esterification of DNA molecules is related to the mechanistic role of **1** for hydrolyzing dimethyl phosphate (Scheme II).

In conclusion, **1** efficiently hydrolyzes dimethyl phosphate at neutral pH. The equilibrium constant for complexation of dimethyl phosphate to **1** is 2.8 M^{-1}. The cobalt-bound phosphate diester is hydrolyzed with a half-life of 40 days at neutral pH and 60 °C. By comparison, the half-life for the water rate for dimethyl phosphate hydrolysis at 100 °C is estimated to be 600 000 years. **1**-Promoted hydrolysis of dimethyl phosphate represents the first hydrolysis of an unactivated phosphate diester at neutral pH.

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Acid-Catalyzed Amino-Migration of *O*-Phenylhydroxylamines

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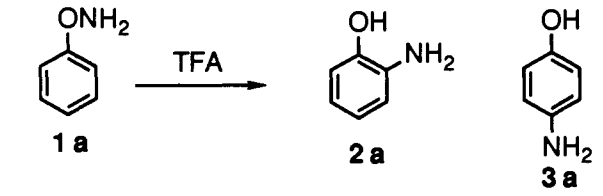
Abstract: The mechanism of amino-migration of *O*-phenylhydroxylamine (**1a**) was studied. It was found that **1** rearranges to give 2-aminophenol (50%) and 4-aminophenol (7%) in trifluoroacetic acid (TFA). The predominance of the ortho rearrangement of **1** clearly distinguishes this process from the Bamberger rearrangement. From cross-coupling experiments employing stable isotopes, it was clarified that the ortho rearrangement proceeds intramolecularly and the para rearrangement involves both intra- and intermolecular processes. Good first-order kinetics were obtained for the rearrangement. The Hammett plot (σ^+) with a large negative slope ($\rho = -7.8$) indicates that initial heterolytic N–O bond cleavage of **1** occurs and generates a positive charge on the oxygen atom with considerable delocalization into the aromatic ring. An ion–molecule pair involving a phenoxenium ion and an ammonia molecule as an intermediate rationalizes all of the results. In this pair, intramolecular combination to the ortho position proceeds preferentially over that to the para position. Formation of catechol and hydroquinone can be explained in terms of nucleophilic attack of TFA on the phenoxenium ion in a solvent-separated pair.

Introduction

Rearrangement of *N*-phenylhydroxylamine[1] to 4-aminophenol in aqueous sulfuric acid is well-known as the Bamberger rearrangement, which was discovered at the end of the nineteenth century. It has been believed that in this rearrangement the hydroxyl group is introduced into the aromatic ring via nucleophilic attack of a hydrosulfate ion upon the anilenium ion that is generated by the heterolytic N–O bond cleavage of O-protonated *N*-phenylhydroxylamine. Bamberger carried out the rearrangement of *N*-phenylhydroxylamine in nucleophilic solvents such as alcohols, hydrogen halides, phenols, and anilines and observed that they are incorporated into the aromatic ring.[2] Ingold et al.[3] examined the rearrangement of *N*-phenylhydroxylamine in ^{18}O-rich acidic water and found that the products are ^{18}O-enriched. Gassman et al. carried out the methanolysis of a series of *N*-*tert*-butyl-*N*-chloroanilines in the presence of silver trifluoroacetate.[4] The products obtained from these solvolyses differ greatly, depending on the nature of the substituent on the aromatic ring. The stronger the electron-donating power of the substituent, the higher the yield of anisidines and cyclohexadienones. In general, it has been proposed that the formation of all of these products involves the initial formation of a positively charged aromatic species.

In contrast to *N*-phenylhydroxylamine, *O*-phenylhydroxylamine is a relatively new compound, synthesized by Bungardner and Lilly in 1962,[5] so its properties have been less well studied. Among analogs of *O*-phenylhydroxylamines, *N*-acyl-*O*-phenylhydroxylamines have been studied by Endo et al. They reported acid-catalyzed rearrangements of *N*-benzoyl-*O*-phenylhydroxylamine to catechol derivatives,[6] *N*-alkyl-*N'*-phenoxyureas to *N*-alkyl-*N*-(2-hydroxyphenyl)ureas,[7] and *O*-aryl-*N*-acetoacetylhydroxylamines to benzofurans.[8] All of these reactions are considered

Scheme I



to involve concerted [3,3] sigmatropic rearrangements. In addition, the authors described acid-catalyzed nucleophilic substitutions of *N*-acyl-*O*-phenylhydroxylamines in the presence of aromatic nucleophiles such as benzenes.[9] A typical example is the reaction of *N*-tosyl-*O*-phenylhydroxylamine with benzene to give 2-hydroxybiphenyl and 4-hydroxybiphenyl in a mixture of trifluoromethanesulfonic acid (TFSA) and trifluoroacetic acid (TFA). Endo has proposed the intermediacy of phenoxenium ion, in which the positive charge is not on the electronegative oxygen but is delocalized on the aromatic ring, generated by the rate-

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Scheme II

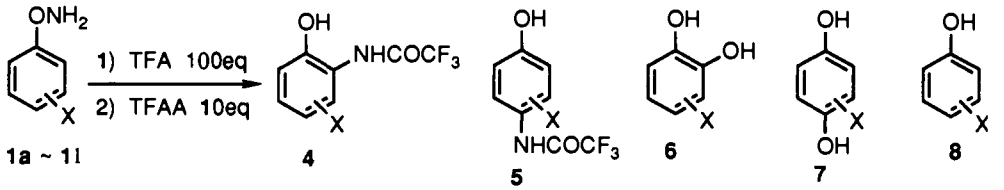

Table I. Product Distribution of TFA-Catalyzed Rearrangement of 1a–1l[a]

X	t/°C	time/h	4 (2-NH2:6-NH2)	5	6 2-OH	6 6-OH	7	8
H (1a)	60	4	50	7	7		16	0
3-Me (1b)	50	4	43 (30:70)	0	5	3	17	0
4-Me (1c)	−20	6	69	0	tr[c]			0
4-Et (1d)	−20	6	77	0	0			2
4-Pr (1e)	−15	4	79	0	0			3
3-MeO (1f)	37	4.5	53 (25:75)	tr	tr	0	10	5
4-Cl (1g)	30	5.5	53	0	21			4
4-F (1h)	10	2.5	48	0	1			3
3-Cl (1i)	60	13	16 (6:94)	2	0		0	20
3-F (1j)	70	6	18 (28:72)	2	0		0	20
2-Me (1k)	−10	4	28 (57[b]:43)	4	0		9	0
2,6-Me (1l)	−20	1	31[b]	1	0		11	10

[a] No separable and identified product was obtained except for the products described in this table. [b] Isolated as dimer 11. [c] Trace.

determining N–O bond cleavage of the protonated *N*-tosyl-*O*-phenylhydroxylamine, similar to the anilenium ion in the Bamberger rearrangement.

On the other hand, the chemistry of *O*-phenylhydroxylamine itself has scarcely been studied until now. We have recently discovered that the amino group of *O*-phenylhydroxylamine (**1a**) migrates to the 2- and 4-position of the aromatic ring to give 2-aminophenol (**2a**) (50%) and 4-aminophenol (**3a**) (7%) in the presence of TFA (Scheme I). This observation has been recorded in the reaction of *O*-phenylhydroxylamine hydrochloride into benzofurans.[10] The distinctive feature of this rearrangement is the predominancy of the ortho rearrangement. This phenomenon is quite opposite the Bamberger rearrangement, where the para rearrangement is the major, and occasionally the sole, process. Therefore, the mechanism of the rearrangement of **1** seemed to differ from the intermolecular process involving a cationic species seen in the case of the Bamberger rearrangement. In addition, it has been found that when *O*-(2-biphenylyl)hydroxylamine was allowed to react in TFA, 2-amino-2-phenyl-3,5-cyclohexadienone, an intermediate of the reaction, was trapped as *N*-trifluoroacetate.[11] With these data in mind, we embarked on a detailed study of the amino-migration of **1**, as described in this paper.

The essential question to be answered is that of how the rearrangement proceeds. If a *free* phenoxenium ion participates in the rearrangement by analogy with the rearrangement of *N*-phenylhydroxylamine, then the para rearrangement would be the major process, because the phenoxenium ion has been shown to have the maximum positive charge distribution and the highest LUMO coefficient at the 4-position.[12] To resolve this problem, we designed three experiments: (1) product analyses of the rearrangements of ring-substituted *O*-phenylhydroxylamines **1** to establish the universality of the preference of the ortho rearrangement; (2) cross-coupling experiments employing stable isotopes to clarify the intramolecularity of the rearrangement; and (3) application of the Hammett rule to elucidate the nature of the reaction center. Through these experiments, the character of amino-migration of **1** was elucidated.

Results

TFA-Catalyzed Rearrangement of *O*-Phenylhydroxylamines: Products. *O*-Phenylhydroxylamine (**1a**) at room temperature is a colorless oil that can be distilled under reduced pressure. The pK_{BH^+} of **1a** was determined to be 2.43 ± 0.08 by measurements of UV absorbance. When **1a** was treated with 1 equiv of TFA (H_0 = −2.71), the corresponding salt was produced. The salt was stable enough to be recrystallized with dichloromethane and *n*-hexane. But, it has been found that when **1a** was dissolved in a large excess (more than 60 equiv) of TFA at an elevated temperature (60 °C, 4 h), its amino group migrated to give 2-aminophenol (**2a**) and 4-aminophenol (**3a**). To facilitate isolation and to obtain accurate product yields, the amino-migrated products **2a** and **3a** were isolated as trifluoroacetamides **4a** and **5a** by the addition of 10 equiv of trifluoroacetic anhydride (TFAA) to the reaction mixture after the substrates had disappeared. Other products were catechol (**6a**) and hydroquinone (**7a**) (Scheme II). Occasionally, when a substituent was present in the aromatic ring, phenol (**8**) was obtained. Products obtained from 12 kinds of substituted **1** in the presence of TFA are listed in Table I. In all cases except for those of **1c**, **1d**, **1e**, **1k**, and **1l**, 100 equiv of TFA was used. The five substrates mentioned were so reactive in neat TFA that they were allowed to react with 10 equiv of TFA diluted with dichloromethane.

Substrates that have a substituent at position 4 (**1c**, **1d**, **1e**, **1g**, and **1h**) and substrates that have an electron-donating substituent at position 3 (**1b** and **1f**) showed effective migration of their amino group to the ortho position (more than ca. 50% isolated yield). On the other hand, for substrates that have a halogen atom at the meta position (**1i** and **1j**), the yields of amino-migrated products were lower and formation of phenol (**8**) proceeded to a significant degree. No separable and identified product was obtained except for the products described in Table I. Those that have a substituent at position 3 afford two kinds of ortho-migrated products, i.e., products of migration to positions 2 and 6. Of the two, rearrangement to position 6, apart from the substituent, prevailed over that to position 2. The structures were established unambiguously on the basis of elemental analyses and spectral properties or identification with an authentic sample.

Even the substrates without a substituent at position 4 afforded 2(or 6)-aminophenols **4** as the major product, and the yield of 4-aminophenols **5** was low or undetectable on chromatography. This result is quite opposite the Bamberger rearrangement and the silver ion-promoted methanolysis of *N*-alkyl-*N*-chloroaniline,[4] in which rearrangement to position 4 proceeds preferentially.

If the phenoxenium ion were intercepted as an intermediate, nucleophiles coexisting in the reaction system would be incorporated into the aromatic ring. To examine this hypothesis, a TFA-catalyzed rearrangement of **1a** in the presence of a nu-

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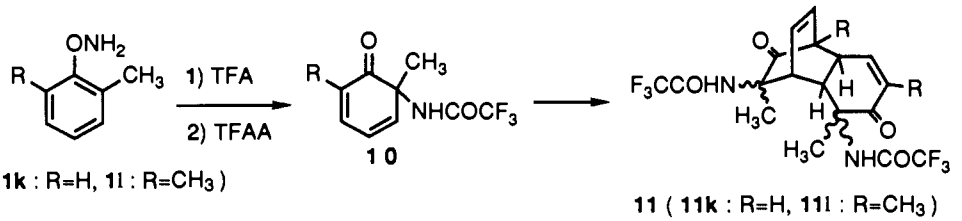
Scheme III



1 (**1k** : R=H, **1l** : R=CH_3) **10** **11** (**11k** : R=H, **11l** : R=CH_3)

Table II. TFA-Catalyzed Rearrangement of **1a** in the Presence of Nucleophiles and 100 Equiv of TFA

nucleophile	*t*/°C	time/h	yield (%) 2	3	6	7	8	9
TFA[a]	60	4	50[b]	7[b]	7	16		
TFA[a]/CF_3COONa (10 equiv)	60	6	56[b]	5[b]	9	17	<1	
TFA[a]/CF_3COONa (30 equiv)	60	6	60[b]	6[b]	7	19		
TFA[a]/CH_3COOH (50 equiv)	60	8	39	3		2		8

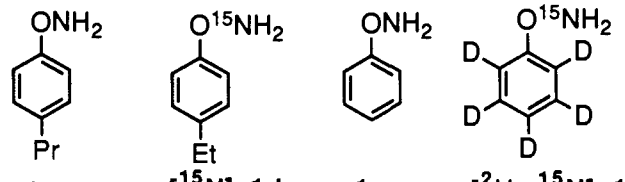
[a] 100 equiv of TFA. [b] Aminophenols were isolated as trifluoroacetamides **4a** and **5a**.

cleophile was carried out (Table II). As the nucleophile, either sodium trifluoroacetate (the counteranion of TFA) or acetic acid, which possesses stronger nucleophilicity than TFA, was chosen. Yield results show that the reaction is little influenced by the addition of trifluoroacetate ion. The four products **4a**, **5a**, **6a**, and **7a** were not affected significantly, even in the presence of 30 equiv of the salt. Similarly, in the reaction in the presence of acetic acid, the products were **2a** (39%), **3a** (3%), **7a** (2%), and 4-acetoxyphenol **9** (8%). In spite of the presence of 50 equiv of acetic acid, the acetate **9**, which reacted with acetic acid, appeared to have been largely formed by consumption of **6a** and **7a**. As a whole, the effect of added nucleophile is not evident.

Substrates **1k** and **1l** have substituents at the ortho position. The amino-migrated products (to the ipso position of the methyl group), 2,4-cyclohexadienone derivatives, were isolated as dimers. The structures of dimers were deduced from comparison with the results for *O*-(2-biphenylyl)hydroxylamine, where a stable monomer and dimer were isolated.[11] But in this case, **10** rapidly dimerizes into **11** (Scheme III). The structures of **11k** and **11l** were established on the basis of elemental analyses and spectral properties.

Catechol (**4**) and hydroquinone (**5**) are formed by the incorporation of a hydroxy group at positions 2 and 4, respectively. In contrast to the case of formation of aminophenols, more hydroquinone (**5**) was produced than catechol (**4**) (when position 4 is not occupied by a substituent), coinciding with the orientation of the Bamberger rearrangement.

Cross-Coupling Experiments. One of the most important keys to solving the mechanism of the amino-migration is its intramolecularity. To examine this, two kinds of cross-coupling experiments employing stable isotopes (^2H and ^{15}N) were designed. One is the combination of *O*-(4-propylphenyl)hydroxylamine (**1e**) and [^{15}N]-*O*-(4-ethylphenyl)hydroxylamine (**1d**), and the other is that of unlabeled **1a** and [$^2H_5$,^{15}N]-**1a**. Labeled substrates were prepared according to modification of Carpino's method.[13]



1e [^{15}N] **1d** **1a** [$^2H_5$,^{15}N] **1a**

A. Cross-Coupling Experiments of [^{15}N]-*O*-(4-Ethylphenyl)-hydroxylamine (1d) and Unlabeled *O*-(4-Propylphenyl)-hydroxylamine (1e). [^{15}N]-**1d** and unlabeled **1e** were chosen because they underwent amino-migration to position 2 in high yield and the reaction rates were almost equal to each other at 0 °C. This combination was judged to be the most suitable for examining the intramolecularity of the ortho rearrangement. Cross-coupling experiments were carried out at 0.13 and 0.0065 M for substrates (equimolar mixture of [^{15}N]-**1d** and **1e**) at 0 °C. Crude product fractions which contained **4d** and **4e**, without further purification, were analyzed by GC-MS. Mass fragmentometry (MF) was done, and ^{15}N abundance was evaluated from the area ratio of *m/e* 233/234 (**4d**) and 247/248 (**4e**), respectively. Calculations were carried out according to eq 1, which was derived by taking into account the contribution of not only the isotope of nitrogen but also isotopes of carbon, hydrogen, and oxygen.[14]

$$\xi = 0.889\,6962/(0.889\,6962\alpha + 0.788\,7286) \quad (1)^{15}$$

Here, ξ and α represent ^{14}N abundance and area ratio of *m/e* 233/234 (for **4d**) or 247/248 (for **4e**) obtained from GC-MS, respectively. The ^{15}N abundance of the substrates was evaluated by examining 2-aminophenols obtained independently of the reaction of the single substrate, because they decomposed on the GC column. The results are presented in Table III.

Table III. Nitrogen Isotope Distribution of Unlabeled **1e** and [^{15}N]-**1d**[a] and of Products of Cross-Coupling Experiments of Unlabeled **1e** and [^{15}N]-**1d**

substrate	conc/M	4e ^{14}N/%	4e ^{15}N/%	4d ^{14}N/%	4d ^{15}N/%
1e	0.13	98.7 ± 0.3	1.3 ± 0.3		
[^{15}N]-**1d**	0.13			4.0 ± 0.4	96.0 ± 0.5
1e + [^{15}N]-**1d**	0.13	97.4 ± 0.6	2.6 ± 0.6	4.8 ± 0.4	95.2 ± 0.4
1e + [^{15}N]-**1d**	6.5×10^{-3}	98.0 ± 1.1	2.1 ± 0.9	4.8 ± 0.2	95.2 ± 0.3

[a] Mean value of five measurements (±SD).

From Table III, it was found that the analysis by GC-MS includes an error of about 1%, because the ^{15}N abundance of unlabeled **1e** must be inherently equal to the natural abundance, 0.4%,[14] whereas the observed value was 1.3%. Despite such errors, an extremely important conclusion about the distribution of ^{15}N can be derived. The ^{15}N abundance of the products did not vary from that of the substrates. That is, most of the ^{15}N contained inherently in labeled **1d** was transferred to **4d**, and most of the ^{14}N contained inherently in unlabeled **1e** was transferred to **4e**. This conclusion was not affected by the concentration of the substrate, since rearrangement under conditions where the sub-

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(15) Adopting natural abundance value of isotopes of 98.9% for ^{12}C, 1.10% for ^{13}C, 99.9985% for ^1H, 0.015% for ^2H, 99.63% for ^{14}N, 0.37% for ^{15}N, 99.762% for ^{16}O, and 0.038% for ^{17}O,

$$\text{(area of } m/e \text{ 233)} = 0.989\,10 \times 0.999\,8510 \times \xi \times 0.997\,622 = 0.889\,696\,2\xi$$

$$\text{(area of } m/e \text{ 234)} = (0.9899 \times 0.0110 \times 10) \times 0.999\,8510 \times \xi \times 0.97622 + 0.98910 \times (0.999\,859 \times 0.000\,15 \times 10) \times \xi \times 0.997\,622 + 0.989\,10 \times 0.999\,8510 \times (1 - \xi) \times 0.997\,622 + 0.989\,10 \times 0.999\,8510 \times \xi \times (0.997\,62 \times 0.000\,38 \times 2) = -0.788\,728\,6\xi + 0.889\,6962$$

So that, substituting the area ratio of *m/e* 233/234 into α,

$$\alpha = (-7.887\,286\xi + 0.999\,6962)/0.889\,696\,2\xi$$

Therefore,

$$\xi = 0.889\,6962/(0.889\,696\,2\alpha + 0.788\,7286) \quad (1)$$

Table IV. Nitrogen Isotope Distribution of Unlabeled **1a** and [$^2H_5$,^{15}N]-**1a**[a] and of Products of Cross-Coupling Experiments of Unlabeled **1a** and [$^2H_5$, ^{15}N]-**1a**

substrate	conc/M	[$^1H_4$]-**4a**		[$^2H_4$]-**4a**		[$^1H_4$]-**5a**		[$^2H_4$]-**5a**	
		^{14}N/%	^{15}N/%	^{14}N/%	^{15}N/%	^{14}N/%	^{15}N/%	^{14}N/%	^{15}N/%
1a	0.13	98.1 ± 0.4	1.9 ± 0.3			97.8 ± 0.9	2.2 ± 0.4		
[$^2H_5$,^{15}N]-**1a**	0.13			2.6 ± 0.2	97.4 ± 0.2			3.1 ± 0.1	96.9 ± 0.1
1a + [$^2H_5$,^{15}N]-**1a**	0.13	97.8 ± 0.7	2.2 ± 0.6	2.4 ± 0.1	97.7 ± 0.2	74.0 ± 0.9	26.0 ± 0.4	24.3 ± 0.7	75.7 ± 0.8
1a + [$^2H_5$,^{15}N]-**1a**	0.013	98.5 ± 0.2	1.5 ± 0.2	1.6 ± 0.3	98.4 ± 0.3	92.9 ± 0.3	7.1 ± 0.2	6.9 ± 0.1	93.1 ± 0.1

[a] Mean value of five measurements of MF (±SD).

strate concentration was 0.13 and 0.0065 M gave the same result within experimental error.

B. Cross-Coupling Experiments of [$^2H_5$,^{15}N]-1a and Unlabeled 1a. For the purpose of examining the intramoleularity of the para rearrangement, substrates which exhibit similar reaction rates and which give the 4-migrated product **3** in high yield must be chosen. However, among **1a–1l** listed in Table I, no combination satisfies this requirement. We therefore chose unlabeled **1a** and doubly labeled [$^2H_5$,^{15}N]-**1a** and examined whether this combination is suitable for a cross-coupling experiment. First, these substrates must not exchange their aromatic protons with the proton of TFA. To examine this point, [$^2H_5$]-**1a** (aromatic protons were substituted by deuteriums) was subjected to the reaction, and the ^2H abundance of the amino-migrated products **4a** and **5a** was determined by whole-molecule ion mass spectroscopy. Calculations of the hydrogen isotope abundance of [$^2H_5$]-**1a** were carried out in the range of *m/e* 109 (M)–115 (M + 6). So as to avoid a complex calculation, it was assumed that the ratio of masses *m/e* 115/114 was the same as that of 114/113, because *m/e* 114 and 113 had the highest peaks and contributions from elements other than hydrogen could not be neglected.[16] Similarly, hydrogen isotope abundance values of [$^2H_4$]-**4a** and [$^2H_4$]-**5a** were calculated in the range of *m/e* 205 (M)–210 (M + 5). It was assumed that the ratio of masses *m/e* 210/209 was the same as that of 209/208, because *m/e* 209 and 208 had the highest peaks.[17] In each calculation, contributions from elements other than hydrogen to lower peaks was neglected. Though this method is approximate, it has been applied to the calculation of kinetic isotope effect in the benzidine rearrangement.[18] Values of deuterium abundance (%) of [$^2H_5$]-**1a**, [$^2H_4$]-**4a**, and [$^2H_4$]-**5a** were 96.7 ± 1.0, 97.3 ± 0.1, and 95.5 ± 0.3, respectively. Obviously, deuterium exchange did not occur to any significant degree within the timescale of the rearrangement.

Also, to examine the intramolecularity of the rearrangement, unlabeled **1a** and [$^2H_5$,^{15}N]-**1a** must react with nearly equal rates. We determined the rate of rearrangement of [$^2H_5$,^{15}N]-**1a** by means of deuterium complete decoupled ^{13}C NMR. Details of the measurement are described in the Experimental Section. Comparing the mean value of k_{obsd} measured by ^{13}C NMR, it was found that **1a** reacts faster than [$12H_5$]-**1a** by a factor of 1.1. Thus, we postulated that **1a** and [$^2H_5$]-**1a** reacted with equal rates at 60 °C, and they are therefore suitable as substrates for examining the intramolecularity of the para rearrangement.[19,20]

Cross-coupling experiments were carried out at 0.13 and 0.013 M for substrates (equimolar mixture of [$^2H_5$,^{15}N]-**1a** and unlabeled **1a**) at 60 °C. The reaction at 0.013 M was intended for examining the influence of substrate concentration on intramolecularity. The crude products obtained were chromatographed, and products **4a** and **5a** were isolated. ^{15}N abundance for **4a** and **5a** was analyzed by GC-MS. MFs were measured, and the ^{15}N abundance was evaluated from the relative ratio of *m/e* 206/205 ([$^1H_4$]-**4a** and [$^1H_4$]-**5a**) and 210/209 ([$^2H_4$]-**4a** and [$^2H_4$]-**5a**), respectively. Calculations were carried out according to eq 2 for [$^2H_4$]-**4a** and [$^2H_4$]-**5a** and eq 3 for [$^1H_4$]-**4a** and [$^1H_4$]-**5a**; these

$$\xi = (0.802\,907 - 0.077\,059\alpha)/(0.732\,011\alpha + 0.730\,613) \quad (2)[21]$$

$$\xi = 0.910\,143/(0.910\,143\alpha + 0.827\,647) \quad (3)$$

were derived by taking into account the contributions of isotopes of not only nitrogen but also other elements.[14] The ^{15}N abundance of substrates was evaluated by measuring each of those of the amino-migrated products derived from their original substrate independently. The results are presented in Table IV. In eqs 2 and 3, ξ represents the ^{14}N abundance and α represents the relative abundance of masses of 206/205 (for [$^2H_4$]-**4a** and [$^2H_4$]-**5a**) and 210/209 (for [$^1H_4$]-**4a** and [$^1H_4$]-**5a**), respectively.

From Table IV, it is apparent that analysis by GC-MS involves an error of about 1%, as is the case above. Notwithstanding such errors, very important results about the source of ^{15}N can be derived. For the ortho rearrangement, the ^{15}N abundance of the products did not vary from that of the substrates (from Table IV). That is, most of the ^{15}N contained inherently in [$^2H_5$,^{15}N]-**1a** was distributed to [$^2H_4$]-**4a**, and most of the ^{14}N contained inherently in unlabeled **1a** was distributed to unlabeled **4a**. No influence of the concentration of the substrates was observed. This result

(16) In the range of *m/e* 109 (M) ~ 115 (M + 6),

(relative abundance of ^2H) =
(115) × 5 + {(114) − (113) × (115)/(114)} × 5 + {(113) + (113) × (115)/(114)} × 4 + (112) × 3 + (111) × 2 + (110)

(relative abundance of ^1H) = {(113) + (113) × (115)/(114)} + (112) × 2 + (111) × 3 + (110) × 4 + (109) × 5

Here, (M) represents the peak intensity of *m/e* M.

(17) In the range of *m/e* 205 (M) ~ 210 (M + 6) of masses,

(relative abundance of ^2H) = (210) × 4 + {(209) − (208) × (210)/(209)} × 4 + {(208) + (208) × (210)/(209)} × 3 + (207) × 2 + (206)

(relative abundance of ^1H) =
{(208) + (208) × (210)/(209)} + (207) × 2 + (206) × 3 + (205) × 4

(18) Shine, H. J.; Park, K. H.; Brownawell, M. L.; Filippo, J. S., Jr. *J. Am. Chem. Soc.* **1984**, *106*, 7077–7082.

(19) [$^2H_5$,^{15}N]-**1a** was employed in the actual cross-coupling experiment. Kinetic isotope effect between ^{14}N and ^{15}N was neglected.

(20) Strictly speaking, a substituent effect of deuterium exists. From conductivity measurements, the substituent constant of deuterium was estimated to be −0.0024 for both meta and para positions.[35] On the basis of this value, employing the reaction constant ρ, −7.9, [$^2H_5$]-**1a** would react faster by a factor of 1.12 than unlabeled **1a**, which is opposite the experimental result. But in this case, two ortho positions are also substituted by deuterium, so the substituent effect would be very complex. In any event, the substituent effect of deuterium is slight, so we considered it to be negligible.

(21) Equations 2 and 3 were derived by the following steps:

(area of *m/e* 209) =
0.9898 × 0.999 852 × 0.9694 × ξ × 0.997 622 + 0.9898 × 0.999 852 × 0.9693 × 0.031 × (1 − ξ) × 3 × 0.997 622 = 0.732 011ξ + 0.077 059

(area of *m/e* 210) =
(0.9897 × 0.0110 × 8) × 0.999 852 × 0.9694 × ξ × 0.997 62 + 0.9898 × (0.999 85 × 0.000 15 × 2) × 0.9694 × ξ × 0.997 622 + 0.9898 × 0.999 852 × 0.9694 × (1 − ξ) × 0.999 7622 + 0.9898 × 0.999 852 × 0.9694 × ξ × (0.997 62 × 0.000 38 × 2) = −0.730 613ξ + 0.802 907

So that, substituting the area ratio of *m/e* 233/234 into α,

$$\alpha = (-0.730\,613\xi + 0.802\,907)/(0.732\,011\xi + 0.077\,059)$$

Therefore,

$$\xi = (0.802\,907 - 0.077\,059\alpha)/(0.732\,011\alpha + 0.730\,613) \quad (2)$$

Similarly, substituting the area ratio of *m/e* 206/205 into α,

$$\alpha = (-0.827\,647\xi + 0.910\,143)/0.910\,143\xi$$

Therefore,

$$\xi = 0.910\,176\,43/(0.910\,176\,43\alpha + 0.827\,647) \quad (3)$$

Table V. Observed First-Order Rate Constants for *O*-Phenylhydroxylamines **1a–1l**[a]

substrate	δ for integral	k_{obsd}/s^{-1}		
1a (H)		51.0 °C	60.7 °C	70.3 °C
	7.56 (t, 2 H)	$(1.06 \pm 0.02) \times 10^{-4}$	$(4.82 \pm 0.11) \times 10^{-4}$	$(1.87 \pm 0.02) \times 10^{-3}$
	7.32 (d, 2 H)		$(4.70 \pm 0.01) \times 10^{-4}$	
1b (3-Me)	2.41 (s, 3 H)	41.4 °C	51.0 °C	60.7 °C
		$(2.30 \pm 0.05) \times 10^{-4}$	$(9.44 \pm 0.03) \times 10^{-4}$	$(3.72 \pm 0.00) \times 10^{-3}$
1c (4-Me)	2.40 (s, 3 H)	−7.9 °C	1.1 °C	9.1 °C
		$(1.85 \pm 0.04) \times 10^{-4}$	$(7.92 \pm 0.32) \times 10^{-4}$	$(2.69 \pm 0.11) \times 10^{-4}$
1d (4-Et)	2.60 (q, 2 H)	−10.0 °C	−3.1 °C	4.9 °C
		$(1.70 \pm 0.05) \times 10^{-4}$	$(4.92 \pm 0.12) \times 10^{-4}$	$(1.84 \pm 0.06) \times 10^{-4}$
1e (4-Pr)	7.30 (d, 2 H)	−6.9 °C	2.1 °C	9.2 °C
		$(2.65 \pm 0.11) \times 10^{-4}$	$(1.26 \pm 0.07) \times 10^{-3}$	$(3.06 \pm 0.06) \times 10^{-3}$
1f (3-MeO)	7.45 (t, 1 H)	39.5 °C	49.1 °C	58.7 °C
		$(2.10 \pm 0.03) \times 10^{-4}$	$(9.02 \pm 0.11) \times 10^{-4}$	$(3.70 \pm 0.21) \times 10^{-4}$
1g (4-Cl)	7.30 (d, 2 H)	28.9 °C	38.5 °C	48.2 °C
		$(1.86 \pm 0.05) \times 10^{-4}$	$(8.86 \pm 0.48) \times 10^{-4}$	$(3.41 \pm 0.09) \times 10^{-3}$
1h (4-F)	7.37 (m, 3 H)	26.0 °C	32.7 °C	41.4 °C
		$(3.40 \pm 0.08) \times 10^{-4}$	$(1.02 \pm 0.03) \times 10^{-3}$	$(3.51 \pm 0.15) \times 10^{-3}$
1i (3-Cl)	7.40 (t, dd, 2 H)	64.5 °C	72.2 °C	81.0 °C
		$(3.77 \pm 0.11) \times 10^{-5}$	$(1.05 \pm 0.07) \times 10^{-4}$	$(3.38 \pm 0.08) \times 10^{-4}$
1j (3-F)	7.08 (m, 3 H)	65.5 °C	73.2 °C	81.1 °C
		$(5.82 \pm 0.04) \times 10^{-5}$	$(1.69 \pm 0.03) \times 10^{-4}$	$(4.26 \pm 0.12) \times 10^{-4}$

[a] In an NMR sample tube with 100 equiv of TFA and 2 equiv of 1,2-dichloroethane.

is consistent with the ^{15}N distribution in the cross-coupling experiment of [^{15}N]-**1d** and unlabeled **1e**.

For the para rearrangement, in contrast to the ortho rearrangement, the ^{15}N abundance of the products varied dramatically (Table IV). That is, for the reaction at 0.13 M substrate, the ^{14}N abundance of **5a** derived from unlabeled **1a** was 74.0% and the ^{15}N abundance of **5a** derived from doubly labeled [$^2H_5$,^{15}N]-**1a** was 75.7%, while the ^{14}N abundance of unlabeled substrate **1a** was 98.1% and the ^{15}N abundance of doubly labeled substrate **1a** was 97.4%. It is obvious that during the para rearrangement, considerable scrambling of the nitrogen isotope occurred and the amino groups were in part introduced externally. For the reaction at 0.013 M substrate, the ^{14}N abundance of **5a** derived from unlabeled **1a** was 92.9% and the ^{15}N abundance of **5a** derived from doubly labeled [$^2H_5$,^{15}N]-**1a** was 93.1%. The degree of scrambling is considerably smaller compared to the reaction at 0.13 M substrate.

The question now arises of what is the source of the amino group that was introduced externally? For the purpose of investigating the origin of the amino group incorporated intermolecularly, we carried out an experiment in which only doubly labeled substrate was allowed to react in the presence of ammonium trifluoroacetate as the source of amino group. If ^{14}N were introduced into the para rearranged product **5a**, the protonated substrate or ammonium ion would be the partner of the intermolecular para rearrangement. Practical experiments and calculations were carried out as described for the cross-coupling experiment of unlabeled **1a** and [$^2H_5$,^{15}N]-**1a**, except for the addition of 30 equiv of [^{14}N]ammonium trifluoroacetate. The ^{15}N abundance values of products were 97.0 ± 0.3 for [$^2H_5$]-**4a** and 96.6 ± 0.4 for [$^2H_5$]-**5a**. Obviously, not only for [$^2H_5$]-**4a** but also for [$^2H_5$]-**5a**, no scrambling of the nitrogen isotope occurred during the rearrangement and no ^{14}N was introduced to the products from ammonium trifluoroacetate. This eliminates the possibility of the involvement of any nitrogen species derived from the ammonium ion which may be split from the substrate.

Kinetic Measurements of Reaction Rates. As was already pointed out, the reactivity and product distribution of **1** are extremely dependent upon the nature of the substituent on the aromatic ring. That is, an electron-donating substituent at position 2 or 4 of **1** promotes the amino-migration efficiently. The stronger the ability of electron withdrawal, the slower the rate of formation of amino-migrated products **2** and **3**. To estimate these effects quantitatively, we measured the reaction rates of **1a–1j** in TFA by the use of NMR (400 MHz). A solution of the substrate in 100 equiv of TFA and 2 equiv of dichloromethane as an internal reference was allowed to react in the NMR instrument at a suitable temperature for measurements. The temperatures indicated by the NMR instrument were calibrated by measuring the differences of chemical shift between methyl protons and the hydroxy proton of methanol,[22] as described in the Experimental Section. Signals of substrates which do not overlap with those of products were chosen, and from the integral values with respect to the internal reference, the amounts of substrates unconverted were evaluated. For all of the reactions measured, first-order kinetics for substrates were observed. The results are given in Table V, together with signals adopted for integration. Each substrate was measured at three different temperatures at intervals of ten degrees, and activation parameters were determined. From extrapolation of the Arrhenius plot, the first-order rate constant (k_{obsd}) at 25 °C was determined. The results are given in Table VI. No appreciable difference in activation parameters among these substrates was observed. In particular, the activation entropy turned out to have a large positive value (8–19 eu).

Table VI. Extrapolated First-Order Rate Constants for **1a–1j** and Activating Parameters

substrate	k(25 °C)/s^{-1}	$\Delta H^{\ddagger}$/ kJ mol^{-1}	$\Delta G^{\ddagger}$/ kJ mol^{-1}	$\Delta S^{\ddagger}$/ eu
1a (H)	1.23×10^{-6}	135	107	22.4
1b (3-Me)	1.62×10^{-5}	124	100	19.3
1c (4-Me)	2.49×10^{-2}	96	82	10.7
1d (4-Et)	3.04×10^{-2}	95	82	10.4
1e (4-Pr)	2.82×10^{-2}	93	82	9.0
1f (3-MeO)	1.85×10^{-5}	127	100	21.6
1g (4-Cl)	1.01×10^{-4}	120	96	19.4
1h (4-F)	2.96×10^{-4}	116	93	18.3
1i (3-Cl)	6.67×10^{-8}	132	114	14.4
1j (3-F)	1.34×10^{-7}	124	112	9.6

Next, to get information relating to the amino-migration and the transition-state structure, the relationship between Hammett's substituent constants and k_{obsd} was examined by employing a 3- or 4-substituted **1a–1j**. The Hammett plot of σ^+ vs log k_{obsd} is presented in Figure 1. Though the correlation is not excellent (r = 0.93), a very large negative reaction constant (ρ is −7.9) was obtained. A better correlation was obtained for σ^+ than for σ (r = 0.65).

Discussion

Elimination of *Free* Phenoxenium Ion as an Intermediate. Since pK_{BH^+} of **1a** is 2.41, **1a** is completely protonated in TFA (H_0 = −2.71). As shown in Table I, rearrangements of substrates that have an electron-donating substituent on the aromatic ring easily proceeded at low temperatures and gave amino-migrated products

(22) Van Geet, A. L. *Anal. Chem.* **1970**, *42*, 679–680.

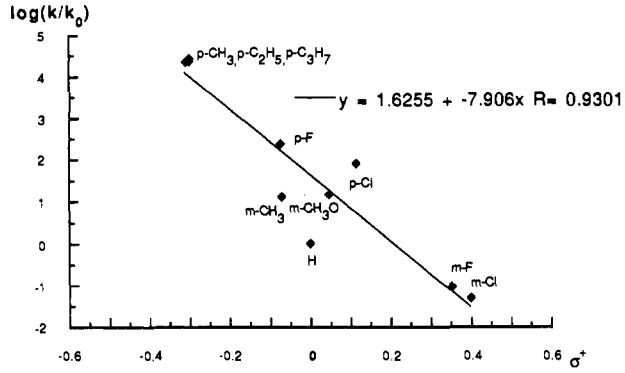
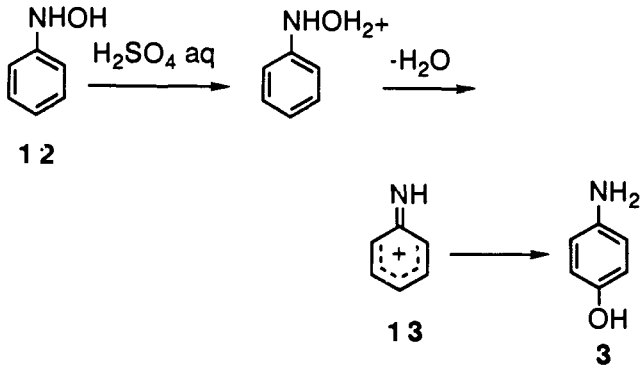


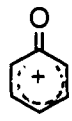
Figure 1. Hammett plot for the rearrangement of *O*-phenylhydroxylamine **1a–j** adopting σ^+.

Scheme IV



2 and **3** in high yield. On the other hand, rearrangements of substrates that have an electron-withdrawing substituent on the aromatic ring needed a higher temperature and a prolonged reaction time. Qualitatively, the reaction is characterized by the generation of a positive charge on the reaction center, and nucleophilic attack participates in the reaction. In the case of the rearrangement of **1k** and **1l**, amino-migration to the ipso position of the methyl group gave **10** (followed by dimerization to **11**), showing that the amino-migration to the ortho position in preference to the para position is retained in the cases of **1k** and **1l**, as well as the intermediacy of the dienones. It is worth noting that the formation of **2** is always greater than that of **3**. This is quite opposite the Bamberger rearrangement[1] and methanolysis of **14**.[4] In the case of the Bamberger rearrangement, *N*-phenylhydroxylamine (**12**) gave 4-aminophenol (**3a**) exclusively in aqueous sulfuric acid (Scheme IV). The intermediacy of anilenium ion **13** has been proposed, though participation of the free ion is not vigorously proved. Nucleophilic attack of water or sulfuric acid on **13** followed by rearomatization gave 4-aminophenol (**3a**). Under certain conditions, 2-aminophenol (**2a**) was formed, but the yield was low. In the solvolysis of *N*-*tert*-butyl-*N*-chloroaniline, the formation of 4-anisidine derivatives **16** occurs in preference to 2-anisidine derivatives **15** (Scheme V). However, the silver ion-promoted reaction of the same substrate yielded the 2-chloroaniline derivative **17** rather than the 4-chloroaniline derivative **18**. The formation of anisidine derivatives can be interpreted in terms of the involvement of *free* anilienium ion in the rate-determining step followed by nucleophilic attack of methanol. The ring chlorination is considered to proceed via a "tight pair" **19** involving an anilenium ion and a chloride ion.

The simplest mechanism for the major reaction of *O*-phenylhydroxylamine, the acid-catalyzed amino-migration, is the involvement of the *free* phenoxenium ion **20**. The phenoxenium



20

ion **20** has been discussed in connection with oxidative coupling of phenols,[23] electrochemical generation,[24] and pyrolysis of arylpyridinium salts.[25] The acid-catalyzed reaction of *N*-tosyl-*O*-phenylhydroxylamines with benzene also involves the phenoxenium ion. The acid-catalyzed reaction of *N*-tosyl-*O*-phenylhydroxylamine in nucleophilic solvents affords products in which the solvents are introduced at the para position of the aromatic ring.

Ab initio calculations of geometry, charge delocalization, and LUMO coefficients of **20** on the basis of the STO-3G basis set were carried out.[12] The C–O bond of **20** has the character of a double bond rather than a single bond. The ring charge increases by +1.002. On the basis of electronegativities, it would be anticipated that the oxygen nucleus is much less able to bear a positive charge than the nitrogen. Positive charge is distributed on para and ortho positions, in this order, and little on meta positions and the hetero atom. Similar results were obtained for the LUMO coefficients. These results are similar to those for the anilenium ion.

On the basis of these calculations, the reaction site of **20** to a nucleophilic reagent will be the para position rather than the ortho position. In the cases of the Bamberger rearrangement and the methanolysis of **14**, experimental results are in good accord with predictions based on calculations for anilenium ions. However, the experimental results for the present reaction were different from the prediction by calculation: preferential ortho rearrangement rather than para rearrangement. How can this strange phenomenon be explained? Evidently, the reaction does not proceed via a *free* phenoxenium ion. If *free* phenoxenium ion were formed in the rate-determining step, an increased concentration of trifluoroacetate ion would increase the nucleophilic reaction between **20** and the trifluoroacetate ion so that the yields of amino-migrated products would decrease. Addition of 30 equiv of sodium trifluoroacetate, however, did not significantly affect the product distribution of **1a**. Acetic acid is a far better nucleophile than TFA. However, even with 50 equiv of acetic acid, only 8% of **9** was formed by nucleophilic attack with consumption of hydroquinone, and the amino-migration to the ortho position remained the major path. This phenomenon is in contrast with the silver ion-promoted methanolysis of *N*-*tert*-butyl-*N*-chloroaniline to 4-anisidine (**16**) as the major path.

Intramolecularity of the Amino-Migration. The cross-coupling experiment employing [^{15}N]-**1d** and unlabeled **1e** proved that the rearrangement to the ortho position proceeds intramolecularly. Intramolecular rearrangement was demonstrated by the reaction at low concentration (0.0065 M) of the substrate, as well as at high concentration (0.13 M). The nitrogen isotope abundance of the products (**4d** and **4e**) was not significantly affected in the presence of the other substrate. The amino group rearranges to the original aromatic ring regardless of the concentration of the substrate. Furthermore, consistent results were obtained from the cross-coupling experiment of unlabeled **1a** and [$^2H_5$,^{15}N]-**1a**. That is, the distribution of the nitrogen isotope to **4a** indicates that the amino-migration to the ortho position is intramolecular.

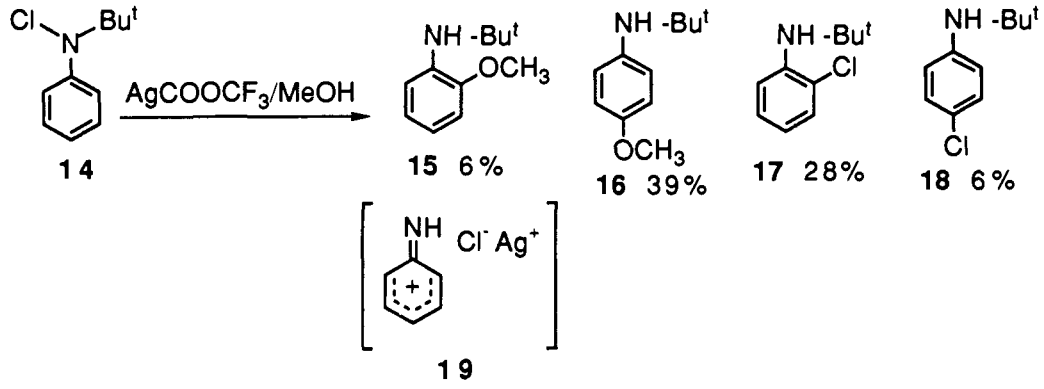
In contrast to the ortho rearrangement, the ^{15}N abundance of the products in which the amino group rearranged to the para position varied dramatically. For the reaction in the presence of 100 equiv of TFA (substrate concentration is 0.13 M), the ^{14}N abundance of unlabeled **5a** decreased by 24% compared to that of the original unlabeled **1a**. Similarly, the ^{15}N abunance of [$^2H_4$]-**5a** decreased by 21% compared to its original doubly labeled **1a**. It is obvious that during the para rearrangement, scrambling

(23) Adler, E.; Falkehag, I.; Smith, B. *Acta Chem. Scand.* **1962**, *16*, 529–540. Schwartz, M. A.; Rose, B. F.; Holton, R. A.; Scott, S. W.; Vishnuvajjala, B. *J. Am. Chem. Soc.* **1977**, *99*, 2571–2578. Davis, B. R.; Gash, D. M.; Woodgate, P. D.; Woodgate, S. D. *J. Chem. Soc., Perkin Trans. I* **1982**, 1499–1507.

(24) Wilhelm Steueber, F.; Dimroth, K. *Chem. Ber.* **1966**, *99*, 258–263. Rieker, A. *Tetrahedron Lett.* **1969**, 2611–2615.

(25) Abromovitch, R. A.; Kato, S.; Singer, G. M. *J. Am. Chem. Soc.* **1971**, *93*, 3074–3075. Abromovitch, R. A.; Alvernhe, G.; Bartnik, R.; Dassanayake, N. L.; Inbasekaran, M. N. *J. Am. Chem. Soc.* **1981**, *103*, 4558–4565. Iijima, H.; Endo, Y.; Shudo, K.; Okamoto, T. *Tetrahedron* **1984**, *40*, 4981–4985.

Scheme V



14 15 6% 16 39% 17 28% 18 6%

19

of the nitrogen isotope occurred and amino groups were in part introduced externally. Furthermore, if the rearrangement exclusively proceeded intermolecularly, the nitrogen isotope abundance of both the products (unlabeled **5a** and [$^2H_4$]-**5a**) would be nearly 50%. However, the resulting values were intermediate between those of the intramolecular process and of the intermolecular process. This result undoubtedly indicates that the para rearrangement involves both intra- and intermolecular processes and that they proceed in an almost equal ratio at this condition. This scrambling was greatly reduced when the cross-coupling experiment was performed at a lower concentrations (0.013 M) of the substrate (Table IV).

The ^{15}N abundance of the products **4a** and **5a** from [$^2H_5$,^{15}N]-**1a** in the presence of 30 equiv of ammonium trifluoroacetate did not differ from that of the starting doubly labeled substrate [$^2H_5$,^{15}N]-**1a**. This indicates that the amino group introduced intermolecularly does not originate from the ammonium ion in any form. This is reasonable, considering that the protonated ammonium ion does not possess nucleophilicity. For the same reason, the protonated substrate (though it exists in high concentration) is unsuitable as a partner of amino group exchange. In addition, this eliminates the possibility of the formation of any nucleophile (such as free ammonia molecule) from the ammonium ion formed concomitantly with the production of catechol and hydroquinone.

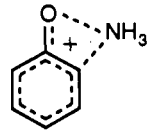
Application of the Hammett Rule. From measurements of the reaction rates of **1a–1j** in TFA, a significant substituent dependence became apparent. The overall increase in rate in going from the 3-chloro derivative **1j** to the 4-propyl derivative **1e** was 5.9×10^5. This very large change in rate in going from a strong electron-withdrawing substituent to an electron-donating substituent provides convincing evidence for the ionic nature of the rearrangement. Furthermore, the very large rate decrease in going from an electron-donating substituent to an electron-withdrawing group is consistent with a mechanism comprising heterolytic cleavage of the N–O bond of the protonated substrate via a transition state which involves loss of ammonia molecule and the generation of positive charge on oxygen. The better agreement for σ^+ ($\rho = -7.9$, $r = 0.93$) than for σ ($\rho = -7.2$, $r = 0.65$) indicates that the reaction center of the rearrangement can resonate with the substituent on the aromatic ring. Gassman has presented the ρ value of −9.2 for the ionization of *N*-phenylhydroxamic acids.[26] The anology of the ρ values reinforces the formation of positively charged species in the rearrangement.

The correlation ($r = 0.93$) obtained from the parameter (σ^+) treatment does not seem to be excellent. The deviation from linearity of the Hammett plot was not attributable to inaccuracy of temeprature or other experimental factors. Two possibilities can be considered when a series of reactions deviates from a linear relationship of the Hammett plot. One possibility is that the reaction mechanism varies in the series of substrates.[27] Though the rates are consistent with the first-order equation, we cannot exclude the partial involvement of other processes. The other possibility is a concerted reaction. That is, treatments using the substituent constant for the reactant and simultaneously the substituent constant for the products (intermediates or, more correctly, transition states) are known to give an improved correlation of the Hammett plot in the Claisen rearrangement[28] and the hydrolysis of aspirins.[29] In the case of amino-migration to position 2 of **1**, the substituent at the para position in the reactant is at the meta position, based on the product. Similarly, substituents at the meta position in the reactant are at the para position, based on the amino-migrated product (to position 6). For the purpose of examining the possibility of a concerted rearrangement, reaction constants were determined according to eq 4, employing two substituent constants. Here, σ_1 represents

$$\log (k/k_0) = \rho_1\sigma_1 + \rho_2\sigma_2 + \rho_3 \quad (4)$$

the substituent constant for the reactant (σ_p when X is at the para position, σ_m when at the meta position). Similarly, σ_2 represents the substituent constant for the product (σ_m when X is at the meta position, σ_p when at the para position). As in the case of the one-parameter treatment, four kinds of combination of σ^+ and σ, ρ_1, ρ_2, and ρ_3 were determined to be in conformity with eq 4. Of the four, the combination of σ^+ as σ_1 and σ as σ_2 afforded the best correlation: $\log (k/k_0) = -8.45\sigma_1 + 2.22\sigma_2 + 1.62$ ($r = 0.95$). Though ρ_1 has a much larger absolute value (−8.45) than ρ_2 (2.22) and is negative, the most important conclusion is that this result is not significantly better than that obtained by the one-parameter treatment.

Evidence for a dissociative process in the rearrangement of **1** is provided by the positive activation entropy ($\Delta S^\ddagger$). Relatively large positive activation entropies were observed, as listed in Table VI. If the amino-migration were a concerted process, the transition state would have a four-membered gemoetry, as shown by **21**.



21

This can be classified as a [1,3] sigmatropic rearrangement, forbidden by orbital symmetric restriction from being suprafacially concerted. On the basis of this concept, the possibility of a concerted rearrangement of **1** was eliminated.

Mechanism of the Amino-Migration. As a reaction path that is consistent with all of the experimental facts stated above we considered the ion pair mechanism that has been developed by Winstein[30] (Scheme VI). In this case, the pair is not an ion–ion

(26) Gassman, P. G.; Ganrud, J. E. *J. Am. Chem. Soc.* **1984**, *106*, 1498–1499. Gassman, P. G.; Granrud, J. E. *J. Am. Chem. Soc.* **1984**, *106*, 2448–2449.

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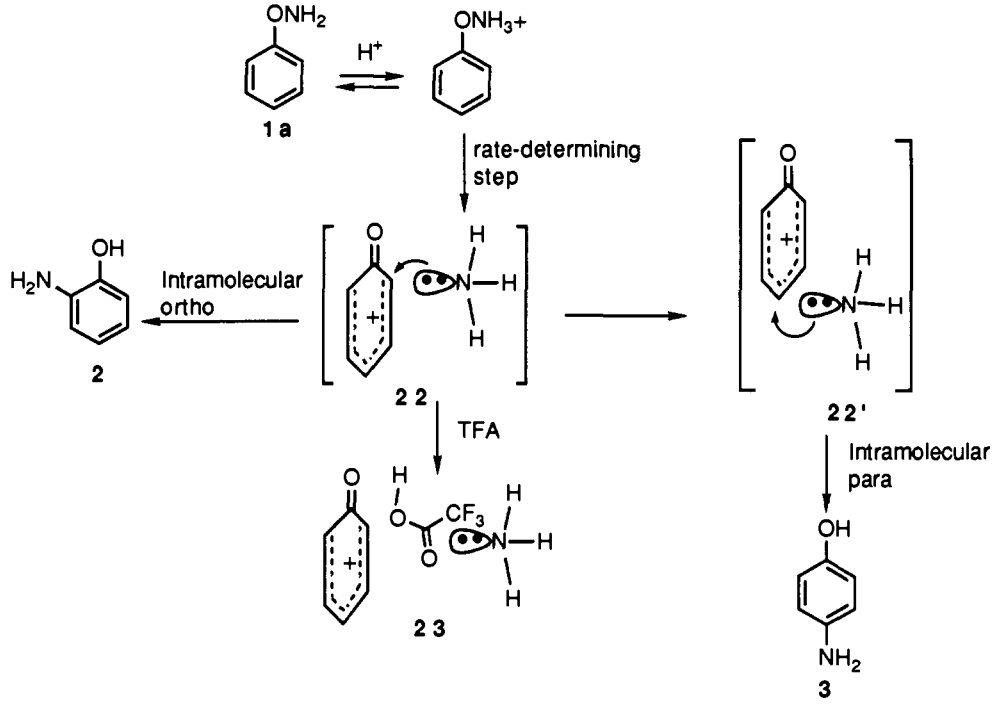
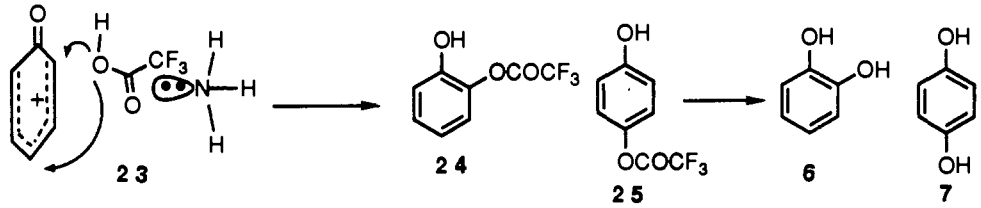
(29) Fersht, A. R.; Kirby, A. J. *J. Am. Chem. Soc.* **1967**, *89*, 4853–4857.

(30) Harris, J. M. *Progress in Physical Organic Chemistry*; Wiley Interscience: New York, 1974; Vol. 11, pp 89–173.

Scheme VI



Scheme VII



pair but an ion–molecule pair (**22**) involving a phenoxenium ion and an ammonia molecule. This pair is very tightly held in the solvent cage and does not dissociate to free ion and molecule. The initial step of the rearrangement to **22** is the rate-determining heterolytic N–O bond cleavage of protonated **1**. The driving force for this cleavage would presumably be the extreme ease of the elimination of the ammonia. As shown in Scheme I, the ammonia molecule is situated in a position favorable to combining intramolecularly with the ortho position of the aromatic ring. This is why rearrangement to the ortho position of **1** prevails. In some of the pairs, the ammonia molecule shifts around the aromatic ring so that it may combine with the para position, as shown in **22′**. This is the intramolecular para rearrangement, which is a major process at the lower concentration (0.013 M).

In regard to the intermolecular para rearrangement, the pathway depends on the concentration of the substrate (0.13 vs 0.013 M substrate, Table VI). This result suggests that the intermolecular para process proceeds via a bimolecular reaction of the intimate or solvent-separated pairs, which may be formed by attack of TFA, to the intimate pairs **22** and **22′**. However, a clear interpretation of the intermolecular para process is not derived from the kinetic results, because the process is a very small part of the overall process.

Here, another possibility for N–O bond cleavage, homolytic cleavage to generate a phenoxy radical and an ammonium cation radical, should be considered. As far as we know, no application of the Hammett rule to generation of a phenoxy radical from a protonated species with a high ρ value has been reported. One might expect that the charge on the aromatic ring would not vary significantly from reactant and transition state, so the ρ value would not be large, but no clear evidence is available on the feasibility of a radical–radical ion mechanism.

Formation of Catechols and Hydroquinones. Catechol (**6**) and hydroquinone (**7**) were formed in the rearrangements of most of **1** listed in Table I. We do not have much information on the formation of these compounds. Formation of **6** and **7** can be explained simply as nucleophilic attack of the trifluoroacetate ion (or trifluoroacetic acid) on the *free* phenoxenium ion itself but more plausibly as a combination of the participation of trifluoroacetic acid and the phenoxenium ion in the solvent-separated pair **23** (Scheme VII). TFA has a weak nucleophilicity (N = −5.55) and a strong ionizing power (Y = 5.0). Therefore, TFA would accelerate the formation of **23** and stabilize it. Nucleophilic attack by TFA or trifluoroacetate on the phenoxenium ion in **23** affords the esters **24** and **25** followed by hydrolysis to give **6** and **7** during workup. If **6** and **7** were formed via nucleophilic attack of free trifluoroacetic acid (or its anion) on the ion–molecule pair (**22** or **23**), addition of salt would result in an increased formation of **6** and **7** (Table II). If *free* phenoxenium ion were formed in the rate-determining step, increased concentration of trifluoroacetic acid (or its anion) would result in an increased yield of **6** and **7**. But formation of **6** and **7** was not affected significantly, even in the presence of 30 equiv of salt. The solvent-separated pair **23**, involving trifluoroacetic acid intervening between phenoxenium ion and ammonium molecule, is consistent with the experimental results.

Finally, the formation of phenol needs comment. This compounds seem to be produced particularly from substrates with a 3-chloro or a 3-fluoro substituent. In both cases, the rates of disappearance of the substrates are the slowest (Table V). The phenol formation may be independent of the amino-migration or catechol (hydroquinone) formation, but we have no information on the mechanism involved at present.

Summary and Conclusion

The amino group of *O*-phenylhydroxylamine (**1a**) was found to rearrange to give **2a** as the major product and **3a** as the minor product in TFA.

Cross-coupling experiments employing stable isotopes (^{15}N and ^{2}H) were carried out, and the products were analyzed by GC-MS. The ^{15}N abundance in the ortho-migrated products was amost equal to that of the starting materials. This indicates that the ortho rearrangement proceeds via an intramolecular process. Scrambling of the nitrogen isotope was observed for the para rearrangement at higher concentrations of the substrate. The para rearrangement involves both intra- and intermolecular processes, and the intra/inter ratio depends on the concentration of the substrate. The amino group introduced intermolecularly does not originate from a free ammonium ion.

Rates of the rearrangement of ten substituted compounds **1** were measured by NMR. Good first-order kinetics were obtained with a positive entropy of activation. The Hammett plot (σ^+) was found to show a large negative slope ($\rho = -7.9$). Though the correlation is not excellent ($r = 0.93$), it is deduced that initial heterolytic N–O bond cleavage of **1** occurs to generate a positive charge on oxygen followed by considerable delocalization into the aromatic ring. The correlation was not significantly improved by a two-parameter treatment. This, together with the positive activation entropy, suggests that the reaction involves a dissociative process but not a concerted process.

All of the results described above indicate intermediacy of the pair involving a phenoxenium ion and an ammonia molecule as the intermediate generated by N–O bond cleavage of protonated **1**. In this ion–molecule pair, intramolecular combination to the ortho position proceeds preferentially over that to the para position. Though the intermolecular para process depends on the concentration of substrate and could be presumed to involve the solvent-separated pairs, further study should be required for understanding the process. The formation of catechol and hydroquinone can be interpreted in terms of nucleophilic attack of TFA (or its anion) on phenoxenium ion in the solvent-separated pair.

Experimental Section

Melting points were obtained on a Yanagimoto micro hot plate and were not corrected. ^{1}H-NMR spectra were determined with a JEOL JMN-GSX500 spectrometer in the solvent stated, with tetramethylsilane as an internal reference. ^{13}C-NMR spectra were determined with a JEOL JMN-GSX500 spectrometer in the solvent stated, with trifluoroacetic acid as an internal reference. IR spectra were obtained on a Shimadzu IR-408 spectrophotometer (neat or KBr tablet). UV spectra were obtained on a Shimadzu UV-200s spectrophotometer. Whole-molecule ion mass spectra were taken on a JEOL JMS-D 300. GC-MS spectra were taken on a Hewlett-Packard instrument, Model 5890, equipped with a data system Model MSD-5970. Flash column chromatography was performed on silica gel (Merck Art. 9385 kieselgel 60) or alumina (Merck Art. 1094 Aluminiumoxid 90). Thin layer chromatography was performed on silica gel (Merck Art. 11696 TLC-kieselgel 60 HF) or alumina (Merck Art. 5713 Aluminiumoxid 60 F 254). Microanalyses were carried out in the microanalytical laboratory of this facility.

Preparation of 1. **1a** was prepared according to the report by Cadogan and Rouley.[31] **1b–1l** were prepared as described in a previous paper.[32] All of the substrates except **1l** were distilled under reduced pressure for purification and stored in sealed tubes at −20 °C. Purity was satisifactory in terms of NMR. ***O*-Phenylhydroxylamine (1a).** Colorless oil, yield 68%, bp 23 °C (0.12 mmHg). MS *m/e*: 109 (M^+). ^{1}H NMR ($CDCl_3$): δ 7.26 (dd, 2 H, *J* = 8.8, 7.3 Hz), 7.11 (dd, 2 H, *J* = 8.8, 1.5 Hz), 6.92 (tt, 1 H, *J* = 7.3, 1.5 Hz), 5.75 (br s, 2 H). ***O*-(3-Methylphenyl)hydroxylamine (1b).** Pale orange oil, yield 70%, bp 34 °C (0.08 mmHg). MS *m/e*: 123 (M^+). ^{1}H NMR ($CDCl_3$): δ 7.17 (t, 1 H, *J* = 8.3 Hz), 6.92–6.97 (m, 2 H), 6.76 (d, 1 H, *J* = 8.3 Hz), 5.6 (br s, 2 H), 2.33 (s, 3 H). ***O*-(4-Methylphenyl)hydroxylamine (1c).** Colorless oil, yield 71%, bp 32 °C (0.09 mmHg). MS *m/e*: 123 (M^+). ^{1}H NMR ($CDCl_3$): δ 7.08 (dt, 2 H, *J* = 9.2, 1.9 Hz), 7.02 (dt, 2 H, *J* = 9.2, 1.9 Hz), 5.6 (br s, 2 H), 2.28 (s, 3 H). ***O*-(4-Ethylphenyl)hydroxylamine (1d).** Colorless oil, yield 64%, bp 49 °C (0.09 mmHg). MS *m/e*: 137 (M^+). ^{1}H NMR ($CDCl_3$): δ 7.11 (dt, 2 H, *J* = 8.8, 2.8 Hz), 7.05 (dt, 2 H, *J* = 8.8, 2.8 Hz), 5.5 (br s, 2 H), 2.58 (q, 2 H, *J* = 8.0 Hz), 1.20 (t, 3 H, *J* = 8.0 Hz). ***O*-(4-Propylphenyl)hydroxylamine (1e).** Colorless oil, yield 73%, bp 61 °C (0.12 mmHg). MS *m/e*: 151 (M^+). ^{1}H NMR ($CDCl_3$): δ 7.08 (dt, 2 H, *J* = 8.8, 2.2 Hz), 7.04 (dt, 2 H, *J* = 8.8, 2.2 Hz), 5.3 (br s, 2 H), 2.52 (t, 2 H, *J* = 7.3 Hz), 1.59 (sext, 2 H, *J* = 7.3 Hz), 0.92 (t, 3 H, *J* = 7.3 Hz). ***O*-(3-Methoxyphenyl)hydroxylamine (1f).** Colorless oil, yield 52%, bp 56–58 °C (0.08 mmHg). MS *m/e*: 139 (M^+). ^{1}H NMR ($CDCl_3$): δ 7.18 (t, 1 H, *J* = 8.0 Hz), 6.75 (t, 1 H, *J* = 2.6 Hz), 6.71 (ddd, 1 H, *J* = 8.0, 2.6, 0.8 Hz), 6.50 (ddd, 1 H, *J* = 8.0, 2.6, 0.8 Hz), 5.2–6.0 (br s, 2 H), 3.79 (s, 3 H). ***O*-(4-Chlorophenyl)hydroxylamine (1g).** Colorless oil, yield 63%, bp 42 °C (0.12 mmHg). MS *m/e*: 143 (M^+), 145 ($M^+ + 2$). ^{1}H NMR ($CDCl_3$: δ 7.21 (dt, 2 H, *J* = 9.1, 2.2 Hz), 7.07 (dt, 2 H, *J* = 9.1, 2.2 Hz), 5.2–6.2 (br s, 2 H). ***O*-(4-Fluorophenyl)hydroxylamine (1h).** Colorless oil, yield 45%, bp 30 °C (0.25 mmHg). MS *m/e*: 127 (M^+). ^{1}H NMR ($CDCl_3$): δ 7.07 (ddt, 2 H, *J* = 10.6, 4.4, 2.6 Hz), 6.96 (ddt, 2 H, *J* = 10.6, 8.1, 2.6 Hz), 5.85 (br s, 2 H). ***O*-(3-Chlorophenyl)hydroxylamine (1i).** Colorless oil, yield 68%, bp 40 °C (0.1 mmHg). MS *m/e*: 143 (M^+), 145 ($M^+ + 1$). ^{1}H NMR ($CDCl_3$): δ 7.21 (t, 2 H, *J* = 2.2 Hz), 7.17 (t, 1 H, *J* = 8.1 Hz), 6.98 (ddd, 1 H, *J* = 8.1, 2.2, 1.5 Hz), 6.91 (ddd, 1 H, *J* = 8.1, 2.2, 1.5 Hz), 5.8 (br s, 2 H). ***O*-(3-Fluorophenyl)hydroxylamine (1j).** Colorless oil, yield 64%, bp 30 °C (0.16 mmHg). MS *m/e*: 127 (M^+). ^{1}H NMR ($CDCl_3$): δ 7.19 (ddd, 1 H, *J* = 8.4, 8.0, 6.4 Hz), 6.94 (ddd, 1 H, *J* = 11.2, 2.4, 2.4 Hz), 6.86 (ddd, 1 H, *J* = 8.0, 2.4, 1.6 Hz), 6.64 (dddd, 1 H, *J* = 8.4, 8.0, 2.4, 1.6 Hz), 5.4 (br s, H). ***O*-(2-Methylphenyl)hydroxylamine (1k).** Colorless oil, yield 53%, bp 34 °C (0.13 mmHg). MS *m/e*: 123 (M^+). ^{1}H NMR ($CDCl_3$): δ 7.40 (d, 1 H, *J* = 8.2 Hz), 7.17 (dd, 1 H, *J* = 8.2, 7.4 Hz), 7.08 (d, 1 H, *J* = 7.4 Hz), 6.86 (dd, 1 H, *J* = 8.2, 7.4 Hz), 5.2 (br s, 2 H), 2.18 (s, 3 H). ***O*-(2,6-Dimethylphenyl)hydroxylamine (1l).** Pale orange oil, yield 38%. MS *m/e* 137 (M^+). ^{1}H NMR ($CDCl_3$): δ 6.93–7.03 (m, 3 H), 6.1 (br s, 2 H), 2.35 (s, 6 H).

Measurement of pK_{BH^+} of 1a. pK_{BH^+} of **1a** was determined by measuring UV absorbance changes in sulfuric acid at pH = 6.68, 4.70, 3.05, 2.38, 1.41, and 0.25. Absorbances at 270 nm (min), 273 nm (max), and 278 nm (shoulder) for m_{BH^+} and m_B were evaluated, and pK_{BH^+} was determined according to eq 5. Here, m_B and m_{BH^+} represent the concentration of free base and that of protonated base, respectively. A, A_B, and A_{BH^+} represent absorbance at arbitrary pH, at pH when all of the substrate exists as base, and at pH when all of the substrate exists as conjugated acid, respectively. At pH 6.68, it was considered that all of **1a** exists as the free base, and at pH 0.25, as the conjugated acid. The mean value of six measurements at pH 3.05 and 2.38 was 2.43 ± 0.08.

$$pK_{BH^+} = pH + \log (m_{BH^+}/m_B) = pH + \log \{(A - A_B)/(A_{BH^+} - A)\} \quad (5)$$

TFA-Catalyzed Rearrangement of 1a, 1b, 1f, 1g, 1h, 1i, and 1j. As an example, the rearrangement of **1a** in the presence of 100 equiv of TFA will be described. TFA (34.9 g, 30 mmol, 100 equiv to the substrate **1a**) which had previously been cooled to 0 °C was added to 327 mg (3.0 mmol) of **1a** at 0 °C, and the mixture was stirred until the substrate was completely dissolved. Under an argon atmosphere (exclusion of light is not important), the mixture was allowed to react at 60 °C for 4 h until the substrate was no longer detectable on TLC. To the reaction mixture was added 6.30 g (30 mmol, 10 equiv) of TFAA at 0 °C, and the whole was stirred for 2 h. TFA and TFAA were removed by evaporation under reduced pressure without heating, followed by extraction with ethyl acetate (100 mL × 3) and 2 N sodium hydrogen carbonate (100 mL). The combined organic phases were dried over magnesium sulfate and filtered. After evaporation of the solvent under reduced pressure, the residue was flash chromatographed (eluent: *n*-hexane–ethyl acetate 5:1, then 3:1, finally 2:1) to give 50% of **4a**, 6% of **5a**, 6% of **6a**, and 18% of **7a**. Reactions other than that of **1a** in the presence of 100 equiv of TFA were carried out similarly. Reaction temperatures and reaction periods are given in Table I.

***N*-(2-Hydroxyphenyl)trifluoroacetamide (4a).** Recrystallized from benzene; colorless plates, mp 149.0–151.0 °C. MS *m/e*: 205 (M^+). ^{1}H NMR ($CDCl_3$): δ 8.41 (br s, 1 H), 7.97 (dd, 1 H, *J* = 8.0, 1.6 Hz), 7.14 (dt, 1 H, *J* = 8.1, 1.6 Hz), 7.02 (dt, 1 H, *J* = 8.0, 1.1 Hz), 6.93 (dd, 1 H, *J* = 8.1, 1.1 Hz), 5.89 (s, 1 H). Anal. Calcd for $C_8H_6F_3NO_2$: C, 46.84; H, 2.95; N, 6.23. Found: C, 47.08; H, 2.71; N, 6.64. ***N*-(4-Hydroxyphenyl)trifluoroacetamide (5a).** Recrystallized from benzene; colorless needles, mp 169.0–170.0 °C. MS *m/e*: 205 (M^+). ^{1}H NMR ($CDCl_3$): δ 7.78 (br s, 1 H), 7.43 (dt, 2 H, *J* = 8.8, 2.2 Hz), 6.86 (dt, 2 H, *J* = 8.8, 2.2 Hz), 4.88 (br s, 1 H). Anal. Calcd for $C_8H_6F_3NO_2$: C, 46.84; H, 2.95; N, 6.83. Found: C, 46.99; H, 3.03; N, 6.96. ***N*-(2-Hydroxy-4-methylphenyl)trifluoroacetamide (4b).** Recrystallized from benzene; colorless needles, mp 192.5–193.0 °C. MS *m/e*: 219 (M^+). ^{1}H NMR ($CDCl_3$): δ 8.33 (br s, 1 H), 7.76 (d, 1 H, *J* = 7.8 Hz), 6.80 (dd, 2 H, *J* = 7.8, 1.4 Hz), 6.75 (d, 1 H, *J* = 1.4 Hz), 6.10 (s, 1 H), 2.18 (s, 3 H). Anal. Calcd for $C_9H_8F_3NO_2$: C, 49.32; H, 3.68; N, 6.39. Found: C, 49.48; H, 3.66; N, 6.33. ***N*-(2-Hydroxy-6-methylphenyl)trifluoroacetamide (4b).** ^{1}H NMR ($CDCl_3$): δ 7.95 (br s, 1 H), 7.10 (t, 2 H, *J* = 8.0 Hz), 6.90 (dd, 1 H, *J* = 8.0, 1.1 Hz), 6.86 (dd, 1 H, *J* =

(31) Cadogan, J. I. G.; Rouley, A. G. *Synth. Commun.* **1977**, *7*, 365–366.
(32) Endo, Y.; Shudo, K.; Okamoto, T. *Synthesis* **1980**, 461–463.

8.0, 1.1 Hz), 5.0 (br s, 1 H), 2.23 (s, 3 H). **N-(2-Hydroxy-4-methoxyphenyl)trifluoroacetamide (4f).** Recrystallized from benzene; colorless plates, mp 181.5–183.0 °C. MS *m/e* 235 (M^+). ^1H NMR ($CDCl_3$): δ 8.1–8.3 (br s, 1 H), 7.63 (d, 1 H, *J* = 7.3 Hz), 6.53 (dd, 1 H, *J* = 7.3, 2.9 Hz), 6.52 (d, 1 H, *J* = 2.9 Hz), 6.34 (s, 1 H), 3.76 (s, 3 H). Anal. Calcd for $C_9H_8F_3NO_3$: C, 45.96; H, 3.42; N, 5.96. Found: C, 46.01; H, 3.27; N, 5.77. **N-(2-Hydroxy-6-methoxyphenyl)trifluoroacetamide (4f).** Recrystallized from benzene; colorless needles, mp 81.5–82.0 °C. MS *m/e*: 235 (M^+). ^1H NMR ($CDCl_3$): δ 8.57 (s, 1 H), 7.16 (t, 1 H, *J* = 8.4 Hz), 6.70 (dd, 1 H, *J* = 8.4, 1.1 Hz), 6.52 (dd, 1 H, *J* = 8.4, 1.1 Hz), 3.92 (s, 3 H). Anal. Calcd for $C_9H_8F_3NO_3$: C, 45.96; H, 3.42; N, 5.96. Found: C, 46.06; H, 3.47; N, 6.21. **N-(4-Hydroxy-2-methoxyphenyl)trifluoroacetamide (5f).** Recrystallized from *n*-hexane–AcOEt; colorless needles, mp 135.5–137.0 °C. MS *m/e*: 235 (M^+). ^1H NMR ($CDCl_3$): δ 8.38 (br s, 1 H), 8.11 (d, 1 H, *J* = 8.4 Hz), 6.49 (d, 1 H, *J* = 2.5 Hz), 6.44 (dd, 1 H, *J* = 8.4, 2.5 Hz), 5.23 (br s, 1 H), 3.89 (s, 3 H). **N-(5-Chloro-2-hydroxyphenyl)trifluoroacetamide (4g).** Recrystallized from benzene; colorless plates, mp 233.0–234.5 °C. MS *m/e*: 239 (M^+), 241 ($M^+ + 2$). ^1H NMR ($CDCl_3$): δ 8.3–8.4 (br s, 1 H), 8.10 (d, 1 H, *J* = 2.6 Hz), 7.09 (dd, 1 H, *J* = 8.8, 2.6 Hz), 6.85 (d, 1 H, *J* = 8.8 Hz). Anal. Calcd for $C_8H_5ClF_3NO_2$: C, 40.10; H, 2.10; N, 5.85. Found: C, 40.23; H, 2.05; N, 5.76. **N-(5-Fluoro-2-hydroxyphenyl)trifluoroacetamide (4h).** Recrystallized from benzene; pale brown needles, mp 182.5–194.0 °C. MS *m/e*: 223 (M^+). ^1H NMR ($CDCl_3$): δ 8.47 (br s, 1 H), 7.94 (dd, 1 H, *J* = 10.1, 3.0 Hz), 6.79–7.88 (m, 2 H), 5.70 (s, 1 H). Anal. Calcd for $C_8H_5F_4NO_2$: C, 43.06; H, 2.26; N, 6.28. Found: C, 43.26; H, 1.98; N, 6.43. **N-(4-Chloro-2-hydroxyphenyl)trifluoroacetamide (4i).** Recrystallized from benzene; pale brown prisms, mp 223.0–224.0 °C. MS *m/e*: 239 (M^+), 241 ($M^+ + 2$). ^1H NMR ($CDCl_3$): δ 8.35 (br s, 1 H), 7.92 (d, 1 H, *J* = 8.8 Hz), 6.99 (dd, 1 H, *J* = 8.8, 2.2 Hz), 6.96 (dd, 1 H, *J* = 2.2 Hz), 6.28 (s, 1 H). **N-(6-Chloro-2-hydroxyphenyl)trifluoroacetamide (4i).** MS *m/e*: 239 (M^+), 241 ($M^+ + 2$). ^1H NMR ($CDCl_3$): δ 8.45 (br s, 1 H), 7.70 (br s, 1 H), 7.22 (t, 1 H, *J* = 8.1 Hz), 7.08 (d, 1 H, *J* = 2.8 Hz), 7.04 (dd, 1 H, *J* = 8.1, 2.8 Hz). **N-(2-Chloro-4-hydroxyphenyl)trifluoroacetamide (5i).** MS *m/e*: 239 (M^+), 241 ($M^+ + 2$). ^1H NMR ($CDCl_3$): δ 8.22 (br s, 1 H), 8.09 (d, 1 H, *J* = 9.2 Hz), 6.96 (d, 1 H, *J* = 2.9 Hz), 6.80 (dd, 1 H, *J* = 9.2, 2.9 Hz), 5.23 (s, 1 H). **N-(4-Fluoro-2-hydroxyphenyl)-trifluoroacetamide (4j).** Recrystallized from benzene; dark brown needles, mp 184.0–185.0 °C. MS *m/e*: 223 (M^+). ^1H NMR ($CDCl_3$): δ 8.3 (br s, 1 H), 7.83 (dd, 1 H, *J* = 10.0, 6.4 Hz), 6.72 (ddd, 1 H, *J* = 9.6, 6.4, 1.8 Hz), 6.70 (dd, 1 H, *J* = 9.6, 1.8 Hz), 6.42 (s, 1 H). Anal. Calcd for $C_8H_5F_4NO_2$: C, 43.06; H, 2.26; N, 6.28. Found: C, 43.21; H, 2.46; N, 6.19. **N-(6-Fluoro-2-hydroxyphenyl)trifluoroacetamide (4j).** Recrystallized from benzene; colorless needles, mp 192.5–193.0 °C. MS *m/e*: 223 (M^+). ^1H NMR ($CDCl_3$): δ 8.3 (br s, 1 H), 7.8 (br s, 1 H), 7.22 (ddd, 1 H, *J* = 8.4, 7.2, 6.8 Hz), 6.87 (dt, 1 H, *J* = 8.4, 1.4 Hz), 6.77 (ddd, 1 H, *J* = 10.0, 7.2, 1.4 Hz). **N-(2-Fluoro-4-hydroxyphenyl)trifluoroacetamide (5j).** MS *m/e*: 223 (M^+). ^1H NMR ($CDCl_3$): δ 7.96 (t, 1 H, *J* = 9.2 Hz), 7.9 (br s, 1 H), 6.69 (dd, 1 H, *J* = 11.6, 2.8 Hz), 6.65 (ddd, 1 H, *J* = 9.2, 2.8, 1.6 Hz), 5.7 (br s, 1 H).

TFA-Catalyzed Rearrangement of 1c, 1d, 1e, 1k, and 1l. A general procedure in the presence of 10 equiv of TFA for the reaction will be described for **1c**. 185 mg (1.5 mmol) of **1c** was dissolved in 4 mL of dichloromethane at −20 °C with stirring. To the mixture was added a solution of 1.71 g (15 mmol, 10 equiv) of TFA in 10 mL of dichloromethane at −20 °C. Stirring was continued for 6 h under argon with shielding from light until the substrate was no longer detectable on TLC. During the course of the reaction, dry ice was added piece by piece to the bath to maintain the temperature close to −20 °C. After the reaction, 3.15 g (15 mmol, 10 equiv) of TFAA was added, and stirring was continued for a further 2 h. After routine workup as described in the case of **1a**, the crude residue was flash chromatographed (eluent: *n*-hexane–ethyl acetate 8:1, then 5:1, finally 3:1) to give 69% of **2c** and a trace of **4c**. Other reactions in the presence of 10 equiv of TFA were carried out in a similar manner.

N-(2-Hydroxy-5-methylphenyl)trifluoroacetamide (4c). Recrystallized from benzene; colorless plates, mp 193.0–194.0 °C. MS *m/e*: 219 (M^+). ^1H NMR ($CDCl_3$): δ 8.35 (br s, 1 H), 7.77 (d, 1 H, *J* = 1.8 Hz), 6.94 (dd, 1 H, *J* = 8.8, 1.4 Hz), 6.82 (d, 1 H, *J* = 8.8 Hz), 5.78 (s, 1 H), 2.32 (s, 3 H). Anal. Calcd for $C_9H_6F_3NO_2$: C, 49.32; H, 3.68; N, 6.39. Found: C, 49.53; H, 3.62; N, 6.53. **N-(2-Hydroxy-5-ethylphenyl)trifluoroacetamide (4d).** Recrystallized from benzene; colorless cottonlike fibers, mp 182.0–183.0 °C. MS *m/e*: 233 (M^+). ^1H NMR ($CDCl_3$): δ 8.4 (br s, 1 H), 7.77 (d, 1 H, *J* = 2.0 Hz), 6.97 (dd, 1 H, *J* = 8.8, 2.0 Hz), 6.85 (d, 1 H, *J* = 8.8 Hz), 5.70 (s, 1 H), 2.60 (q, 2 H, *J* = 8.0 Hz), 1.21 (t, 3 H, *J* = 8.0 Hz). Anal. Calcd for $C_{10}H_{10}F_3NO_2$: C, 51.50; H, 4.32; N, 6.01. Found: C, 51.79; H, 4.11; N, 5.97. **N-(2-Hydroxy-5-propylphenyl)trifluoroacetamide (4e).** Recrystallizied from benzene; colorless cottonlike fibers, mp 163.5–164.0 °C. MS *m/e*: 247 (M^+). ^1H NMR ($CDCl_3$): δ 8.37 (br s, 1 H), 7.75 (d, 1 H, *J* = 2.2 Hz), 6.94 (dd, 1 H, *J* = 8.0, 2.2 Hz), 6.83 (d, 1 H, *J* = 8.0 Hz), 5.81 (br s, 1 H), 2.54 (t, 2 H, *J* = 7.7 Hz), 1.60 (sext, 2 H, *J* = 7.7 Hz), 0.92 (t, 3 H, *J* = 7.7 Hz). Anal. Calcd for $C_{11}H_{12}F_3NO_2$: C, 53.44; H, 4.89; N, 5.67. Found: C, 53.47; H, 4.87; N, 5.73. **N-(2-Hydroxy-3-methylphenyl)trifluoroacetamide (4k) (6-NH_2).** Recrystallized from dichloromethane–hexane; colorless needles, mp 109.5–110.0 °C. MS *m/e*: 219 (M^+). ^1H NMR ($CDCl_3$): δ 8.42 (br s, 1 H), 7.73 (d, 1 H, *J* = 8.8 Hz), 7.04 (d, 1 H, *J* = 8.1 Hz), 6.91 (t, 1 H, *J* = 8.1 Hz), 5.71 (s, 1 H), 2.05 (s, 3 H). Anal. Calcd for $C_9H_8F_3NO_2$: C, 49.32; H, 3.68; N, 6.39. Found: C, 49.55; H, 3.53; N, 6.65. **4k (Dimer of 2-NH_2-11k).** Recrystallized from dichloromethane–hexane; colorless prisms, mp 137.0–137.5 °C. MS *m/e*: 438 (M^+). ^1H NMR ($CDCl_3$): δ 7.8 (br s, 1 H), 6.50 (dd, 1 H, *J* = 10.2, 3.7 Hz), 6.47 (s, 1 H), 6.30 (dt, 1 H, *J* = 7.0, 7.0, 1.5 Hz), 6.15 (dd, 1 H, *J* = 10.2, 1.5 Hz), 6.05 (ddd, 1 H, *J* = 7.0, 6.2, 1.6 Hz), 3.59 (dddd, 1 H, *J* = 7.6, 3.7, 2.9, 1.5 Hz), 3.51 (dd, 1 H, *J* = 7.6, 1.6 Hz), 3.49 (ddd, 1 H, *J* = 6.2, 2.9, 1.5 Hz), 3.27 (dt, 1 H, *J* = 7.0, 1.6, 1.6 Hz), 1.60 (s, 3 H), 1.42 (s, 3 H). Anal. Calcd for $C_{18}H_{16}F_6N_2O_4$: C, 49.32; H, 3.68; N, 6.39. Found: C, 49.32; H, 3.47; N, 6.51. **N-(4-Hydroxy-3-methylphenyl)trifluoroacetamide (5k).** Recrystallized from dichloromethane–hexane; colorless cotton-like fibers, mp 139.0–140.0 °C. MS *m/e* 219 (M^+). ^1H NMR ($CDCl_3$): δ 7.8 (br s, 1 H), 7.31 (d, 1 H, *J* = 2.5 Hz), 7.25 (d, 1 H, *J* = 8.4, 2.5 Hz), 6.76 (d, 1 H, *J* = 8.4 Hz), 5.0 (s, 1 H), 2.24 (s, 3 H). Anal. Calcd for $C_9H_8F_3NO_2$: C, 49.32; H, 3.68; N, 6.39. Found: C, 49.24; H, 3.52; N, 6.31. **4l (Dimer of 2-NH_2-11l).** Recrystallized from dichloromethane–hexane; pale yellow prisms, mp 180.5–181.0 °C. MS *m/e*: 466 (M^+). ^1H NMR ($CDCl_3$): δ 7.87 (s, 1 H), 6.49 (s, 1 H), 6.29 (dq, 1 H, *J* = 4.4, 1.2 Hz), 6.26 (dd, 1 H, *J* = 8.0, 6.8 Hz), 5.70 (dd, 1 H, *J* = 8.0, 1.6 Hz), 3.50 (dd, 1 H, *J* = 8.0, 1.6 Hz), 3.41 (dt, 1 H, *J* = 6.8, 1.6, 1.6 Hz), 3.02 (ddd, 1 H, *J* = 8.0, 4.4, 1.2 Hz), 1.87 (t, 3 H, *J* = 1.2, 1.2 Hz), 1.56 (s, 3 H), 1.47 (s, 3 H), 1.41 (s, 3 H). Anal. Calcd for $C_{20}H_{20}F_6N_2O_4$: C, 51.51; H, 4.32; N, 6.01. Found: C, 51.58; H, 4.10; N, 6.02. **N-(3,5-Dimethyl-4-hydroxyphenyl)trifluoroacetamide (5l).** Colorless needles. MS *m/e*: 233 (M^+). ^1H NMR ($CDCl_3$): δ 7.70 (br s, 1 H), 7.18 (s, 2 H), 4.69 (br s, 1 H), 2.25 (s, 6 H).

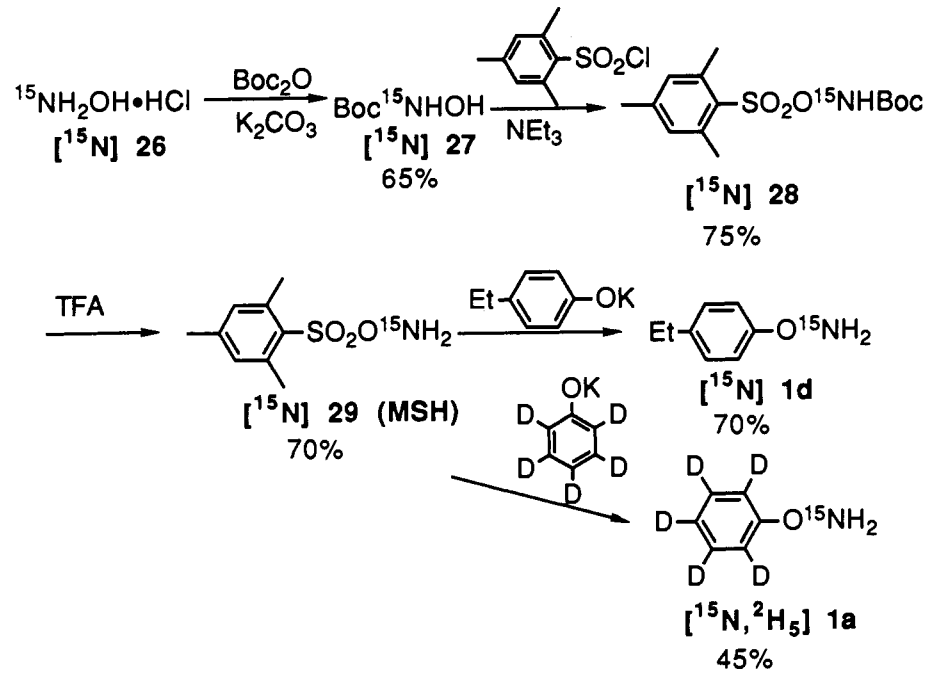
Rearrangement of 1a in a TFA–AcOH System. A mixture of 22.8 g (200 mmol, 100 equiv) of TFA and 6.00 g of acetic acid (100 mmol, 50 equiv) that had previously been cooled at 0 °C was added to 219 mg (2.0 mmol) of **1a** at 0 °C, and the whole was stirred until the substrate completely dissolved. Under an argon atmosphere with exclusion of light, the mixture was allowed to react at 60 °C for 8 h. After routine workup, the crude residue was flash chromatographed (eluent: *n*-hexane–ethyl acetate 5:1, then 3:1, finally 2:1) to give 39% of **2a**, 3% of **3a**, 2% of **7a**, and 8% of **9**.

Rearrangement of 1a in a TFA–Sodium Trifluoroacetate System. TFA (22.8 g, 200 mmol, 100 equiv) which had previously been cooled to 0 °C was added to 219 mg (2.0 mmol) of **1a** and 2.72 g (20 mmol, 10 equiv) of sodium trifluoroacetate at 0 °C, and the mixture was stirred until the substrate was completely dissolved. Under an argon atmosphere with exclusion of light, the mixture was allowed to react at 60 °C for 4 h. When 30 equiv of salt was added, the salt did not completely dissolve. The heterogeneous mixture was further stirred and heated at 60 °C for 6 h. The reaction mixture was cooled, and then 4.20 g (20 mmol, 10 equiv) of TFAA was added at 0 °C and stirring was continued for 2 h. After workup, the crude mixture was flash chromatographed (eluent: *n*-hexane–ethyl acetate 5:1, then 3:1, finally 2:1) to give **4a**, **5a**, **6a**, and **7a** in the yields cited in Table II. **Independent Synthesis of 9.** Compound **7a** (440 mg) was dissolved in a mixture of 410 mg (4.0 mmol, 1.0 equiv) of acetic anhydride and 2.0 mL of acetic acid with stirring. After the solution became homogeneous, a drop of concentrated sulfuric acid was added, and the whole was stirred at ambient temperature for 1 h. The mixture was extracted with ethyl acetate (30 mL × 3) and 2 N sodium hydrogencarbonate (60 mL). The combined organic phases were dried over magnesium sulfate and filtered. After evaporation of the solvent under reduced pressure, the residue was flash chromatographed (eluent: *n*-hexane–ethyl acetate 5:1, then 3:1) to give 65% of **27** as a colorless oil. **4-Acetoxyphenol (9).** MS *m/e*: 152 (M^+). ^1H NMR ($CDCl_3$): δ 6.89 (dt, 2 H, *J* = 9.1, 2.4 Hz), 6.73 (dt, 2 H, *J* = 9.1, 2.4 Hz), 5.7 (br s, 1 H), 2.28 (s, 3 H).

Preparation of [^{15}N]-1d. [^{15}N]Hydroxylamine hydrochloride (**26**) and [$^2H_6$]phenol were chosen as the sources of stable isotopes. For protection of the amino group of hydroxylamine, Carpino employed *tert*-butoxycarbonyl azide.[13] But we decided to employ di-*tert*-butyl dicarbonate, since the latter gave **27** in higher yield than the former. The final step is electrophilic amination of phenoxide ion by (mesitylenesulfonyl)hydroxylamine (**29**) (MSH).[33] The total yields based on [^{15}N]-**12** were

(33) Tamura, Y.; Minamikawa, J.; Sumoto, K.; Fujii, S.; Ikeda, M. *J. Org. Chem.* **1973**, *38*, 1239–1241.

Scheme VIII



26% for [^{15}N]-**1d** and 14% for [$^2H_5$,^{15}N]-**1a** (Scheme VIII).

Sodium bicarbonate (550 mg, 4.0 mmol, 1.1 equiv) was dissolved in a solution of 500 mg (7.2 mmol) of [^{15}N]-**26** in 2.0 mL of water with stirring in an ice bath. To this solution was added 2.0 mL of THF, and then 1.75 g (4.0 mmol, 1.1 equiv) of di-*tert*-butyl dicarbonate in 15 mL of THF was added dropwise over 1 h. The time taken for this dropping affects the yield of [^{15}N]-**27** significantly. Further stirring was continued at ambient temperature for 1 h after dropping had been completed. The solution was concentrated to about 3 mL under reduced pressure without heating, followed by extraction with 5 mL of brine and 25 mL × 3 of dichloromethane. The combined orbanic phases were dried over magnesium sulfate and filtered. After evaporation of the solvent under reduced pressure, the residue was flash chromatographed (eluent: *n*-hexane–ethyl acetate 5:1, then 3:1, finally 9:4) to give 65% (610 mg, 4.55 mmol) of [^{15}N]-**27** as colorless needles. [^{15}N]-**27** was used for the next reaction without further purification. [^{15}N]-**27** (610 mg, 4.55 mmol) was dissolved in 3 mL of DMF at 0 °C with stirring and 460 mg (4.55 mmol, 1.0 equiv) of triethylamine was added. Then 995 mg (4.55 mmol, 1.0 equiv) of freshly purified mesitylenesulfonyl chloride was added in small portions for 20 min. The time taken for this addition affects the yield of [^{15}N]-**28** significantly. During addition, the reaction flask was fitted with a calcium chloride tube to exclude water. Stirring was continued for a further 1 h after addition had been completed. The yellow viscid material was taken up in 30 mL of ice water, followed by extraction with dichloromethane (30 mL × 2). The combined organic phases were washed with water (80 mL × 3) and dried over magnesium sulfate. After filtration, the solvent was removed under reduced pressure without heating. The residue was flash chromatographed (eluent: benzene, and then benzene–ethyl acetate 35:1) to give 75% (1086 mg, 3.43 mmol) of [^{15}N]-**28** as colorless plates. [^{15}N]-**28** was used for the next reaction without further purification. 1080 mg (3.42 mmol) of [^{15}N]-**28** was dissolved in 6.0 g of TFA at 0 °C and stirred for 10 min. The solution was poured into 100 mL of ice water, and the precipitates generated were collected by filtration, washed with cold water, and dissolved in 30 mL of cold ether. The solution was transferred to a separatory funnel, and the water phase was discarded. The organic phases were concentrated to about 3 mL under reduced pressure without heating. *n*-Hexane was added. The precipitate generated was filtered and dried in vacuo to give 680 mg of [^{15}N]-**29** as colorless needles. Potassium *tert*-butoxide (350 mg, 3.16 mmol, 1.0 equiv) was dissolved in a solution of 4-ethylphenol (390 mg, 3.16 mmol), 1.0 equiv) in 6 mL of methanol. Methanol was evaporated and the residue was dried in vacuo to give a solid. To a solution of this solid in 3 mL of DMF was added a solution of [^{15}N]-**29** in 3 mL of DMF previously prepared at −20 °C as a bolus, and the mixture was stirred at −20 °C for 1 h. The solvent was removed under reduced pressure while the temperature of the bath was maintained below 50 °C. The residue was extracted with 80 mL of water and 100 mL of dichloromethane. The organic phases were washed with 2 N NaOH and then brine (100 mL × 2), dried over magnesium sulfate, and filtered. After evaporation of the solvent under reduced pressure, the residue was flash chromatographed (eluent: *n*-hexane–dichloromethane 5:2) to give 54% (based on [^{15}N]-**29**, 263 mg, 4.55 mmol) of [^{15}N]-**1d** as an orange oil. [^{15}N]-**1d**, which is chromatographically pure, was used for the cross-coupling experiment without further purification.

Preparation of [$^2H_5$]-1a. Unlabeled **28** (3.16 g, 10.0 mmol) and 800 mg of [$^2H_6$]-phenol (8.0 mmol, 1.0 equiv) gave 369 mg (34% based on unlabeled **28**, 42% based on [$^2H_6$]-phenol) of [$^2H_5$]-**1a** as an orange oil in the same manner as described for the preparation of [^{15}N]-**1d**.

Preparation of [$^2H_5$,^{15}N]-1a. [^{15}N]-**29** (570 mg, 2.65 mmol, 73%) was prepared in the same manner as described for the preparation of [^{15}N]-**1d**. This and 270 mg of [$^2H_6$]-phenol (2.65 mmol, 1.0 equiv) gave 110 mg (46% based on [^{15}N]-**29**, 14% based on [^{15}N]-**26**) of [$^2H_5$,^{15}N]-**1a** as an orange oil. [$^2H_5$,^{15}N]-**1a**, which is chromatographically pure, was used for the cross-coupling experiment without further purification.

Possibility of Proton Exchange of [$^2H_5$]-1a in TFA. Starting from 57 mg of [$^2H_5$]-**1a**, 59 mg (54%) of **4a**, 6 mg (6%) of **5a**, 4 mg (6%) of **6a**, and 10 mg (18%) of **7a** were isolated after rearrangement in TFA. For [$^2H_5$]-**1a**, **4a**, and **5a**, deuterium abundance was measured by whole-molecular ion mass spectroscopy (JEOL, D300), calibrated according to eqs 6 and 7 for [$^2H_5$]-**1a** and according to eqs 8 and 9 for **4a** and **5a**, respectively. Here, for example, (115) represents the peak intensity at *m/e* 115.

$$^2H \text{ abundance} = (115 \times 5 + \{(114) - (113) \times (115)/114)\} \times 5 + \{(113) + (113) \times (115)/(114)\} \times 4 + (112) \times 3 + (111) \times 2 + (110) \quad (6)$$

$$^1H \text{ abundance} = \{(113) + (113) \times (115)/(114)\} + (112) \times 2 + (111) \times 3 + (110) \times 4 + (109) \times 5 \quad (7)$$

$$^2H \text{ abundance} = (210) \times 4 + \{(209) - (208) \times (210)/(209)\} \times 4 + \{(208) + (208) \times (210)/(209)\} \times 3 + (207) \times 2 + (206) \quad (8)$$

$$^1H \text{ abundance} = \{(208) + (208) \times (210)/(209)\} + (207) \times 2 + (206) \times 3 + (205) \times 4 \quad (9)$$

Measurement of the Reaction Rate of [$^2H_5$]-1a by ^{2}H Complete Decoupled ^{13}C NMR. [$^2H_5$]-**1a** (48 mg, 0.42 mmol) was dissolved in 4.79 g (42 mmol, 100 equiv) of TFA with stirring at 0 °C. Without an internal reference, the solution was pipetted into 6 NMR sample tubes to 3.5 cm[34] from the bottom under an argon atmosphere. The tubes were sealed and stored in a dry ice–acetone bath which had been maintained at −30 to −40 °C before the reaction. All these tubes were then immersed in a thermostated bath maintained at 60 ± 0.1 °C, and the clock was started. Two minutes later, one tube was dipped into the dry ice–acetone

(34) When TFA was poured to a higher level, the upper part of the liquid was outside the thermostated region of the probe.

(35) Streitwiether, S. Jr.; Klein, H. S. *J. Am. Chem. Soc.* **1963**, *85*, 2759–2763.

bath to quench the reaction. This point was regarded as the start of the reaction. Thereafter, tubes were quenched at 10-min intervals. For all of them, deuterium-decoupled ^{13}C NMR was measured at 23 °C. One thousand accumulations were needed for quantitative analysis. Any reaction which proceeded during accumulation at 23 °C was neglected. Integrals of signals of the substrate (δ 156.1, 129.2, 127.8, 116.8) relative to that of the reference carboxylic acid proton of TFA at δ 116.5 (q) were observed, and the first-order rate constant k_{obsd} (3.51 ± 0.21) × 10^{-4} s^{-1} was evaluated.

Measurement of the Rate of Unlabeled 1a by ^1H Complete Decoupled ^{13}C NMR. Unlabeled **1a** was examined by proton complete decoupled ^{13}C NMR (JEOL JMN-GSX 500) in accordance with the deuterium complete decoupled ^{13}C NMR method described above, and k_{obsd} (3.89 ± 0.08) × 10^{-4} s^{-1} was obtained.

Cross-Coupling Experiment of [^{15}N]-1d and Unlabeled 1e. A mixture of 35.5 mg (0.257 mmol) of [^{15}N]-**1d** and 37.0 mg (0.245 mmol) of unlabeled **1e** was dissolved in 2.0 mL of dichloromethane and stirred at −20 °C. Next, 570 mg (5.0 mmol, 10 equiv) of TFA in 1.5 mL of dichloromethane which had been cooled to −20 °C was added gently to the solution. This condition corresponds to 0.13 M substrate and 1.30 M TFA. Under an argon atmosphere with exclusion of light, the flask was transferred to an ice bath, and stirring was continued for 2 h at 0 °C. To the reaction mixture was added 1.05 g (5.0 mmol, 10 equiv) of TFAA, and stirring was continued for 2 h. TFA and TFAA were removed by evaporation under reduced pressure without heating, followed by extraction with ethyl acetate (30 mL × 2) and 2 N sodium hydrogen carbonate (20 mL). The combined organic phases were dried over magnesium sulfate and filtered, and then the solvent was removed under reduced pressure. The red-brown residue (142 mg) obtained was used for GC-MS. Mass spectra were obtained on a Hewlett-Packard instrument, Model 5890, equipped with a data system Model MSD-5970. A sample was injected in solution (ethyl acetate). Conditions of measurement were as follows. Column, DB1 30-m; column diameter, 0.25 mm; column head pressure, 13 psi; film thickness, 25 mm; injection port, 150 °C; oven, 100 °C; transfer line, 300 °C; column temperature, initially 100 °C, increasing at 15 °C/min to 200 °C. For peaks with retention times of 5.8 min (**4d**) and 6.5 min (**4e**), mass fragmentometry (MF) was conducted, and the abundance of the nitrogen isotope was evaluated from the area ratio of m/e 233/234 (for **4d**) and 247/248 (for **4e**). The calculation was carried out according to eq 1. When the reaction was carried out with diluted substrate, a mixture of 36.7 mg (0.266 mmol) of [^{15}N]-**1d** and 40.7 mg (0.270 mmol) of unlabeled **1e** in 20 mL of dichloromethane, 11.4 g (200 mmol, 200 equiv) of TFA in 50 mL of dichloromethane, and 2.10 g (10 mmol, 20 equiv) of TFAA was employed. This condition corresponds to 0.0065 M substrates and 0.13 M TFA. The procedure was in accordance with that described above, and 156 mg of residue was obtained. It was used for GC-MS without purification procedure.

^{15}N Abundance of [^{15}N]-1d. A mixture of 17.0 mg (0.130 mmol) of [^{15}N]-**1d** in 1.0 mL of dichloromethane, 140 mg (1.3 mmol, 10 equiv) of TFA in 1.0 mL of dichloromethane, and 270 mg (1.3 mmol, 10 equiv) of TFAA was employed. The procedure was in accordance with that described above, and the red-brown residue obtained was used for GC-MS without further purification.

Cross-Coupling Experiment of [$^2H_5$,^{15}N]-1a and Unlabeled 1a. A mixture of 39.5 mg (0.346 mmol) of [$^2H_5$,^{15}N]-**1a** and 37.8 mg (0.347 mmol) of unlabeled **1a** was dissolved in dichloromethane. Dichloromethane was evaporated under reduced pressure without heating, and then 7.98 g (70 mmol, 100 equiv) of TFA which had been cooled to 0 °C was added carefully to the residue at 0 °C. Under an argon atmosphere with exclusion of light, the flask was transferred to an oil bath that had been maintained at 60 °C. Stirring was continued for 1.75 h. Next, 1.47 g (7.0 mmol, 10 equiv) of TFAA was added at 0 °C, and stirring was continued for 2 h. TFA and TFAA were removed by distillation under reduced pressure, followed by extraction with ethyl acetate (40 mL × 2) and 2 N sodium hydrogen carbonate (20 mL). The combined organic phases were dried over magnesium sulfate and filtered, and then the solvent was removed under reduced pressure. The blood-red residue (170 mg) obtained was flash chromatographed (eluent: *n*-hexane–ethyl acetate 5:1, then 3:1, finally 2:1) to give 65 mg (yield 45%) of **4a**, 6 mg (yield 6%) of **5a**, 3 mg (yield 6%) of **6a**, and 12 mg (yield 18%) of **7a**. When the reaction was carried out under diluted conditions (0.013 M substrate), 6.9 mg of [$^2H_5$,^{15}N]-**1a**, 8.6 mg of unlabeled **1a**, 15.85 g of TFA, and 2.92 g of TFAA were employed; 13.7 mg (yield 50%) of **4a**, 0.8 mg (yield 5%) of **5a**, 1.4 mg (yield 6%) of **6a**, and 2.0 mg (0.018 mmol, yield 13%) of **7a** were isolated. The combined fractions containing **4a** and **5a** were used for GC-MS. Mass spectra were obtained on a Hewlett-Packard instrument, Model 5890, equipped with a data system Model MSD-5970. A sample was injected in solution (ethyl acetate). Conditions of measurement are as follows. Column, DB5 30-m; column diameter, 0.25 mm; column head pressure, 13 psi; film thickness, 25 mm; injection port, 150 °C; oven, 100 °C; transfer line, 300 °C; column temperature, initially 100 °C, increasing 15 °C/min to 200 °C. For peaks with retention times of 6.3 min (**4a**) and 6.5 min (**5a**), MF was done, and the abundance of the nitrogen isotope was evaluated from the area ratio of m/e 206/205 (for [$^1H_4$]-**4a** and [$^1H_4$]-**5a**) and 210/209 (for [$^2H_4$]-**4a** and [$^2H_4$]-**5a**), respectively. Calculations were carried out according to eq 2 for [$^2H_4$]-**4a** and [$^2H_4$]-**5a** and eq 3 for [$^1H_4$]-**4a** and [$^1H_4$]-**5a**.

^{15}N Abundance of [$^2H_4$,^{15}N]-1a. A mixture of 16.0 mg of [$^2H_4$,^{15}N]-**1a**, 1.60 g of TFA, and 300 mg of TFAA was employed. The procedure was performed in accordance with that described above, and 14.2 mg (yield 49%) of **4a**, 2.3 mg (yield 7%) of **5a**, 0.9 mg (yield 6%) of **6a**, and 2.1 mg (yield 13%) of **7a**. **4a** and **5a** were used for GC-MS.

Rearrangement of [$^2H_5$,^{15}N]-1a in the Presence of Ammonium Trifluoroacetate. A mixture of 11.5 mg of [$^2H_5$,^{15}N]-**1a**, 1.14 g of TFA, 393 mg of ammonium trifluoroacetate, and 210 mg of TFAA was employed. The procedure was performed in accordance with that described above to give 9.9 mg (yield 49%) of **4a**, 2.0 mg (yield 8%) of **5a**, 0.9 mg (yield 10%) of **6a**, and 1.9 mg (yield 17%) of **7a**. **2a** and **3a** were used for GC-MS.

Measurement of the Reaction Rates of 1a–1j. The general procedure used is as follows. To a mixture of the substrate and 2 equiv of 1,2-dichloroethane was added 100 equiv of freshly distilled TFA with stirring in a dry ice–acetone bath previously maintained at −15 °C. The homogeneous mixture was carefully poured into NMR sample tubes up to 3.5 cm from the bottom.[34] For **1c–1e**, which are especially reactive in TFA, the Pasteur pipet and NMR sample tube were cooled to −15 °C before use. After argon bubbling, the sample tubes were sealed and stored in a bath at −40 to −50 °C until just before measurement. The D-signal had been locked at 23 °C with TFA-*d* previously, and practical measurement was executed under no lock. A sample tube was loaded on the probe, which was temperature-regulated as appropriate. A time 2 or 3 min later, after the temperature in the probe had equilibrated, was taken as the start of the reaction. An accumulation number was selected in the range of 1–16 times in accordance with the reaction period. Signals of the substrate which did not overlap with those of products were chosen, and, from the integrals relative to the internal reference (δ 3.70), the amount of substrate unconverted was evaluated. In general, sampling was executed 8 times during 1–1.5 half-lives of the substrate.

Temperature Correction of NMR Probe. Concentrated hydrochloric acid was added to absolute methanol so that the concentration of acid was 0.03%. The mixture was poured into an NMR sample tube up to 3.5 cm from the bottom[34] and sealed. Measurements were done with a JEOL JMN GSX-400. The D-signal had been locked at 23 °C with methanol-d_4 previously, and practical measurement was executed under no lock. Three minutes later, after the temperature in the probe had equilibrated, one accumulation was executed. From the chemical shift difference between methyl protons and hydroxyl proton, the corrected temperature in the probe was evaluated.

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