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Kinetics and Mechanism of the Pyridinolysis of *S*-Aryl Phenyl Phosphonochloridothioates in Acetonitrile

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Kinetic studies on the reactions of Y-*S*-aryl phenyl phosphonochloridothioates with X-pyridines have been carried out in MeCN at 55.0 ºC. The Hammett and Brönsted plots for substituent X variations in the nucleophiles are biphasic concave upwards with a break point at X = H. The Hammett plots for substituent Y variations in the substrates are biphasic concave upwards with a break point at Y = H, and the sign of ρ_Y is changed from unusual negative ($\rho_Y < 0$) with the weaker electrophiles to positive ($\rho_Y > 0$) with the stronger electrophiles. The stepwise mechanism is proposed on the basis of the ρ_X, β_X, and ρ_{XY} values as follows: a rate-limiting leaving group departure from the intermediate involving a frontside attack and product-like TS for the stronger nucleophiles and weaker electrophiles; a rate-limiting leaving group departure from the intermediate involving a backside attack and product-like TS for the weaker nucleophiles and electrophiles; a rate-limiting bond formation involving a frontside attack for the stronger nucleophiles and electrophiles; a rate-limiting bond formation involving a backside attack for the weaker nucleophiles and stronger electrophiles. The substituent effects of X and Y on the pyridinolysis mechanisms of $R_1R_2P(=S)Cl$-type substrates are discussed.

Key Words : Biphasic free energy correlation, Phosphoryl transfer reaction, Pyridinolysis, *S*-Aryl phenyl phosphonochloridothioates

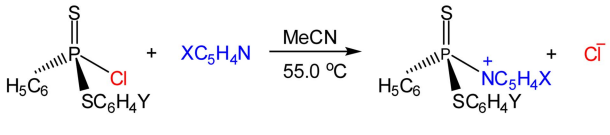
Introduction

The experimental (pyridinolysis,[1] anilinolysis,[2] and benzylaminolysis[3]) and theoretical studies[4] on the phosphoryl transfer reactions have been studied extensively by this lab. Surprising substituent effects were observed for the pyridinolyses: (i) in bis(4-methoxyphenyl) Z-aryl phosphates [$(4\text{-MeO-C}_6H_4O)_2P(=O)(OC_6H_4Z)$], the free energy correlations for both substituent X and Z variations in the nucleophiles and leaving groups, respectively, were biphasic concave downwards;[1b] (ii) in Y-aryl phenyl isothiocyanophsphates [$(PhO)(YC_6H_4O)P(=O)(NCS)$], the free energy correlations for substituent X variations in the nucleophiles were biphasic concave upwards while those for substituent Y variations in the substrates were biphasic concave downwards;[1c] (iii) in Y-aryl phenyl chlorothiophosphates [$(PhO)(YC_6H_4O)P(=S)Cl$], the free energy correlations for substituent X variations in the nucleophiles were biphasic concave upwards while those for substituent Y variations in the substrates were biphasic concave downwards;[1j] (iv) in Y-*O*-aryl methyl phosphonochloridothioates [$Me(YC_6H_4O)P(=S)Cl$], the free energy correlations for substituent X variations in the nucleophiles were discrete biphasic with a break region while those for substituent Y variations in the substrates were biphasic concave downwards;[1k] (v) in *O,O*-diphenyl Z-*S*-aryl phosphorothioates [$(PhO)_2P(=O)(SC_6H_4Z)$], the free energy correlations for substituent Z variations in the leaving groups were biphasic concave downwards with a max point, and the anomalous negative sign of ρ_Z was observed with better leaving groups;[1e] (vi) in Z-*N*-aryl-*P,P*-diphenyl phosphinic amides [$Ph_2P(=O)NHC_6H_4Z$], the free energy correlations for substituent Z variations in the leaving groups were biphasic concave upwards with a min point, and the anomalous negative sign of ρ_Z was observed with poor leaving groups.[1l]

Herein, the reactions of Y-*S*-aryl phenyl phosphonochloridothioates with X-pyridines in acetonitrile (MeCN) at 55.0 ± 0.1 ºC (Scheme 1) have been carried out kinetically to gain further information into the phosphoryl transfer reactions. The MO theoretical structure with bond angles and natural bond order (NBO) charges [B3LYP/6-311+G(d,p) level of theory][5] of *S*-phenyl phenyl phosphonochloridothioate show that the three oxygens and chlorine has more or less distorted tetrahedral geometry with the phosphorus atom at the center (Fig. 1). The substituent effects of the nucleophiles (X) and substrates (Y) on the reaction mechanism are investigated by comparing the free energy correlations of the relevant pyridinolyses of $R_1R_2P(=S)Cl$-type substrates in MeCN.

Results and Discussion

The pseudo-first-order rate constants observed (k_{obsd}) for all reactions obeyed eq. (1) with negligible k_0 (≈ 0) in



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

Y = 4-MeO, 3-Me, H, 3-MeO, 4-Cl

Scheme 1. The studied reaction system.

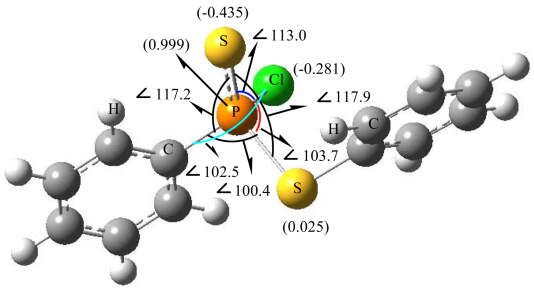


Figure 1. The B3LYP/6-311+G(d,p) geometry of *S*-phenyl phenyl phosphonochloridothioate in the gas phase.

MeCN. The second-order rate constants were determined with at least five pyridine concentrations [XC_5H_4N]. No third-order or higher-order terms were detected, and no complications were found in the determination of k_{obsd} or in the linear plot of eq. (1). This suggests that there are no base-catalysis or noticeable side reactions, and the overall reaction follows the path given by Scheme 1.

$$k_{obsd} = k_0 + k_2[XC_5H_4N] \quad (1)$$

The second-order rate constants [k_2 (M^{-1} s^{-1})] are summarized in Table 1, together with selectivity parameters, ρ_X, β_X, ρ_Y, and ρ_{XY}. The β_X values were determined using pK_a values in water; the slopes from the plots of log k_2(MeCN) against pK_a(H_2O). Justification of this procedure has been experimentally and theoretically provided.[8] The substituent effects of the nucleophiles on the rates are compatible with those for a typical nucleophilic substitution reaction with positive charge development at the nucleophilic N atom (ρ_X < 0 and β_X > 0), although the Hammett (log k_2 *vs* σ_X) and Brönsted [log k_2 *vs* pK_a(X)] plots for substituent X variations exhibit biphasic concave upwards with a break point at X = H (Figs. 2 and 3). However, the substituent effects of the substrates on the rates are not compatible with those for a typical nucleophilic substitution reaction, since the Hammett plots (log k_2 *vs* σ_Y) for substituent Y variations are biphasic upwards with a break point, having *min* value, at Y = H (Fig. 4). As a result, the sign of ρ_Y is changed from unusual negative (ρ_Y < 0) with the weaker electophiles to positive (ρ_Y > 0) with the stronger electrophiles, regardless of the nature of the nucleophiles.

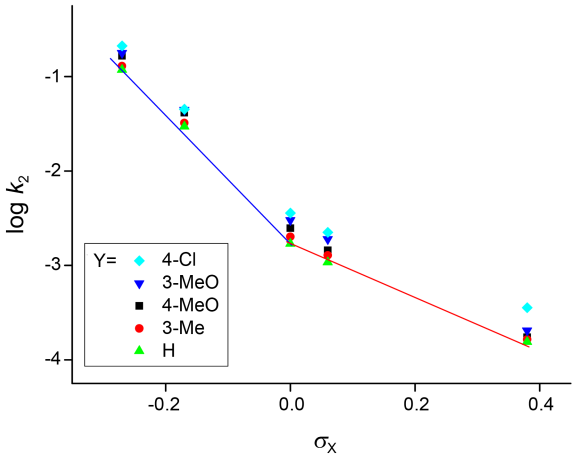


Figure 2. The Hammett plots (log k_2 *vs* σ_X) of the reactions of Y-*S*-aryl phenyl phosphonochloridothioates with X-pyridines in MeCN at 55.0 °C.

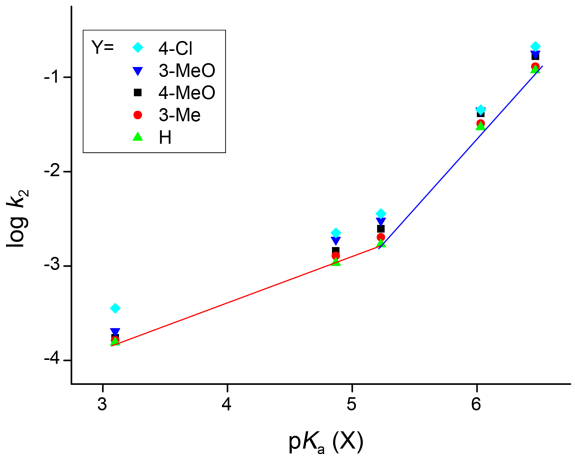


Figure 3. The Brönsted plots [log k_2 *vs* pK_a(X)] of the reactions of Y-*S*-aryl phenyl phosphonochloridothioates with X-pyridines in MeCN at 55.0 °C.

Table 1. Second-Order Rate Constants ($k_2 \times 10^3/M^{-1}$ s^{-1}) and Selectivity Parameters[a] of the Reactions of Y-*S*-Aryl Phenyl Phosphonochloridothioates with X-Pyridines in MeCN at 55.0 ºC

X \ Y	4-MeO	3-Me	H	3-MeO	4-Cl	ρ_Y[b]	ρ_Y[c]
4-MeO	167	130	118	178	212	–0.55 ± 0.00	1.11 ± 0.04
4-Me	41.4	32.2	29.6	44.4	45.2	–0.54 ± 0.00	0.81 ± 0.07
H	2.48	2.02	1.70	3.02	3.59	–0.57 ± 0.03	1.42 ± 0.07
3-Ph	1.45	1.28	1.08	1.90	2.24	–0.43 ± 0.03	1.39 ± 0.07
3-Ac	0.174	0.165	0.155	0.205	0.357	–0.17 ± 0.01	1.57 ± 0.06
$-\rho_X$[d,e]	6.81 ± 0.06	6.73 ± 0.05	6.87 ± 0.07	6.59 ± 0.04	6.55 ± 0.01	ρ_{XY}[b,d,j] =	ρ_{XY}[c,d,l] =
β_X[d,f]	1.48 ± 0.04	1.46 ± 0.03	1.49 ± 0.04	1.43 ± 0.02	1.42 ± 0.03	–0.08 ± 0.05	1.42 ± 0.06
$-\rho_X$[g,h]	2.98 ± 0.04	2.84 ± 0.02	2.70 ± 0.03	3.06 ± 0.01	2.59 ± 0.04	ρ_{XY}[b,g,k] =	ρ_{XY}[c,g,m] =
β_X[g,i]	0.54 ± 0.03	0.51 ± 0.01	0.49 ± 0.02	0.55 ± 0.00	0.46 ± 0.03	0.97 ± 0.03	0.44 ± 0.05

[a]The σ values were taken from ref 6. The pK_a values were taken from ref 7. [b]Y = (4-MeO, 4-Me, H). Correlation coefficients, r, are better than 0.936. [c]Y = (H, 3-MeO, 4-Cl). r ≥ 0.896. [d]X = (4-MeO, 4-Me, H). [e]r ≥ 0.999. [f]r ≥ 0.999. [g]X = (H, 3-Ph, 4-Ac). [h]r ≥ 0.999. [i]r ≥ 0.999. [j]r = 0.998. [k]r = 0.998. [l]r = 0.997. [m]r = 0.994.

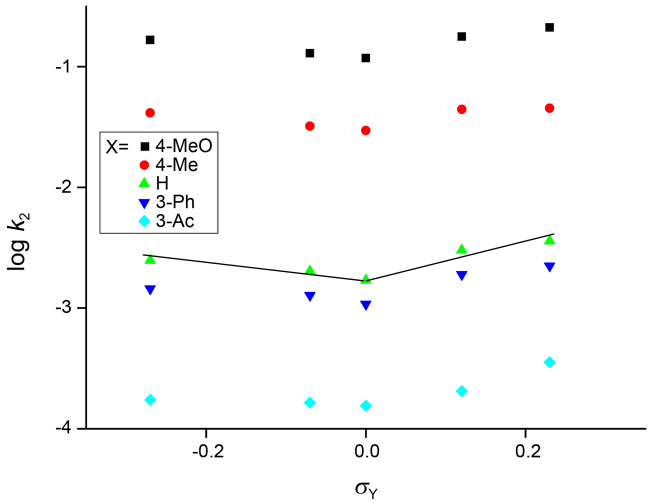


Figure 4. The Hammett plots (log k_2 *vs* σ_Y) of the reactions of Y-*S*-aryl phenyl phosphonochloridothioates with X-pyridines in MeCN at 55.0 °C.

The magnitudes of ρ_X (= –6.55 to –6.87) and β_X (= 1.42-1.49) values with the strongly basic pyridines (X = 4-MeO, 4-Me, H) are greater than those (ρ_X = –2.59 to –3.06 and β_X = 0.46-0.55) with the weakly basic pyridines (X = H, 3-Ph, 3-Ac), indicating greater degree of bond formation (or greater positive charge development at the nucleophilic N atom) for the strongly basic pyridines than for the weakly basic pyridines.

The cross-interaction constants (CICs; ρ_{XY}), eqs. (2), are determined, where X and Y represent the substituents in the nucleophile and substrates, respectively.[9] The sign and magnitude of the CICs have made it possible to correctly interpret the reaction mechanism and degree of tightness of the TS, respectively. In general, the ρ_{XY} has a negative value in a stepwise mechanism with a rate-limiting bond formation and a concerted S_N2. In contrast, it has a positive value for a stepwise mechanism with a rate-limiting leaving group expulsion from the intermediate. The magnitude of ρ_{XY} is inversely proportional to the distance between X and Y through the reaction center.[9]

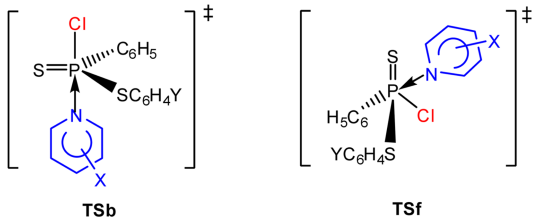
$$\log(k_{XY}/k_{HH}) = \rho_X\sigma_X + \rho_Y\sigma_Y + \rho_{XY}\sigma_X\sigma_Y \quad (2a)$$

$$\rho_{XY} = \partial\rho_X/\partial\sigma_Y = \partial\rho_Y/\partial\sigma_X \quad (2b)$$

Since both Hammett plots for substituent X and Y variations are biphasic with a break point, four values of ρ_{XY} can be obtained by dividing into four blocks: (*a*) ρ_{XY} = –0.08 (r = 0.999) for the stronger nucleophiles and weaker electrophiles (X = 4-MeO, 4-Me, H and Y = 4-MeO, 3-Me, H); (*b*) ρ_{XY} = 0.97 (r = 0.998) for the weaker nucleophiles and electrophiles (X = H, 3-Ph, 3-Ac and Y = 4-MeO, 3-Me, H); (*c*) ρ_{XY} = 1.42 (r = 0.999) for the stronger nucleophiles and electrophiles (X = 4-MeO, 4-Me, H and Y = H, 3-MeO, 4-Cl); (*d*) ρ_{XY} = 0.44 (r = 0.994) for the weaker nucleophiles and stronger electrophiles (X = H, 3-Ph, 3-Ac and Y = H, 3-MeO, 4-Cl). However, the ρ_{XY} values have some problems with credibility because of: (i) the ρ_{XY} values are calculated with nine second-order rate constants for all blocks;[10] (ii) despite the correlation coefficients are good, (r = 0.994-0.998), the variation tendencies of ρ_X and ρ_Y values for *a*, *c*, and *d* blocks are not consistency; (iii) the magnitudes of ρ_X and ρ_Y values with *a* block are *almost constant* (ρ_X = –6.80 ± 0.07 and ρ_Y = –0.55 ± 0.02), indicating ρ_{XY} = 0. Consequently, the sign and magnitude of ρ_{XY} for *b* block can be acceptable while those for *a*, *c*, and *d* blocks cannot be acceptable to discuss the reaction mechanism.

The null of ρ_{XY} value with *a* block can be rationalized by a stepwise mechanism with a rate-limiting leaving group expulsion from the intermediate where the distance between X and Y does not vary from the intermediate to the transition state (TS). The null of ρ_{XY} value suggests the absence of the cross-interaction between X and Y. This phenomenon can be occurred: (i) X and Y are too far apart to interact; (ii) the distance between X and Y does not vary. Thus, the null of ρ_{XY} value indicates a special stepwise mechanism with a rate-limiting bond breaking where the distance between X and Y does not vary from the intermediate to the TS. The unusual *negative* ρ_Y values with the weaker electrophiles suggest that the degree of bond breaking is considerably greater than that of bond formation and positive charge develops at the reaction center P atom in the TS. The negative ρ_Y values could be supporting evidence for a stepwise mechanism with a rate-limiting leaving group departure from the intermediate involving product-like late TS. It is worth noting that the magnitudes of ρ_X and β_X values involving a frontside attack TSf are greater than those involving a backside attack TSb (Scheme 2).[1c]

The authors propose mechanisms for the studied reaction system, divided into four blocks, as follows: (*a*) a stepwise mechanism with a rate-limiting leaving group departure from the intermediate based on the null of ρ_{XY} and negative ρ_Y values, and a frontside attack TSf based on the considerably great magnitudes of ρ_X and β_X; (*b*) a stepwise mechanism with a rate-limiting leaving group departure from the intermediate based on the positive ρ_{XY} and negative ρ_Y values, and a backside attack TSb based on the relatively small magnitudes of ρ_X and β_X values; (*c*) a stepwise mechanism with a rate-limiting bond formation based on the positive ρ_Y values and a frontside attack TSf on the basis of the considerably great magnitude of ρ_X and β_X values; (*d*) a stepwise mechanism with a rate-limiting bond formation based on the positive ρ_Y values and a backside attack TSb on the basis of the relatively small magnitudes of ρ_X and β_X values.



Scheme 2. Backside attack TSb and frontside attack TSf.

Table 2. Summary of the NBO Charges at the Reaction Center P Atom, Second-Order Rate Constants ($k_2 \times 10^3$/M^{-1} s^{-1}) at 35.0 °C, Brönsted Coefficients, and Free Energy Correlations for Substituent X and Y Variations of the Reactions of $R_1R_2P(=S)Cl$-type Substrates with X-pyridines in MeCN

Sub	R_1	R_2	charge at P	$k_2 \times 10^3$[a]	β_X	X variation	Y variation	ref
1	Me	YC_6H_4O	1.432	14.3[b]	0.66-1.04/2.08-2.38[e]	discrete[f]	Λ[h]	1k
2	Ph	YC_6H_4O	1.462	11.2[b]	0.87-0.95	linear	linear	1f
3	Ph	Ph	1.236	1.83	1.53/0.38[e]	V[g]	–	1d
4	MeO	MeO	1.687	1.54[c]	1.09/0.20[e]	V	–	1g
5	EtO	EtO	1.701	1.19[c]	1.02/0.29[e]	V	–	1g
6	Ph	YC_6H_4S	0.999	1.10[b,d]	1.42-1.49/0.46-0.55[e]	V	V[i]	this work
7	Me	Me	1.180	0.744	0.97/0.27[e]	V	–	1h
8	PhO	YC_6H_4O	1.661	0.333[b]	1.36-1.50/0.23-0.48[e]	V	Λ	1j

[a]For the reactions with unsubstituted pyridine (X = H) at 35.0 °C. [b]For the reactions of unsubstituted substrate (Y = H). [c]Extrapolated value from the Arrhenius plot. [d]Experimental value at 35.0 °C. [e]For more/less basic pyridines. [f]Biphasic discrete two plots, neither concave upwards nor downwards. [g]Biphasic concave upwards. [h]Biphasic concave downwards. [i]Biphasic concave upwards with min value.

Table 2 shows the NBO charges in the gas phase [B3LYP/6-311+G(d,p) level of theory][5] at the reaction center P atom, second-order rate constants with unsubstituted pyridine at 35.0 ºC, Brönsted coefficients, and free energy correlations for substituent X (Hammett and Brönsted plots) and Y (Hammett plots) variations of the pyridinolyses of $R_1R_2P(=S)Cl$-type substrates in MeCN. The sequence of the row is the order of the second-order rate constant. The pyridinolysis rates do not show linear correlation with the positive charge at the reaction center P atom, suggesting that the reaction is not charge controlled one.[11] Furthermore, there is no linear correlation between the rate and the size of the two ligands, R_1 and R_2, in contrast to the anilinolyses in which the rates are inversely proportional to the size of the two ligands.[2c-l]

The substituent effects of X and/or Y on the pyridinolyses are surprising.[12] As seen in Table 2, the pyridinolyses of **2** only exhibited linear free energy correlations for both substituent X and Y variations. Regarding nonlinear free energy correlations for substituent X variations (i.e., excluding **2**), the β_X values with more basic pyridines are greater than those with less basic pyridines except **1**, indicating a frontside attack with more basic pyridines and a backside attack with less basic pyridines. In **1**, the free energy correlations for substituent X variations exhibited discrete two plots, and those for substituent Y variations were biphasic downwards with a break point. The authors pointed out that a subtle combination of small (Me) and large (YC_6H_4O) ligands in **1** leads to an unexpected results for the pyridinolysis[1k] and anilinolysis.[2k] The anilinolysis of **1** showed biphasic concave downward Hammett and Brönsted plots with a break region,[2k] which is the only one showing nonlinear free energy correlations among nineteen $R_1R_2P(=O$ or $S)Cl$-type substrates.[2a-l] In **8**, the free energy correlations for substituent X variations exhibited biphasic concave upwards, while biphasic concave downwards with a break point for substituent Y variations. The substrates **1**, **6**, and **8**, show nonlinear free energy correlations for both substituent X and Y variations, however, the substituent effects of X and Y on the reaction mechanisms are different with each other.

In summary, the reactions of Y-*S*-aryl phenyl phosphonochloridothioates with X-pyridines are studied kinetically in MeCN at 55.0 ºC. The Hammett and Brönsted plots for substituent X variations in the nucleophiles are biphasic with a break point at X = H, while the Hammett plots for substituent Y variations in the substrates are biphasic concave upwards with a break point at Y = H. The stepwise mechanism is proposed on the basis of the ρ_X , β_X, and ρ_{XY} values as follows: a rate-limiting bond breaking involving a frontside attack for the stronger nucleophiles and weaker electrophiles; a rate-limiting bond breaking involving a backside attack for the weaker nucleophiles and electrophiles; a rate-limiting bond formation involving a frontside attack for the stronger nucleophiles and electrophiles; a rate-limiting bond formation involving a backside attack for the weaker nucleophiles and stronger electrophiles.

Experimental Section

Materials. Y-*S*-Aryl phenyl phosphonochloridothioates were prepared as described previously.[2h] GR grade pyridines were used without further purification and all other materials were as reported previously.[1]

Kinetic Procedure. Rates were measured conductometrically at 55.0 ºC. The conductivity bridge used in this work was a self-made computer automated A/D converter conductivity bridge. Pseudo-first-order rate constants, k_{obsd} were measured by curve fitting analysis in origin program with a large excess of pyridines, [Substrates] = 1×10^{-3} M and [X-Pyridine] = (0.05-0.13) M. Second-order rate constants, k_2, were obtained from the slope of a plot of k_{obsd} *vs*. [X-Pyridine] with at least five concentrations of pyridine. The k_2 values are the averages of more than three runs.

Product Analysis. Phenyl 3-methoxy-*S*-phenyl phosphonochloridothioate (0.05 M) were reacted with 4-methoxypyridine (0.5 M) in MeCN at 55.0 °C. After more than 15 half-lives, product was isolated by washing products using ethylacetate/*n*-hexane 30% mixture (50 mL) with several attempts. Finally, the product was isolated and dried

under reduced pressure. The respective analytical data of the product gave the following results:

$[(C_6H_5)(3\text{-}MeO\text{-}C_6H_4S)P(=S)(NC_5H_4\text{-}4\text{-}OMe)]^+Cl$: Yellowish lumps, mp 115-116 °C, hygroscopic; ^{1}H-NMR (200 MHz, DMSO (d_6)), δ 4.10 (s, 6H), 7.56 (d, 2H; J = 7.4 Hz), 6.78-7.77 (m, 9H), 8.78 (d, 2H; J = 7.0 Hz); ^{13}C NMR (100 MHz, DMSO (d_6)), δ 55.09 (OCH_3, 1C), 57.12 (OCH_3, 1C), 114.12-159.10 (m, 12C, aromatic), 111.93 (s, 2C, pyr), 143.50 (s, 2C, pyr), 170.83 (s, 1C, pyr); ^{31}P NMR (162 MHz, DMSO (d_6)), δ 77.75 (1P, s); *m/z* 109 (M^+), *m/z* 140 (M^+), *m/z* 188 (M^+), *m/z* 217 (M^+), *m/z* 326 (M^+) fragments.

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References and Notes

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10. In general, more than twenty rate constants are employed to calculate the CIC in order to minimize the experimental error. Despite the employed number of rate constants is less than twenty and the correlation coefficient (r) is not good ($r \le 0.980$), the sign and magnitude of ρ_{ij} value can be acceptable when the variation tendencies of ρ_i and/or ρ_j values for substituent i and/or j variations have consistency. In the present work, however, the sign and magnitude of ρ_{XY} values with *a*, *c*, and *d* blocks cannot be acceptable in spite of the good correlation coefficients ($\rho \ge 0.994$), since the variation tendencies of ρ_X and ρ_Y values do not have consistency.
11. The difference between substrate **2** and **6** (present work) is one ligand: substrate **2** contains YC_6H_4O while **6** contains YC_6H_4S. The NBO charges at the reaction center P atom are 1.462 (**2**) and 0.999 (**6**) in the ground state, and the rate ratio is k_2(**2**)/k_2(**6**) = 11.2 × 10^{-3}/1.10 × 10^{-3} = 10.2. The two substrates would have similar ground state structure and the steric effects on the rate would be the same. Herein, the obtained rate ratio of 10.2 is ascribed to the electronegativity difference between O and S, resulting in great difference of the NBO charges at the reaction center P atom: 1.462(**2**)–0.999(**6**) = 0.463.
12. The substituent effects of X and/or Y on the pyridinolyses of $R_1R_2P(=S)Cl$-type substrates are more significant compared to those of $R_1R_2P(=O)Cl$-type substrates. The authors reported the pyridinolyses of six $R_1R_2P(=O)Cl$-type substrates (refs. 1a, d, g, h, i), however, only the pyridinolysis of dimethyl phosphinic chloride [$Me_2P(=O)Cl$] (ref 1i) exhibited concave upward free energy correlations for substituent X variations.