

Kinetics and Mechanism of the Anilinolysis of Aryl *N,N*-Dimethyl Phosphoroamidochloridates in Acetonitrile[†]

Hasi Rani Barai and Hai Whang Lee*

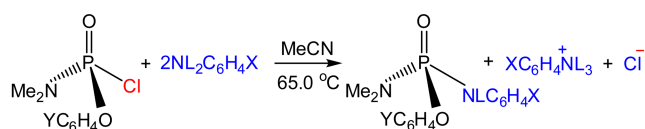
Department of Chemistry, Inha University, Incheon 402-751, Korea. *E-mail: hwlee@inha.ac.kr
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The nucleophilic substitution reactions of Y-aryl *N,N*-dimethyl phosphoroamidochloridates with substituted anilines and deuterated anilines are kinetically investigated in acetonitrile at 65.0 °C. A stepwise mechanism with a rate-limiting leaving group departure from the intermediate is proposed based on the positive ρ_{XY} value. The deuterium kinetic isotope effects involving deuterated anilines show secondary inverse with all the nucleophiles, rationalized by a dominant backside nucleophilic attack.

Key Words : Phosphoryl transfer reaction, Anilinolysis, Aryl *N,N*-dimethyl phosphoroamidochloridates, Deuterium kinetic isotope effects, Cross-interaction constant

Introduction

The nucleophilic substitution reactions of tetracoordinate phosphorus involving a leaving group of chloride have been extensively studied, experimentally^{1,2} and theoretically,³ in this lab. Two main types of displacement processes are well known in neutral phosphoryl and thiophosphoryl group transfer reactions: a stepwise mechanism involving a trigonal bipyramidal pentacoordinate (TBP-5C) intermediate and a concerted displacement at phosphorus through a single pentacoordinate transition state (TS). Continuing the kinetic studies on the phosphoryl transfer reactions, the reactions of Y-aryl *N,N*-dimethyl phosphoroamidochloridates with substituted anilines ($\text{XC}_6\text{H}_4\text{NH}_2$) and deuterated anilines ($\text{XC}_6\text{H}_4\text{ND}_2$) have been kinetically investigated in acetonitrile (MeCN) at 65.0 ± 0.1 °C (Scheme 1). The kinetic results of the present work are discussed based on the selectivity parameters and deuterium kinetic isotope effects (DKIEs). The aim of this work is to gain further information on the substituent effects, DKIEs and mechanism of the phosphoryl transfer reactions.



L = H, D

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

Scheme 1. Studied reactions of Y-aryl *N,N*-dimethyl phosphoroamidochloridates with $\text{XC}_6\text{H}_4\text{NH}_2(\text{D})_2$ in MeCN at 65.0 °C.

Results and Discussion

Tables 1-4 summarize the second-order rate constants, k_{H} with anilines, k_{D} with deuterated anilines, Hammett ($\rho_{\text{X(H)}}$)

and $\rho_{\text{X(D)}}$) and Brønsted ($\beta_{\text{X(H)}}$ and $\beta_{\text{X(D)}}$) coefficients for substituent X variation in the nucleophiles, and Hammett coefficients ($\rho_{\text{Y(H)}}$) for substituent Y variation in the substrates, respectively. The Hammett (Fig. 1: $\log k_{\text{H}}$ vs σ_{X} and Fig. S1: $\log k_{\text{D}}$ vs σ_{X}) and Brønsted [Fig. 2: $\log k_{\text{H}}$ vs $\text{p}K_{\text{a}}(\text{X})$ and Fig. S2: $\log k_{\text{D}}$ vs $\text{p}K_{\text{a}}(\text{X})$] plots with X and Hammett plots (Fig. 3: $\log k_{\text{H}}$ vs σ_{Y} and Fig. S3: $\log k_{\text{D}}$ vs σ_{Y}) with Y are shown in Figures 1-3 and Figures S1-S3 (see supporting information). All the free energy correlations with X and Y are linear without breaking point or region. The rate increases with a more electron-donating substituent X and a more electron-withdrawing substituent Y, which is compatible with a typical nucleophilic substitution reaction with positive charge development at the nucleophilic N atom ($\rho_{\text{X}} < 0$) and negative charge development at the reaction center P atom ($\rho_{\text{Y}} > 0$) in the transition state (TS). The rates with anilines are faster than those with deuterated anilines. The magnitudes of the selectivity parameters of $\rho_{\text{X(H)}}$, $\beta_{\text{X(H)}}$ and $\rho_{\text{Y(H)}}$ with anilines are somewhat larger than those ($\rho_{\text{X(D)}}$, $\beta_{\text{X(D)}}$ and $\rho_{\text{Y(D)}}$) with deuterated aniline, suggesting more sensitive to substituent effects of the anilines compared to those of deuterated anilines.

The cross-interaction constant (CIC) is one of the strong tools to clarify the mechanism based on the substituent effects of the nucleophiles, substrates, and/or leaving groups on the reaction rates.⁴ The sign and magnitude of the CIC have made it possible to correctly interpret the reaction mechanism and the degree of tightness of the TS, respectively. The sign of the CIC [ρ_{XY} , Eqs. (1)] is negative in a stepwise reaction with a rate-limiting bond formation (or in a normal $\text{S}_{\text{N}}2$ reaction), and positive in a stepwise reaction with a rate-limiting leaving group expulsion from the intermediate. The magnitude of the CIC is inversely proportional to the distance (or interaction) between X and Y through the reaction center; the tighter the TS, the greater the magnitude of the CIC.

$$\log(k_{\text{XY}}/k_{\text{HH}}) = \rho_{\text{X}}\sigma_{\text{X}} + \rho_{\text{Y}}\sigma_{\text{Y}} + \rho_{\text{XY}}\sigma_{\text{X}}\sigma_{\text{Y}} \quad (1a)$$

[†]This paper is to commemorate Professor Myung Soo Kim's honourable retirement.

Table 1. Second-Order Rate Constants ($k_H \times 10^4/M^{-1} s^{-1}$) of the Reactions of Y-Aryl *N,N*-Dimethyl Phosphoroamidochloridates with $XC_6H_4NH_2$ in MeCN at 65.0 °C

X \ Y	4-MeO	4-Me	H	3-MeO	4-Cl
4-MeO	8.21 ± 0.01	9.71 ± 0.01	11.7 ± 0.1	14.9 ± 0.1	18.8 ± 0.2
4-Me	4.03 ± 0.01	4.50 ± 0.02	4.99 ± 0.01	6.72 ± 0.01	9.39 ± 0.01
3-Me	1.75 ± 0.01	2.19 ± 0.01	2.48 ± 0.01	3.55 ± 0.01	5.40 ± 0.01
H	1.05 ± 0.01	1.32 ± 0.01	1.62 ± 0.01	2.19 ± 0.01	3.46 ± 0.01
3-MeO	0.456 ± 0.002	0.592 ± 0.001	0.769 ± 0.002	1.07 ± 0.01	1.81 ± 0.01
4-Cl	0.219 ± 0.003	0.287 ± 0.001	0.388 ± 0.001	0.553 ± 0.001	0.938 ± 0.001
3-Cl	0.0609 ± 0.0002	0.102 ± 0.002	0.149 ± 0.01	0.226 ± 0.002	0.372 ± 0.001

Table 2. Second-Order Rate Constants ($k_D \times 10^4/M^{-1} s^{-1}$) of the Reactions of Y-Aryl *N,N*-Dimethyl Phosphoroamidochloridates with $XC_6H_4ND_2$ in MeCN at 65.0 °C

X \ Y	4-MeO	4-Me	H	3-MeO	4-Cl
4-Me	4.44 ± 0.01	4.83 ± 0.01	5.24 ± 0.01	6.94 ± 0.02	9.52 ± 0.02
3-Me	2.23 ± 0.01	2.43 ± 0.02	2.68 ± 0.01	3.77 ± 0.01	5.53 ± 0.01
H	1.48 ± 0.01	1.52 ± 0.01	1.83 ± 0.01	2.41 ± 0.01	3.57 ± 0.01
4-Cl	0.355 ± 0.001	0.394 ± 0.001	0.488 ± 0.001	0.676 ± 0.001	1.06 ± 0.01
3-Cl	0.124 ± 0.001	0.184 ± 0.001	0.216 ± 0.001	0.295 ± 0.001	0.432 ± 0.001

Table 3. Hammett ($\rho_{X(H)}$ and $\rho_{X(D)}$) and Brönsted ($\beta_{X(H)}$ and $\beta_{X(D)}$) Coefficients with X for the Reactions of Y-Aryl *N,N*-Dimethyl Phosphoroamidochloridates with $XC_6H_4NH_2(D_2)$ in MeCN at 65.0 °C

Y	4-MeO	4-Me	H	3-MeO	4-Cl
$-\rho_{X(H)}$	3.27 ± 0.03 (0.999)	3.06 ± 0.02 (0.999)	2.89 ± 0.04 (0.999)	2.79 ± 0.03 (0.999)	2.61 ± 0.02 (0.999)
$-\rho_{X(D)}$	2.83 ± 0.03 (0.999)	2.61 ± 0.03 (0.999)	2.54 ± 0.02 (0.999)	2.52 ± 0.01 (0.999)	2.46 ± 0.02 (0.999)
$\beta_{X(H)}$	1.16 ± 0.03 (0.999)	1.08 ± 0.04 (0.996)	1.02 ± 0.05 (0.998)	0.99 ± 0.05 (0.997)	0.92 ± 0.03 (0.998)
$\beta_{X(D)}$	1.00 ± 0.04 (0.999)	0.92 ± 0.05 (0.997)	0.90 ± 0.04 (0.999)	0.89 ± 0.04 (0.998)	0.87 ± 0.04 (0.998)

Table 4. Hammett Coefficients ($\rho_{Y(H)}$ and $\rho_{Y(D)}$) with Y for the Reactions of Y-Aryl *N,N*-Dimethyl Phosphoroamidochloridates with $XC_6H_4NH_2(D_2)$ in MeCN at 65.0 °C

X	4-MeO	4-Me	3-Me	H	3-MeO	4-Cl	3-Cl
$\rho_{Y(H)}$	0.70 ± 0.02 (0.992)	0.70 ± 0.05 (0.954)	0.91 ± 0.06 (0.965)	0.96 ± 0.05 (0.975)	1.11 ± 0.06 (0.978)	1.19 ± 0.05 (0.983)	1.47 ± 0.04 (0.992)
$\rho_{Y(D)}$	-	0.63 ± 0.05 (0.943)	0.74 ± 0.06 (0.939)	0.74 ± 0.06 (0.947)	-	0.91 ± 0.06 (0.962)	0.98 ± 0.05 (0.980)

$$\rho_{XY} = \partial^2 \log(k_{XY}/k_{HH}) / \partial \sigma_X \partial \sigma_Y = \partial \rho_X / \partial \sigma_Y = \partial \rho_Y / \partial \sigma_X \quad (1b)$$

Figure 4 shows the plots of $\rho_{X(H \text{ or } D)}$ vs σ_Y and $\rho_{Y(H \text{ or } D)}$ vs σ_X to determine the $\rho_{XY(H \text{ or } D)}$ values according to Eq. (1b). The $\rho_{XY(H)}$ and $\rho_{XY(D)}$ values are calculated with thirty five and twenty five second-order rate constants, respectively, giving acceptable correlation coefficients.⁵ The sign of both $\rho_{XY(H)}$ and $\rho_{XY(D)}$ is positive, and the magnitude of $\rho_{XY(H)}$ (= 1.22) with anilines is nearly two times greater than that ($\rho_{XY(D)}$ = 0.64) with deuterated anilines. Thus, the authors propose a stepwise mechanism with a rate-limiting leaving

group departure from the intermediate based on the positive sign of $\rho_{XY(H)}$ and $\rho_{XY(D)}$. The greater magnitude of $\rho_{XY(H)}$ with anilines compared to that of $\rho_{XY(D)}$ with deuterated anilines indicates that the interaction between X and Y with anilines is greater than that with deuterated anilines in the TS. This suggests that the TS with anilines is more tight compared to that with deuterated anilines. The suggestion is in line with the greater magnitudes of $\rho_{X(H)}$, $\beta_{X(H)}$ and $\rho_{Y(H)}$ with anilines than those ($\rho_{X(D)}$, $\beta_{X(D)}$ and $\rho_{Y(D)}$) with deuterated aniline.

In addition to the CICs, the DKIEs (k_H/k_D) are also one of

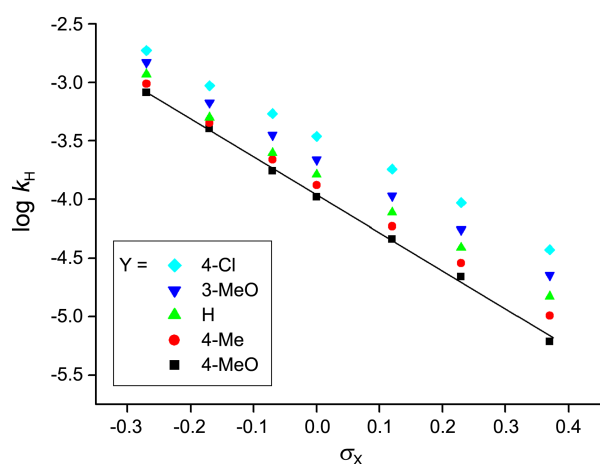


Figure 1. Hammett plots ($\log k_H$ vs σ_X) with X of the reactions of Y-aryl *N,N*-dimethyl phosphoroamidochloridates with $\text{XC}_6\text{H}_4\text{NH}_2$ in MeCN at 65.0 °C.

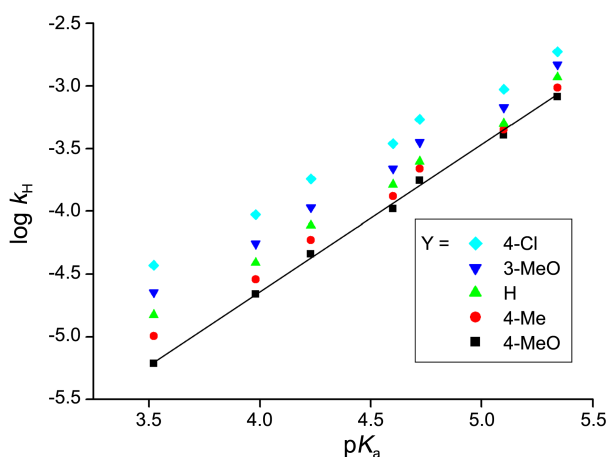


Figure 2. Brønsted plots [$\log k_H$ vs $\text{p}K_a(\text{X})$] with X of the reactions of Y-aryl *N,N*-dimethyl phosphoroamidochloridates with $\text{XC}_6\text{H}_4\text{NH}_2$ in MeCN at 65.0 °C.

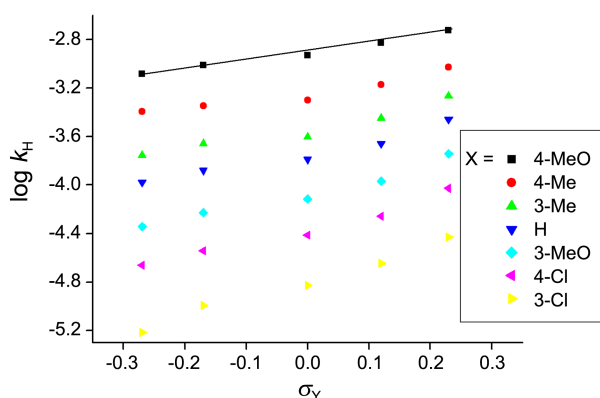


Figure 3. Hammett plots ($\log k_H$ vs σ_Y) with Y of the reactions of Y-aryl *N,N*-dimethyl phosphoroamidochloridates with $\text{XC}_6\text{H}_4\text{NH}_2$ in MeCN at 65.0 °C.

the strong tools to clarify the reaction mechanism. When partial deprotonation of the aniline occurs in a rate-limiting step by hydrogen bonding (e.g. TSf in Scheme 2), the k_H/k_D

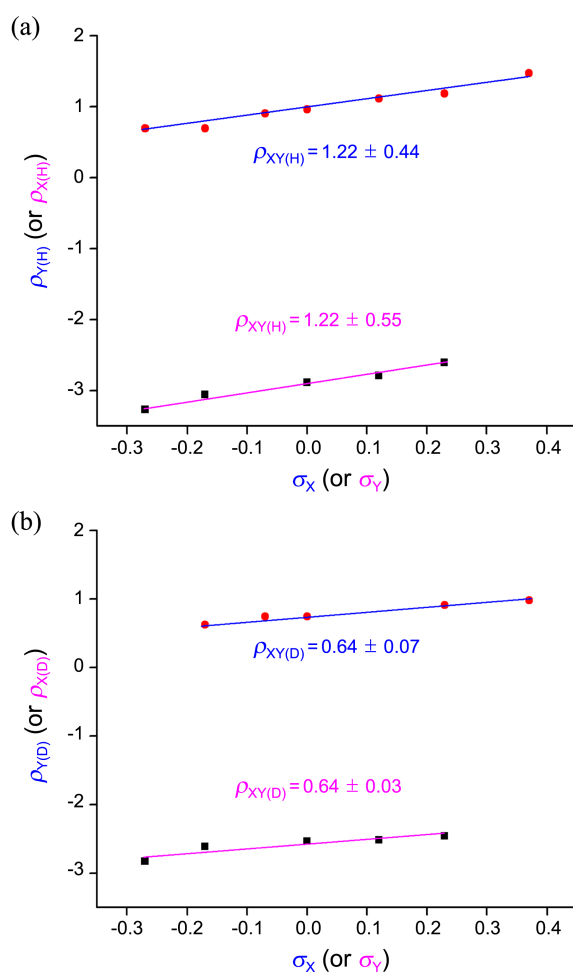
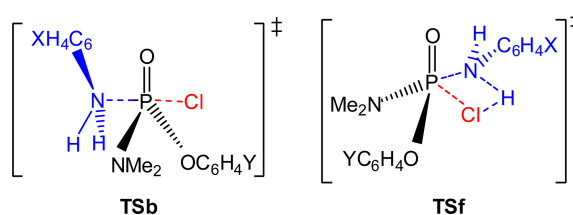


Figure 4. Plots of $\rho_{\text{Y}(\text{H or D})}$ vs σ_X and $\rho_{\text{X}(\text{H or D})}$ vs σ_Y of the reactions of Y-aryl *N,N*-dimethyl phosphoroamidochloridates with $\text{XC}_6\text{H}_4\text{-NH}_2(\text{D}_2)$ in MeCN at 65.0 °C. The obtained values by multiple regression are (a) $\rho_{\text{XY}(\text{H})} = 1.22 \pm 0.05$ ($r = 0.995$) with anilines and (b) $\rho_{\text{XY}(\text{D})} = 0.64 \pm 0.05$ ($r = 0.993$) with deuterated anilines.

values are greater than unity, primary normal ($k_H/k_D > 1.0$).⁶ In contrast, the DKIEs can only be secondary inverse ($k_H/k_D < 1.0$) when an increase in the steric congestion occurs in the bond-making process (e.g. TSb in Scheme 2), because the N–H(D) vibrational frequencies invariably increase upon going to the TS.⁷ In this respect, DKIEs have provided a useful means to determine the TS structures in the nucleophilic substitution reactions, and how the reactants, especially through changes in substituents, alter the TS structures. Incorporation of deuterium in the nucleophile has an advant-



Scheme 2. Backside attack involving in-line-type TSb and front-side attack involving a hydrogen bonded, four-center-type TSf.

Table 5. DKIEs (k_H/k_D) of the Reactions of Y-Aryl *N,N*-Dimethyl Phosphoroamidochloridates with $\text{XC}_6\text{H}_4\text{NH}(\text{D})_2$ in MeCN at 65.0 °C

X \ Y	4-MeO	4-Me	H	3-MeO	4-Cl
4-Me	0.908 ± 0.003 ^a	0.932 ± 0.005	0.952 ± 0.003	0.968 ± 0.003	0.986 ± 0.002
3-Me	0.785 ± 0.006	0.901 ± 0.009	0.925 ± 0.005	0.942 ± 0.004	0.977 ± 0.003
H	0.710 ± 0.008	0.868 ± 0.009	0.885 ± 0.007	0.909 ± 0.006	0.969 ± 0.004
4-Cl	0.617 ± 0.009	0.728 ± 0.003	0.795 ± 0.003	0.818 ± 0.002	0.885 ± 0.008
3-Cl	0.419 ± 0.004	0.554 ± 0.011	0.690 ± 0.006	0.766 ± 0.007	0.861 ± 0.003

^aStandard error $\{= 1/k_D[(\Delta k_H)^2 + (k_H/k_D)^2 \times (\Delta k_D)^2]^{1/2}\}$ from ref. 9.

Table 6. Activation Parameters for the Reactions of Y-Aryl *N,N*-Dimethyl Phosphoroamidochloridates with Aniline ($\text{C}_6\text{H}_5\text{NH}_2$) in MeCN

Y	<i>t</i> /°C	$k_H \times 10^4/\text{M}^{-1}\text{s}^{-1}$	$\Delta H/\text{kcal mol}^{-1}$	$-\Delta S/\text{cal mol}^{-1}\text{K}^{-1}$
4-MeO	55.0	0.734 ± 0.001	7.7 ± 0.4	54 ± 1
	65.0	1.05 ± 0.01		
	75.0	1.54 ± 0.02		
4-Me	55.0	0.870 ± 0.001	8.0 ± 0.3	53 ± 1
	65.0	1.32 ± 0.01		
	75.0	1.87 ± 0.01		
H	55.0	1.10 ± 0.01	8.1 ± 0.2	52 ± 1
	65.0	1.62 ± 0.01		
	75.0	2.39 ± 0.01		
3-MeO	55.0	1.43 ± 0.01	8.3 ± 0.3	51 ± 1
	65.0	2.19 ± 0.1		
	75.0	3.14 ± 0.1		
4-Cl	55.0	2.26 ± 0.1	8.3 ± 0.3	50 ± 1
	65.0	3.46 ± 0.1		
	75.0	4.98 ± 0.2		

age in that the α -DKIEs reflect only the degree of bond formation, especially for the secondary inverse DKIEs. Thus, the greater the extent of bond formation, the greater the steric congestion, and the smaller the k_H/k_D value becomes.

In the present work, the DKIEs are secondary inverse with all the anilines as seen in Table 5. The secondary inverse DKIEs are substantiated by a backside nucleophilic attack involving in-line-type TSb (Scheme 2). The magnitudes of the k_H/k_D values invariably decrease with a more electron-withdrawing substituent X (4-Me → 3-Cl) and a more electron-donating substituent Y (4-Cl → 4-MeO). This means that the steric congestion in the TS invariably increases as the aniline becomes less basic and the substrate becomes less acidic. In other words, the lower reactivity of the nucleophile results in a greater degree of bond formation, and at the same time, the lower reactivity of the substrate results in a greater degree of bond formation. Accordingly, the minimum value of $k_H/k_D = 0.42$ with X = 3-Cl and Y = 4-MeO indicates very severe steric congestion in the TS,⁸ suggesting great extent of bond formation.

Activation parameters, enthalpies and entropies of activation, are determined as shown in Table 6. The enthalpies of activation are relatively low and entropies of activation are relatively large negative value. The relatively low value of activation enthalpy and large negative value of activation

entropy are typical for the aminolyses of P=O systems.¹⁰

Experimental Section

Materials. HPLC grade acetonitrile (water content 0.005%) were used without further purification. Anilines were redistilled or recrystallized before use. Deuterated anilines were synthesized as reported earlier.¹ Y-Aryl *N,N*-dimethyl phosphoroamidochloridates were prepared by reacting *N,N*-Dimethyl phosphorodichloridate (1 mol) with substituted phenol (1 mol) for 3 h in the presence of triethylamine in methylene chloride on cooling bath at -10.0 °C with constant stirring. Triethylamine hydrochloride was separated by filtration. The filtrate was treated with water-NaHCO₃ and ether for work up after removal of solvent under reduced pressure. Ether extracted organic part was dried over anhydrous MgSO₄ for 2-3 h. The product mixture was isolated by filtration and finally separated through column chromatography (silica gel, ethyl acetate/*n*-hexane) and dried under reduced pressure using oil diffusion pump and were identified by TLC, ¹H-NMR, ¹³C-NMR, ³¹P-NMR and GC-MS. The analytical and spectroscopic data of the substrates gave the following results (see supporting information).

4-Methoxyphenyl *N,N*-Dimethyl phosphoroamidochloridate, [(4-CH₃O-C₆H₄O)(NMe₂)P(=O)Cl]: Colorless liquid; ¹H-NMR (400 MHz, CDCl₃ and TMS) δ 2.81-2.85 (m, 6H), 3.79 (s, 3H), 6.85-6.88 (m, 2H), 7.16-7.17 (m, 2H); ¹³C-NMR (100 MHz, CDCl₃ and TMS) δ 36.78, 55.62, 114.7, 121.4, 143.4, 157.3; ³¹P-NMR (162 MHz, CDCl₃ and TMS) δ 19.32 (1P, PO); GC-MS (EI, *m/z*) 249 (M⁺).

4-Methylphenyl *N,N*-Dimethyl Phosphoroamidochloridate, [(4-CH₃-C₆H₄O)(NMe₂)P(=O)Cl]: Colorless liquid; ¹H-NMR (400 MHz, CDCl₃ and TMS) δ 2.33 (s, 3H), 2.81-2.90 (m, 6H), 6.12-7.17 (m, 4H); ¹³C-NMR (100 MHz, CDCl₃ and TMS) δ 20.77, 36.79, 115.1, 120.2, 130.3, 135.5, 159.7; ³¹P-NMR (162 MHz, CDCl₃ and TMS) δ 18.92 (1P, PO); GC-MS (EI, *m/z*) 233 (M⁺).

Phenyl *N,N*-Dimethyl Phosphoroamidochloridate, [(C₆H₅O)(NMe₂)P(=O)Cl]: Colorless liquid; ¹H-NMR (400 MHz, CDCl₃ and TMS) δ 2.83-2.89 (m, 6H), 7.23-7.28 (m, 3H), 7.35-7.39 (m, 2H); ¹³C-NMR (100 MHz, CDCl₃ and TMS) δ 36.77, 120.4, 125.8, 129.9, 149.9; ³¹P-NMR (162 MHz, CDCl₃ and TMS) δ 18.64 (1P, PO); GC-MS (EI, *m/z*) 219 (M⁺).

3-Methoxyphenyl *N,N*-Dimethyl Phosphoroamidochloridate, [(3-CH₃O-C₆H₄O)(NMe₂)P(=O)Cl]: Colorless liquid; ¹H-NMR (400 MHz, CDCl₃ and TMS) δ 2.82-2.86 (m, 6H),

3.80 (s, 3H), 6.79-6.81 (m, 2H), 6.84-6.86 (m, 1H), 7.23-7.26 (m, 1H); ^{13}C -NMR (100 MHz, CDCl_3 and TMS) δ 36.77, 55.50, 106.5, 111.7, 112.5, 130.2, 150.8, 160.7; ^{31}P -NMR (162 MHz, CDCl_3 and TMS) δ 18.48 (1P, PO); GC-MS (EI, m/z) 249 (M^+).

4-Chlorophenyl *N,N*-Dimethyl Phosphoroamidochloridate, [(4-Cl-C₆H₄O)(NMe₂)P(=O)Cl]: Colorless liquid; ^1H -NMR (400 MHz, CDCl_3 and TMS) δ 2.81-2.89 (m, 6H), 7.21-7.25 (m, 2H), 7.32-7.34 (m, 2H); ^{13}C -NMR (100 MHz, CDCl_3 and TMS) δ 36.76, 121.8, 129.9, 131.3, 148.4; ^{31}P -NMR (162 MHz, CDCl_3 and TMS) δ 18.70 (1P, PO); GC-MS (EI, m/z) 354 (M^+).

Kinetics Measurement. Rates and selectivity parameters were obtained as previously described.¹ Initial concentrations: [Substrate] = 5×10^{-3} M and [X-Aniline] = (0.10-0.30) M.

Product Analysis. Phenyl *N,N*-dimethyl phosphoroamidochloridate was reacted with excess aniline for more than 15 half-lives at 65.0 °C in MeCN. Solvent was evaporated under reduced pressure. The product mixture was treated with ether by a work-up process with dilute HCl and dried over anhydrous MgSO_4 . Then the product was isolated through column chromatography (30% ethyl acetate/*n*-hexane) and then dried under reduced pressure. The analytical and spectroscopic data of the product gave the following results (see supporting information).

[(C₆H₅O)(NMe₂)P(=O)NHC₆H₅]. White solid crystal; mp 117-118.0 °C; ^1H -NMR (400 MHz, CDCl_3 and TMS) δ 2.76-2.79 (m, 6H), 5.26 (s, br., 1H), 6.98-7.33 (m, 10H); ^{13}C -NMR (100 MHz, CDCl_3 and TMS) δ 36.54, 117.5, 120.3, 121.8, 124.7, 129.3, 129.7, 139.5, 150.5; ^{31}P -NMR (162 MHz, CDCl_3 and TMS) δ 11.56 (1P, P=O); GC-MS (EI, m/z) 276 (M^+).

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References and Notes

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