxazaphospholidine 2-sulfide (**3**) with X-pyridines in MeCN at 5.0 °C.

The unusual positive ρ_X and negative β_X values with the weakly basic pyridines can be occurred because of desolvation of ground state (GS),[5] or imbalance of transition state (TS),[6] or isokinetic relationship.[7] In the present work, the positive ρ_X (and negative β_X) value with the less basic pyridines is not ascribed to a desolvation step prior to the rate-limiting nucleophilic attack, since the pyridine nucleophile is neutral and the MeCN solvent is dipolar aprotic. The positive ρ_X value is inadequate to a TS imbalance phenomenon, since an ion-pair pre-equilibrium cannot occur taking into account the nature of the studied substrate. For a large number of reaction series, it is found that $\delta\Delta H^{\neq}$ and $\delta\Delta S^{\neq}$ are proportional, resulting in isokinetic relationship.[7] The observed second-order rate constants with 4-acetyl, 3-cyano, and 4-cyano pyridines at 5.0 °C, 10.0 °C, and 15.0 °C, and enthalpies and entropies of activation are summarized in Table 2. The ρ_X value decreases as the reaction temperature becomes higher as seen in Figure 3: ρ_X = 4.85, 4.00, and 3.24 at 5.0, 10.0, and 15.0 °C, respectively. Thus, the isokinetic temperature is $T_{ISOKINETIC}$ = 312.5 K = 39.3 °C, according to Eq. (2), where the ρ_X value is null, based on: $\Delta H^{\neq}$ =

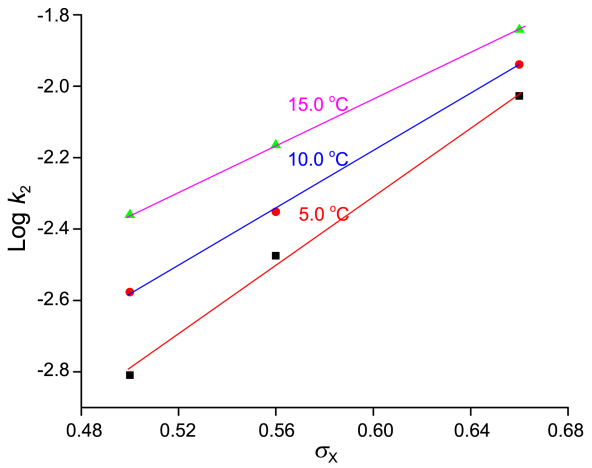


Figure 3. The Hammett plots of log k_2 *vs* σ_X for the reactions of (2*R*,4*R*,5*S*)-(+)-2-Chloro-3,4-dimethyl-5-phenyl-1,3,2-oxazaphospholidine 2-Sulfide (**3**) with X = 4-Ac, 3-CN, and 4-CN pyridines in MeCN. The ρ_X values are 4.85 ± 0.03 (r = 0.998), 4.00 ± 0.01 (r = 0.999), and 3.24 ± 0.01 (r = 1.000) at 5.0, 10.0, and 15.0 °C, respectively.

Table 2. Second-Order Rate Constants at 5.0, 10.0, and 15.0 °C, and Enthalpies and Entropies of Activation for the Reactions of (2*R*,4*R*,5*S*)-(+)-2-Chloro-3,4-dimethyl-5-phenyl-1,3,2-oxazaphospholidine 2-Sulfide (**3**) with X-Pyridines (X = 4-Ac, 3-CN and 4-CN) in MeCN

X	k_2 × 10^2/M^{-1} s^{-1}			$\Delta H^{\ddagger}$/kcal mol^{-1}	$\Delta S^{\ddagger}$/eu
	5.0 °C	10.0 °C	15.0 °C		
4-Ac	0.155 ± 0.001	0.265 ± 0.001	0.456 ± 0.001	15.9 ± 0.2	−14 ± 1
3-CN	0.335 ± 0.002	0.445 ± 0.003	0.684 ± 0.002	10.8 ± 1.4	−31 ± 5
4-CN	0.939 ± 0.007	1.15 ± 0.01	1.44 ± 0.01	6.2 ± 0.3	−45 ± 1

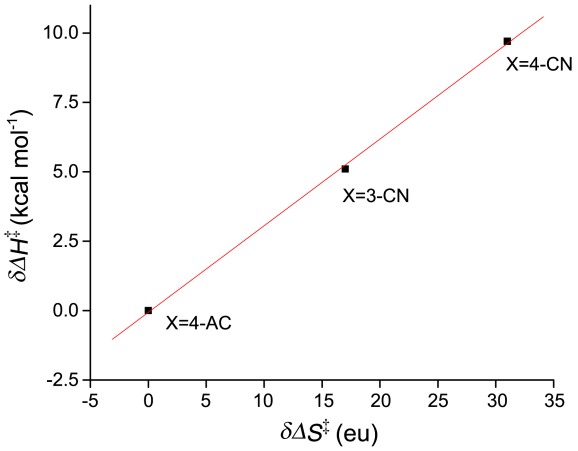


Figure 4. Isokinetic relationship for the reactions of (2*R*,4*R*,5*S*)-(+)-2-Chloro-3,4-dimethyl-5-phenyl-1,3,2-oxazaphospholidine 2-Sulfide (**3**) with 4-Ac, 3-CN, and 4-CN pyridines in MeCN, giving the slope of $T_{ISOKINETIC}$ = 312.5 K = 39.3 °C (r = 0.999).

15.9 and $\Delta S^{\neq}$ = 14 with X = 4-Ac; $\Delta H^{\neq}$ = 10.8 and $\Delta S^{\neq}$ = –31 with X = 3-CN; $\Delta H^{\neq}$ = 6.2 kcal/mol and $\Delta S^{\neq}$ = –45 eu with X = 4-CN (Fig. 4).

$$\delta\Delta G^{\neq} = \delta\Delta H^{\neq} - T\delta\Delta S^{\neq} = 0; \text{ when } \delta\Delta H^{\neq} = T_{ISOKINETIC}\,\delta\Delta S^{\neq} \quad (2)$$

The isokinetic relationships for the pyridinolyses of tetracoordinated phosphorus are also observed when the reaction temperature is considerably low: (i) the pyridinolysis of dimethyl phosphinic chloride [$(Me)_2P(=O)Cl$] yielded positive ρ_X (= +0.16) and negative β_X (= 0.03) values with the weakly basic pyridines in MeCN at 25.0 °C, giving $T_{ISOKINETIC}$ = 249.4 K = 23.8 °C;[8] (ii) the pyridinolysis of methyl phenyl phosphinic chloride [MePhP(=O)Cl] yielded positive ρ_X (= +2.94) and negative β_X (= 0.48) values with the strongly basic pyridines in MeCN at 20.0 °C, giving $T_{ISOKINETIC}$ = 287.5 K = 14.4 °C;[9] and (iii) the pyridinolysis of ethylene phosphorochloridate (**1**) yielded positive ρ_X (= +2.49) and negative β_X (= –0.41) values with the weakly basic pyridines in MeCN at –20.0 °C, giving $T_{ISOKINETIC}$ = 279.7 K = 6.6 °C.[1c] It seems that the pyridinolysis of tetracoordinated phosphorus shows the isokinetic relationship in MeCN at the very low temperature when the free energy relationship exhibits biphasic concave upwards (or downwards) with minimum (or maximum) rate constant.

The second-order rate constants (k_{Pyr} and k_{An}) with unsubstituted pyridine (C_5H_5N) and aniline ($C_6H_5NH_2$) at 35.0 °C, Brönsted coefficients ($\beta_{X,Pyr}$ and $\beta_{X,An}$), and second-order rate constant ratios of the pyridinolysis with C_5H_5N to the anilinolysis with $C_6H_5NH_2$ (k_{Pyr}/k_{An}) for the pyridinolyses and anilinolyses of **1-3** in MeCN are summarized in Table 3. The pyridinolysis rates are considerably faster than the anilinolysis rates of **1-3**. The ratios of k_{Pyr}/k_{An} are strongly dependent upon the substrates, and the smaller the size of the substrate the ratio becomes greater. Note that all the second-order rate constants of the pyridinolyses and anilinolysis of **1-3** in Table 3 are the extrapolated values in the Arrhenius plots.[10] The pK_a values of pyridine and aniline are 12.33 and 10.56 in MeCN[11] (and 5.17 and 4.58 in water),[12] respectively. Even taking into account the greater basicity of pyridine than that of aniline, ΔpK_a = 1.77 in MeCN (and ΔpK_a = 0.59 in water), the pyridinolysis rate is still much faster than the anilinolysis rate.[13] The difference in the rate may be due to resonance energy gain from the benzyl cation type π-complex formation[14] of pyridine with an empty d-orbital of the P atom. This type of π-complex is not possible with aniline because the lone pair on the amino nitrogen is a p-type so that the horizontal π-cloud of the ring overlap with the d-orbital of P marginally. Moreover, regarding the steric effects of the two ligands, the horizontal approach of the aniline ring should cause excessive steric hindrance in contrast to much less steric effects in the vertical approach of the pyridine ring.[13]

The pyridinolysis rate of **3** (P=S system) is 2-7 hundreds times slower than those of **1** and **2** (P=O systems).[15] It is well known that the P=S system is generally less reactive than its P=O counterpart for several reasons, the so-called "thio effect", which is mainly the electronegativity difference between O and S, favoring P=O over P=S.[16]

The activation parameters for the pyridinolyses with C_5H_5N and anilinolyses with $C_6H_5NH_2$ of **1-3** in MeCN are summarized in Table 4. The distinction of the activation parameters between cyclic substrates of **1** and **2** and their

Table 3. Summary of the Second-Order Rate Constants (k_{Pyr} with C_5H_5N and k_{An} with $C_6H_5NH_2$ at 35.0 °C), Brönsted coefficients ($\beta_{X,Pyr}$ and $\beta_{X,An}$), and Rate Ratios of the Pyridinolysis to Anilinolysis (k_{Pyr}/k_{An}) for the Pyridinolyses (XC_5H_4N) and Anilinolyses ($XC_6H_4NH_2$) of **1-3** in MeCN

Substrate	k_{Pyr} [a]	$\beta_{X,Pry}$	k_{An} [f]	$\beta_{X,An}$	k_{Pyr}/k_{An} [k]
1: $cC_2H_4O_2P(=O)Cl$	3,180[b]	1.06/–0.41[e]	0.649[g]	1.56/0.79[j]	4,900
2: $C_6H_4O_2P(=O)Cl$	9,560[c]	0.41/0.07[e]	77.8[h]	1.54/0.35[j]	123
3: $C_6H_5CHOCH(CH_3)N(CH_3)P(=S)Cl$	13.6[d]	1.11/–0.75[e]	0.456[i]	1.46	29.8

[a]The second-order rate constants with unsubstituted pyridine (C_5H_5N) in MeCN at 35.0 °C. [b]Extrapolated value in the Arrhenius plot with kinetic data: k_{Pyr} = 9.98, 28.9, and 88.5 × 10^{-2} M^{-1} s^{-1} at –20.0, –15.0, and –10.0 °C, respectively. See ref. 1c. [c]Extrapolated value in the Arrhenius plot with kinetic data: k_{Pyr} = 2.25, 4.98, and 11.8 M^{-1} s^{-1} at –25.0, –20.0, and –15.0 °C, respectively. See ref 1d. [d]Extrapolated value in the Arrhenius plot with kinetic data: k_{Pyr} = 0.117, 0.288, 0.645, and 1.45 × 10^0 M^{-1} s^{-1} at 5.0, 10.0, 15.0, and 20.0 °C, respectively. [e]Strongly basic/weakly basic pyridines. [f]The second-order rate constants with unsubstituted aniline ($C_6H_5NH_2$) in MeCN at 35.0 °C. [g]Extrapolated value in the Arrhenius plot with kinetic data: k_{An} = 0.671, 4.56, 11.1, and 26.6 × 10^{-3} M^{-1} s^{-1} at –5.0, 5.0, 10.0, and 15.0 °C, respectively. See ref. 1a. [h]Extrapolated value in the Arrhenius plot with kinetic data: k_{An} = 0.531, 0.863, 1.53, and 2.46 × 10^0 M^{-1} s^{-1} at –20.0, –15.0, –10.0, and –5.0 °C, respectively. See ref. 1b. [i]Extrapolated value in the Arrhenius plot with kinetic data: k_H = 1.77, 3.25, 5.45, and 10.1 × 10^{-2} M^{-1} s^{-1} at 5.0, 10.0, 15.0, and 20.0 °C, respectively. See ref. 3. [j]Strongly basic/weakly basic anilines. [k]The second-order rate constant ratios of the pyridinolysis with C_5H_5N to the anilinolysis with $C_6H_5NH_2$ at 35.0 °C.

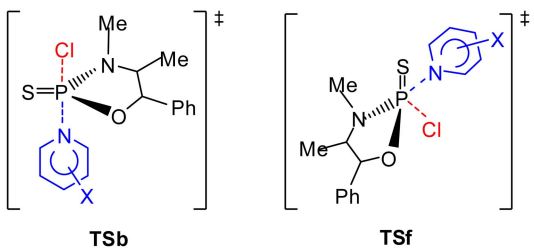
Table 4. Activation Parameters for the Pyridinolyses with C_5H_5N and Anilinolyses with $C_6H_5NH_2$ of **1-3** in MeCN[a]

Substrate	$\Delta H_{Pyr}^{\neq}$	$\Delta S_{Pyr}^{\neq}$	$-T\Delta S_{Pyr}^{\neq}$	$\Delta G_{Pyr}^{\neq}$	$\Delta H_{An}^{\neq}$	$\Delta S_{An}^{\neq}$	$-T\Delta S_{An}^{\neq}$	$\Delta G_{An}^{\neq}$
1: $cC_2H_4O_2P(=O)Cl$	28.4	+49	–15.2	13.2	27.6	+30	–9.3	18.3
2: $C_6H_4O_2P(=O)Cl$	20.5	+26	–8.0	12.5	13.3	–7	2.1	15.4
3: $C_6H_5CHOCH(CH_3)N(CH_3)P(=S)Cl$	26.5	+32	–10.0	16.5	18.0	–2	0.6	18.6

[a]The values of activation parameters of the pyridinolyses and anilinolyses are at 35.0 °C. See the supplementary materials in which the calculation of activation parameters of the present work (pyridinolysis of **3**) is described. The units of $\Delta H^{\neq}$, $T\Delta S^{\neq}$, and $\Delta G^{\neq}$ are kcal mol^{-1} and that of $\Delta S^{\neq}$ is entropy unit (eu; cal mol^{-1} K^{-1}).

acyclic counterparts of diethyl and phenyl ethyl chlorophosphates is much greater enthalpies and entropies of activation with cyclic substrates compared to those with their acyclic counterparts.[1,2] These indicate that the aminolyses of cyclic substrates are much more favorable than those of their acyclic counterparts, due to unusual very large positive (or very small negative) values of the entropy of activation of cyclic substrates. In other words, the much faster aminolysis rates of cyclic substrates compared to their acyclic counterparts are ascribed to favorable entropy of activation change ($\Delta\Delta S^{\neq} >> 0$) over unfavorable enthalpy of activation change ($\Delta\Delta H^{\neq} >> 0$).[17] In general, the negative value of entropy of activation is obtained for the bimolecular nucleophilic substitution reaction since the two molecules of reactants in the GS becomes one activated complex in the TS. Thus, great positive (or very small negative) values of the entropies of activation of the aminolyses suggest that the enormous degree of solvent structure breaking occurs in the TS. This indicates that the degree of the ordered acetonitrile structure breaking is serious enough to give large positive entropy of activation, accompanying large enthalpy of activation, in the TS.[17]

Biphasic concave upward free energy correlations for substituent X variations in the nucleophiles were observed for the pyridinolyses of various substrates in which the greater values of selectivity parameters with the strongly basic pyridines were obtained compared to those with the weakly basic pyridines.[1a,c,2a,8,18] A concerted S_N2 mechanism was proposed and biphasic concave upward free energy correlations was rationalized by a change of nucleophilic attacking direction from a frontside attack TSf with the strongly basic pyridines to a backside attack TSb with the weakly basic pyridines.[1a,c,2a,8,18] In the present work, accordingly, the authors propose a concerted mechanism involving a change of nucleophilic attacking direction from a frontside attack TSf with the strongly basic pyridines to a backside attack TSb with the weakly basic pyridines (Scheme 2). It is worthy of note that a frontside attack TSf yields greater magnitudes of ρ_X and β_X values compared to a backside attack TSb.[19]



Scheme 2. Backside attack TSb and frontside attack TSf.

Experimental Section

Materials. (2*R*,4*R*,5*S*)-(+)-2-Chloro-3,4-dimethyl-5-phenyl-1,3,2-oxazaphospholidine 2-sulfide, commercially available, was used for kinetic studies without further purification. The HPLC grade acetonitrile (less than 0.005% water content) was used without further purification.

Kinetic Measurements. Rates were measured conductometrically as previously described.[1,2,18] The initial concentrations of [substrate] = 5.0×10^{-4} M and [X-pyridine] = (0.05-0.30) M were used for the present work. Pseudo-first-order rate constant values were the average of at least three runs that were reproducible within ± 3%.

Product Analysis. The studied substrate of (2*R*,4*R*,5*S*)-(+)-2-chloro-3,4-dimethyl-5-phenyl-1,3,2-oxazaphospholidine 2-sulfide was reacted with excess pyridine for more than 15 half-lives in MeCN at 5.0 °C. Solvent was removed under reduced pressure. The product was isolated after treatment with ether and MeCN, and then dried under reduced pressure. The analytical and spectroscopic data of the product are summarized as follows (see the supplementary materials).

$[C_6H_5CHOCH(CH_3)N(CH_3)P(=S)NC_5H_5]^+Cl^-$. White solid crystal; mp 191.0-192.0 °C; ^{1}H NMR (400 MHz, MeCN-d_3) δ 1.15-1.19 (aliphatic, 3H, m); 2.83-2.87 (aliphatic, 3H, m); 3.57-3.59 (aliphatic, 1H, m); 5.65-5.68 (aliphatic, 1H, m); 7.49-8.57 (aromatic, 10H, m); ^{13}C NMR (100 MHz, MeCN-d_3) δ 10.18-94.63 (aliphatic, 4C, m); 124.93-147.78 (aromatic, 11C, m); ^{31}P NMR (162 MHz, MeCN-d_3) δ 59.20 (P=S, 1P, s); LC-MS for $C_{15}H_{18}ClN_2OPS$ (EI, *m/z*), 341(M^+).

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