Prototype Pictet−Spengler Reactions Catalyzed by Superacids. Involvement of Dicationic Superelectrophiles

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The Pictet−Spengler reaction, an acid-catalyzed intramolecular cyclization of intermediate imines of 2-arylethylamine to give 1,2,3,4-tetrahydroisoquinolines, has long been limited to active substrates which bear strongly electron-donating groups such as a methoxy or a hydroxy group on the cyclizing benzene ring. In this paper, we present superacid-catalyzed Pictet−Spengler reactions of imines of 2-phenethylamine, including the prototype Pictet−Spengler reaction of *N*-methylene-2-phenethylamine, to give the parent and 1-substituted 1,2,3,4-tetrahydroisoquinolines in moderate to high yields. The yields are dependent on the acidity of the media. A linear relationship was found between the rate of the cyclization and the acidity of the reaction media in kinetic studies of *N*-methylene-2-phenethylamine and related imines, strongly supporting the intervention of an additional protonative activation of the *N*-protonated imines, that is, the involvement of dicationic superelectrophiles, *N*,*N*-diprotonated imines (ammonium−carbenium dications). We further found that the prototype cyclization of the parent *N*-methylene-2-phenethylamine is also catalyzed by TFA to give 1,2,3,4-tetrahydroisoquinoline in good yield, although the cyclization is significantly slower than that catalyzed by superacids. The prototype Pictet−Spengler cyclization of *N*-methylene-2-phenethylamine can thus take place both through the monocation (the *N*-monoprotonated imine) and the dication (the *N*,*N*-diprotonated imine), the latter reaction being predominant in superacids.

The Pictet−Spengler reaction is an acid-catalyzed intramolecular cyclization of the intermediate imine of 2-arylethylamine, formed by condensation with a carbonyl compound, to give 1,2,3,4-tetrahydroisoquinoline derivatives.[1−3] The Pictet−Spengler reaction, as well as the Bischler−Napieralski reaction,[4] is one of the key reactions for construction of the isoquinoline skeleton, which constitutes an important motif of naturally occurring bioactive substances and pharmacophores.[5] For example, unsubstituted (**2a**) and 1-methyl-1,2,3,4-tetrahydroisoquinolines were detected in the brains of humans, rats, and mice and are thought to be relevant to the pathogenesis of Parkinson's disease.[6,7] These simple endogenous tetrahydroisoquinolines are proposed to be biosynthesized from imines derived from 2-phenethylamine and a C1 or C2 carbonyl unit through a mechanism similar to that in the Pictet−Spengler reaction.[7f] The Pictet−Spengler reaction itself has long been believed to have chemical limitations regarding the prerequisite substituents. Although Pictet and Spengler originally reported the formation of the parent 1,2,3,4-tetrahydroisoquinoline by heating at reflux (150 °C) of a mixture of 2-phenethylamine and dimethoxymethane (i.e., an equivalent for formaldehyde) in the presence of concentrated hydrochloric acid,[2] many attempts to reproduce the synthesis of the parent 1,2,3,4-tetrahydroisoquinoline in this *prototype* Pictet−Spengler reaction have failed.[1i,8] For example, Kondo and Ochiai[8] reported the formation of a trace amount of 1,2,3,4-tetrahydroisoquinoline, along with a large amount of bis(2-phenylethylamine)methane under reaction conditions similar to those originally described.[2] Thus, the general consensus hitherto has been that the Pictet−Spengler cyclization is very sensitive to the aromatic substituents of the 2-arylethylamine moiety of the imine **1**, i.e., the prototype Pictet−Spengler reaction of **1a** is impractical, and an electron-donating hydroxy or an alkoxy group at the *para* position of the cyclization site is the minimum requisite for a facile reaction.[1,9,10] In this paper, we will describe superacid-catalyzed prototype and related Pictet−Spengler reactions of imines of 2-phenethylamine (Scheme 1)

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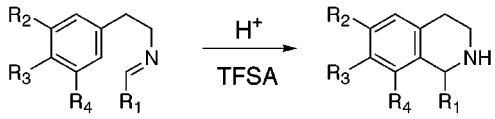
Scheme 1



1a-h **2a-h**

	R_1	R_2	R_3	R_4
a	H	H	H	H
b	$CH(CH_3)_2$	H	H	H
c	C_6H_5	H	H	H
d	*p*-Cl-C_6H_4	H	H	H
e	*p*-CH_3-C_6H_4	H	H	H
f	C_6H_5	CH_3	H	H
g	C_6H_5	CH_3	H	CH_3
h	C_6H_5	OCH_3	OCH_3	H

to give the parent and 1-substituted 1,2,3,4-tetrahydroisoquinoline in moderate to high yields. We also scrutinized the prototype Pictet−Spengler reaction of **1a** and found a reproducible cyclization reaction *in TFA alone* to give the parent 1,2,3,4-tetrahydroisoquinoline. Nevertheless, the cyclization reaction of **1a** in TFA is very slow, being significantly accelerated with further increase of the acidity of the media. In kinetic studies a linear relationship was found between the rate and the acidity of the medium in the superacid-catalyzed cyclization reactions of *N*-methylene-2-phenethylamine **1a** and the relevant *N*-benzylidene-2-phenethylamines (**1c**−**1e**), strongly supporting the involvement of an additional proton transfer to the *N*-protonated imines (**3**) to form superelectrophiles,[11] i.e., the *N*,*N*-diprotonated imines (**4**).

Results and Discussion

The Prototype Pictet−Spengler Reaction. We found that *N*-methylene-2-phenethylamine (**1a**), prepared from 2-phenethylamine and paraformaldehyde, cyclized in the presence of 100 equiv of trifluoromethanesulfonic acid (TFSA) at ambient temperature to give the parent 1,2,3,4-tetrahydroisoquinoline (**2a**). The maximum yield of the cyclized product **2a** was obtained when a somewhat weaker acid, 90% w/w TFSA−10% w/w TFA ($H_0 \approx -12.5$),[12,13] and the following addition order of the acids were used: to a solution of the imine **1a** in trifluoroacetic acid (TFA), weighed TFSA was added at ambient temperature to obtain finally a 90% w/w TFSA−10% w/w TFA acid solution (100 equiv), and the reaction solution was heated at 50 °C for 1 h and then added to a large amount of ice and water. This mixture was basified with aqueous sodium hydroxide and extracted (see Experimental Section) to afford the cyclized product **2a** in 76% yield.[14]

It should be noted that the cyclization reaction of the parent imine **1a** can also be catalyzed by the relatively weak acid TFA alone, which provides a condition similar to the original Pictet−Spengler condition,[1i,2,8,9] although the reaction is significantly slower than that catalyzed by TFSA and TFSA−TFA (Table 1). In TFA at reflux (72 °C) for 20 h, the yield of the cyclized product was 63% in the form of the *N*-benzoyl form of **2a**.[14] The rate of cyclization is accelerated when the acidity of the medium is increased by the addition of TFSA, as judged from the yield of the cyclized product (**2a** or the benzoyl form of **2a** after benzoylation) under unified reaction conditions (50 °C and 1 h): in TFA ($H_0 \approx -2.7$), the cyclized product (**2a**) is virtually undetectable after 1 h; in the acid of $H_0 \approx -9.0$ (1.2% w/w TFSA−98.8% w/w TFA), the cyclized product was formed but in a small amount; in 90% w/w TFSA−10% w/w TFA ($H_0 \approx -12.5$), the yield of **2a** was 76%. The pK_{BH^+} values of imines **1a**−**1e** for *N*-protonation are estimated to be +6 to +8.[15] Thus, **1a** should be completely protonated to form the monocation **3a** even in TFA, where the acidity (H_0) was −2.7 (Scheme 2). In the ^{1}H NMR spectrum of **1a** in TFA at −18 °C, an NH proton was observed at 12.29 ppm and two methylene signals were coupled with the NH signals.[16] The observed acceleration of the cyclization of **1a** upon increase of the acidity of the medium strongly suggested that an additional proton transfer of the iminium cation **3a** is involved in the superacid-catalyzed cyclization of **1a**.

The Superacid-Catalyzed Pictet−Spengler Reactions To Give 1-Substituted 1,2,3,4-Tetrahydroisoquinolines. The aldimines (**1b**−**1e**) bearing a carbon substituent R_1 were also prepared by condensation of 2-phenethylamine and the appropriate aldehydes (R_1-CHO).[17] We found that the cyclizations of the isolated imines **1b**−**1e** can be catalyzed by TFSA (Table 1). In contrast to the behavior of the parent imine **1a**, the cyclization of the imines **1b**−**1e** does not proceed in TFA

(9) Kumar, P.; Dhawan, K. N.; Kishor, K.; Bhargava, K. P.; Satsangi, R. K. *J. Heterocycl. Chem.* **1982**, *19*, 677−679. Although the formation of 1-phenyl-1,2,3,4-tetrahydroisoquinoline (**2c**) from the imine **1c** in TFA was reported, we could not reproduce the result (see Table 1).

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(11) Olah, G. A. *Angew. Chem., Int. Ed. Engl.* **1993**, *32*, 767−788.

(12) The acidity (H_0) of the TFSA−TFA system is described in Saito et al. (Saito, S.; Saito, S.; Ohwada, T.; Shudo, K. *Chem. Pharm. Bull.* **1991**, *39*, 2718−2720). See also: Saito, S.; Sato, Y.; Ohwada, T.; Shudo, K. *J. Am. Chem. Soc.* **1994**, *116*, 2312−2317, footnote 8.

(13) The acidity (stronger than $H_0 = -10$) of the TFSA−TFA acid system which catalyzes the cyclization of **1** would be decreased, because the starting imines **1** and the cyclized products, tetrahydroisoquinolines **2**, are strong nitrogen bases that would be completely *N*-monoprotonated in the acid. To determine the lowering of the acidity of the acid, we used piperidine as a nitrogen base which has a similar structure and basicity to those of **1** and **2**, because piperidine, unlike **1** and **2**, has no strong UV absorption which would interfere with the absorption of indicators (see ref 12). The corrected acidities (H_0) of the TFSA−TFA acid in the presence of 1 mol % of piperidine are shown in Table 4. In the case of 26.2% TFSA−73.8% TFA acid ($H_0 \approx -10$), the decrease of the acidity by the addition of 1 mol % of piperidine is 0.3 in terms of H_0 units, while the addition of 1 mol % of piperidine to 100% TFSA caused the largest lowering of the acidity (by 1.4 in terms of H_0).

(14) The yield of the cyclized product was calculated after conversion to the corresponding benzoyl derivative by benzoylation of the crude amine products to allow convenient purification of the compound. Under the same reaction conditions (in 90% w/w TFSA−10% w/w TFA, 50 °C, 1 h), *N*-benzoyl-1,2,3,4-tetrahydroisoquinoline was formed in 74% yield, along with the *N*-benzoyl derivative of 2-phenethylamine (5% yield), which was generated through decomposition of the starting imine **1a**. This decomposition of the starting imine partially accounts for the limiting conversion (for example, **1b**) particularly under a longer reaction time and a higher reaction temperature. The yield of the cyclized product after benzoylation is comparable with that obtained by the direct separation of **2a**. Benzoylation of the crude reaction mixture obtained in the cyclization reaction of the imine **1a** allows convenient isolation of the crude amines, and also affords good separation of a small amount of an undefined polar byproduct.

(15) (a) Olah, G. A.; Kreienbuhl, P. *J. Am. Chem. Soc.* **1967**, *89*, 4756−4759. (b) Olah, G. A.; Donovan, D. J. *J. Org. Chem.* **1978**, *43*, 860−867. (c) Allen, M.; Roberts, J. D. *Can. J. Chem.* **1981**, *59*, 451−458. (d) Knorr, R.; Ferchland, K.; Hoang, T. P. *Leibigs. Ann. Chem.* **1994**, 943−948. (e) Cordes, E. H.; Jencks, W. P. *J. Am. Chem. Soc.* **1963**, *85*, 2843−2848. The basicity of the related imine *N*-*p*-chlorobenzylidene-1,1-dimethylethylamine (pK_{BH^+} = 6.5) is almost equal to that of *N*-benzylidene-1,1-dimethylethylamine (pK_{BH^+} = 6.7).

(16) In the ^{1}H NMR spectrum of **1a** in TFA at −18 °C, the two methylene signals are observed at 8.10 ppm (J = 8.5 Hz) and 7.87 ppm (J = 8.3 and 17.8 Hz) as a triplet and a quartet signal, respectively. The splittings of these signals are due to the geminal coupling (J = 8 Hz) and the coupling with the NH signal.

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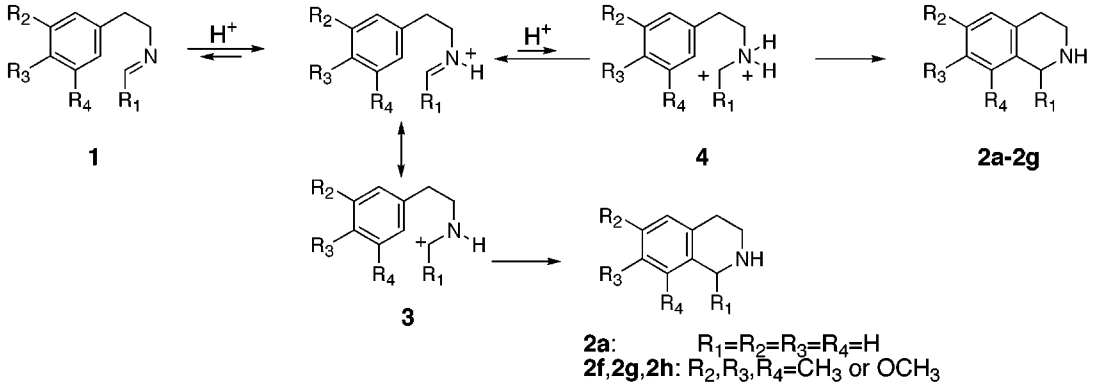
Table 1. Acid-Catalyzed Cyclization of the Imines of 2-Phenethylamine Derivatives

imines	R_1	R_2	R_3	R_4	acid	temp (°C)	time (h)	yield (%) of **2**
1a	H	H	H	H	90% TFSA−10% TFA	50	1	76 (74)[a,b]
					TFA	72[c]	20	(63)[a]
1b	$CH(CH_3)_2$	H	H	H	TFSA	150	13	69
					TFSA	120	17	32
1c	C_6H_5	H	H	H	TFSA	120	15	90
					TFA	72[c]	16	0[d]
					TFA	120[e]	40	0[d]
1d	*p*-ClC_6H_4	H	H	H	TFSA	120	15	94
					TFA	120[e]	40	0
1e	*p*-$CH_3C_6H_4$	H	H	H	TFSA	120	3	90
					TFSA	80	14	85
					TFA	120[e]	40	0[d]
1f	C_6H_5	CH_3	H	H	TFA	72[c]	32	3[f]
					TFSA	60	30	77[g]
1g	C_6H_5	CH_3	H	CH_3	TFA	72[c]	26	50
					TFSA	60	2	94
1h	C_6H_5	OCH_3	OCH_3	H	TFA	30	62	89
					TFA	72[c]	1.2	89

[a] The yield of *N*-benzoyltetrahydroisoquinoline after benzoylation of the crude amines is shown in parentheses. [b] *N*-Benzoyl 2-phenethylamine (5% yield) was generated upon benzoylation of the crude amines. [c] At reflux. [d] 2-Phenethylamine was formed in 10−20% yield through the decomposition of the imine. [e] Sealed. [f] A single isomer (1-phenyl-6-methyltetrahydroisoquinoline). [g] A mixture of two isomers (1-phenyl-6-methyltetrahydroisoqinoline: 1-phenyl-8-methyl-tetrahydroisoqinoline = 3:1).

Scheme 2



even by heating at reflux or at 120 °C in a sealed tube, and the imines were unchanged. On the other hand, in TFSA the alkyl-substituted imine *N*-(2-methylpropylidene)-2-phenethylamine (**1b**) gave a cyclized product (**2b**) in 69% yield at 150 °C for 13 h.

The reaction of **1b** seemed to reach a plateau at 150 °C even at long reaction time (20 h, 60% yield). At lower temperature (120 °C) the cyclization reaction of **1b** in TFSA was retarded, and the yield of the product **2b** was decreased. When the substituent (R_1) of the aldehyde was an aryl group (**1c**−**1e**), the cyclization proceeded efficiently in TFSA at 120 °C to give the cyclized products **2c**−**2e** in high yields (Table 1). The reaction conditions (time and temperature) are partially optimized: for example in the case of the imine **1c**, the yield of **2c** was decreased to 60% in a shorter reaction time (3 h, at 120 °C). Heating is also necessary for a facile reaction: at 60 °C the cyclization reaction of the imine **1c** in TFSA is too slow to be detected. As judged from the reaction time, *p*-methyl **1e** cyclized faster than unsubstituted **1c** and *p*-chloro **1d**. This is compatible with the measured reaction rates of **1c**−**1e** (vide infra).

In a manner similar to that for **1a**, the imine **1c** is also completely monoprotonated in TFA to give the iminium cation **3c**. The ^{1}H NMR spectrum of **1c** in TFA at −10 °C showed a unit proton attached to the nitrogen atom of the imine at 11.2 ppm, and the coupling of the iminomethylene signal with an NH signal to give a doublet at 8.10 ppm (J = 10.9 Hz), supporting the essentially complete *N*-protonation of **1c** in TFA to give the cation **3c**. When the solution of **1c** in TFA was heated at reflux (72 °C) for 16 h, no reaction took place, no cyclized product (**2c**) was obtained, and **3c** remained unchanged (monitored by ^{1}H NMR spectra) (Table 1). This result excludes the contribution of the *N*-protonated imine **3c** as a reactive intermediate in the cyclization of the imine **1c**. We, thus, postulate the intervention of an additional proton transfer to the iminium cation **3c**, and probably **3b**, **3d**, and **3e** in the superacid-catalyzed Pictet−Spengler reactions of the imines **1b**−**1e**. In contrast to the *N*-monoprotonated *N*-methylene-2-phenethylamine (**3a**), the iminium cations **3b**−**3e** lack cyclizing ability, probably due to significant stabilization of the carbenium center by an alkyl or a phenyl group, resulting in deactivation of the electrophilicity of the iminium cation **3**.

Kinetic Studies of the Superacid-Catalyzed Pictet−Spengler Reactions. We measured the rates of the cyclization of the *N*-benzylidene-2-phenethylamines **1c**−**1e** in strong acids of a variety of acidities (TFSA−TFA). The reactions hardly proceed in acid weaker than H_0 = −10, despite complete *N*-monoprotonation of the imines **1** to give the cation **3**. The reactions were carried out in the presence of 100 equiv of the acid (TFSA−TFA) in a sealed NMR tube and heated at 120 (±0.1) °C, and the concentrations of the *N*-protonated imine **3** were deter-

Table 2. Rate Constants for Superacid-Catalyzed Cyclizations of 1a and 1c−1e[a,b]

1a[c]		**1c**[d]		**1d**[d]		**1e**[d]	
H_0	10^5k (s^{-1})	H_0	10^5k (s^{-1})	H_0	10^5k (s^{-1})	H_0	10^5k (s^{-1})
		−12.7	4.95	−12.7	4.93	−12.7	25.50
−12.4	31.8	−12.5	4.52	−12.4	3.64	−12.5	15.20
−12.0	24.7	−12.1	2.43	−12.1	2.52	−12.1	5.99
−11.5	15.8	−11.5	1.10	−11.6	1.29	−11.5	2.12
−11.0	8.69	−11.0	0.55	−10.9	0.52	−11.0	0.79
−10.7	4.99	−10.6	0.29	−10.5	0.23	−10.6	0.39

[a] Corrected values of acidity function of the reaction media (see Table 4 (Experimental Section) and refs 12 and 13). [b] Errors of rates, ±2%. [c] At 20.0 °C. [d] At 120 °C.

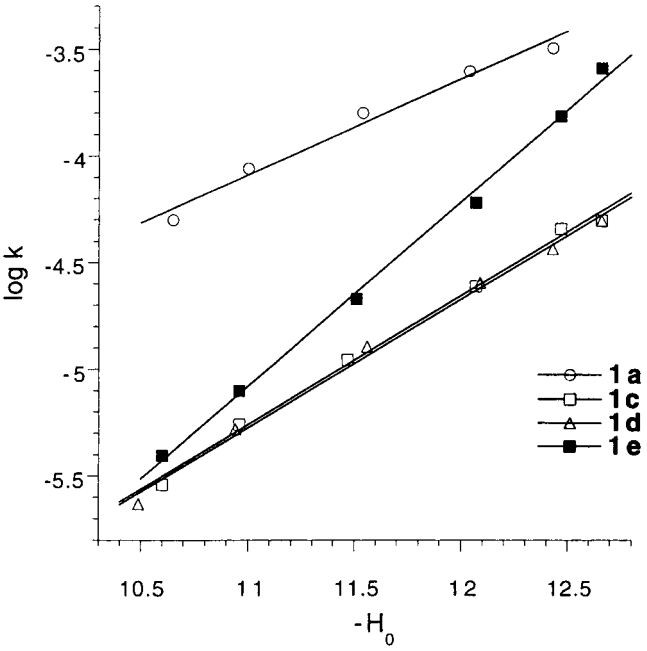


Figure 1. Acidity−rate profiles of the superacid-catalyzed Pictet−Spengler cyclization reactions.

mined from the integral values in the ^{1}H NMR spectra at 23 °C, where the reaction was too slow to be detected.[18] These reactions showed good first-order kinetics, giving linear relationships between the rates and the acidities ($r > 0.99$), the slope being 0.60 for **1c** and **1d** and 0.86 for **1e** (Table 2 and Figure 1). The rate constant of **1c** was coincidently equal to that of **1d**, and they are smaller than that of **1e**. According to the Zucker−Hammett criteria,[19,20] these linear relationships indicate the involvement of additional protonation of the *N*-monoprotonated imines **3**; i.e., the intervention of the dication **4** (vide infra). The activation parameters for the cyclization of **1c**, **1d**, and **1e** were also obtained from the rate constants of cyclization at three different temperatures (110, 120, and 130 °C) (Table 3).[20,21] A smaller enthalpy of activation ($\Delta H^{\ddagger}$, 11.5 kcal mol^{-1}) of **1e** is found as compared with those of **1c** ($\Delta H^{\ddagger}$, 17.7 kcal mol^{-1}) and **1d** ($\Delta H^{\ddagger}$, 18.0 kcal mol^{-1}). This magnitude is consistent with the facile cyclization reaction of **1e**, which proceeds even at 80 °C in TFSA to give the cyclized product **2e** in 85% yield after 14 h.

Table 3. Thermochemical Data for Acid-Catalyzed Cyclizations of 1a in TFA and 1a, 1c, 1d, and 1e in Superacids

	rate constants	10^5k (s^{-1}) at T (°C)[d]	$\Delta G^{\ddagger}$[e,h] (kcal/mol)	$\Delta H^{\ddagger}$[f] (kcal/mol)	$\Delta S^{\ddagger}$[g] (eu)
1a[a]	50.0	4.20			
	60.0	8.03	24.8	16.2	−28.7
	70.0	19.5			
1a[b]	0.0	4.15			
	10.0	12.5	22.0	15.7	−21.1
	20.0	31.8			
1c[c]	110.0	2.66			
	120.0	4.95	27.8	17.7	−33.8
	130.0	8.86			
1d[c]	110.0	2.70			
	120.0	4.93	27.8	18.0	−32.9
	130.0	9.21			
1e[c]	110.0	16.6			
	120.0	25.5	25.3	11.5	−46.3
	130.0	36.9			

[a] At $H_0 = -2.7$ (in TFA). [b] At $H_0 = -12.4$ (in 90% w/w TFSA−10% w/w TFA, the corrected value of acidity function of the medium (Table 4)). [c] At $H_0 = -12.7$ (in TFSA, the corrected value of acidity function of the medium (Table 4)). [d] Errors in temperature, ±0.1 °C. [e] Errors ± 1.5 kcal/mol. [f] Errors ± 0.9 kcal/mol. [g] Errors ± 2.0 eu. [h] At 25 °C (298.15 K).

We also measured the rates of the cyclization of the *N*-methylene-2-phenethylamine **1a** in TFA and in the TFSA−TFA acid system (Table 3). As described, the imine **1a** was completely monoprotonated to give the cation **3a** in TFA. In TFA the cyclization of **3a** showed good first-order kinetics, and the activation parameters for the cyclization of **3a** were obtained from the rate constants of cyclization at three different temperatures (50.0, 60.0, and 70.0 °C);[20,21] the values are shown in Table 3. The reaction of **1a** in TFA below 50 °C is too slow to allow kinetic measurements. The cyclization of **1a** in the TFSA−TFA acid system at 20 °C also showed good first-order kinetics, e.g., in 90% w/w TFSA−10% w/w TFA ($H_0 \approx -12.5$) the rate constant at 20 °C is 3.18×10^{-4} s^{-1} (Table 2), and a linear relationship ($r = 0.99$) between the rate of the cyclization and the acidity of the medium was also found, the slope being 0.45 (Figure 1).[22] This linear relationship supports the postulation that the cyclization of **1a** in the superacid involves an additional proton transfer to the iminium ion **3a**, i.e., the involve-

(18) We confirmed that the imines **1c**−**1e** are fully *N*-monoprotonated in acid at an acidity stronger than $H_0 = -10$ where the kinetic measurements were performed, on the basis of the coupling of the imino methylene as a doublet. The spectrum of **1c** in TFSA ($H_0 = -12.7$) gave essentially the same pattern as that in TFA, and therefore, the concentration of the diprotonated imine (**4c**) seems to be too low to allow for detection by NMR. This conclusion is consistent with the Zucker−Hammett criteria which postulate that such a linear relationship between the rates and the acidities (Figure 1) can be obtained only when the concentration of the diprotonated species is very small.

(19) (a) Zucker, L. Hammett, L. P. *J. Am. Chem. Soc.* **1939**, *61*, 2791−2798. (b) Bonner, T. G.; Thorne, M. P.; Wilkins, J. M. *J. Chem. Soc.* **1955**, 2351−2358. (c) Bonner, T. G.; Barnard, M. *J. Chem. Soc.* **1958**, 4181−4186. (d) Long, F. A.; Paul, M. A. *Chem. Rev.* **1957**, *57*, 935−1010. If the reactive electrophile in the cyclization is the monoprotonated imine, the rates of the reaction will be saturated because the imine **1** is fully monoprotonated even in TFA.

(20) The excellent linear relationships (regression coefficient $r > 0.99$) obtained in the estimation of activation parameters (Table 3) support the postulation that the temperature-dependent changes of H_0 and pK_{BH^+} are canceled out in the TFSA−TFA acid system and thus that the observed rate constant k_{obs} is affected by k_r (the rate constant for cyclization) and not K_e (the ionization constant of the carbodication **4**) at the different temperatures. See: Ohwada, T.; Suzuki, T.; Shudo, K. *J. Am. Chem. Soc.* **1998**, *120*, 4629−4637, footnote 24. Therefore the activation parameters obtained from the kinetic data should represent the thermal parameters in the rate-determining cyclization process. A similar situation is also expected in the case of the monocationic cyclization, i.e., the cyclization of the imine **1a** in TFA.

(21) Moore, J. W.; Pearson, R. G. *Kinetics and Mechanism*; John Wiley & Sons: New York, 1981.

(22) We noted a slight curvature of the plot in the highest acidity region.

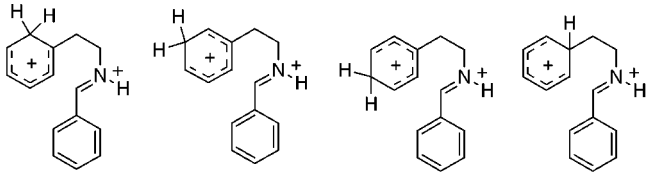
ment of the dication **4a** (vide infra). That is, the acceleration of the reaction of **1a** in the superacid can be attributed to dicationic cyclization. This idea is consistent with the superacid-catalyzed cyclization reactions of the imines **1c**−**1e**. The rate constants of the cyclization of **1a** in 90% w/w TFSA−10% w/w TFA were also measured at three different temperatures (0.0, 10.0, and 20.0 °C), and the activation parameters of the dicationic cyclization were also obtained (Table 3).[20,21] According to the obtained linear relationship between the rate and the acidity ($H_0 < -10$), the reaction rate of the dicationic cyclization of **1a** at the acidity $H_0 \approx -2.7$ (equivalent to the acidity of TFA) is predicted to be 1.6×10^{-8} s^{-1} (at 20 °C). This value is much smaller than the rate of cyclization of **1a** in TFA estimated at 20 °C (2.7×10^{-6} s^{-1}) on the basis of the observed thermal parameters. Therefore, the rate ratio of **1a** between the dicationic cyclization through the dication **4a** (in TFSA−TFA at 20 °C) and the monocationic cyclization through the monocation **3a** (in TFA, the rate estimated at 20 °C) is roughly 10^2. Thus, this deviation also supports the idea that the reaction of **1a** in TFA is not the dicationic cyclization but involves a different pathway, through the monocation **3a**. This situation is reminiscent of the inherent reactivity of the acetyl cation in the acetylation of toluene.[23] The salt, acetylium hexafluoroantimonate ($CH_3CO^+SbF_6^-$), can acetylate toluene slowly in a neutral solvent, suggesting that the acetyl cation itself has the ability to acetylate toluene, but only slowly. The acetylation is accelerated as the acidity of the media is increased, through the intervention of protonated acetyl cation.

In deuterated trifluoromethanesulfonic acid (CF_3SO_3D) at 23 °C for 24 h, the imine **1c** showed no deuterium incorporation of the imino methine proton and the benzene protons attached to the imino group, while the thorough deuterium exchange occurred at all of the phenyl protons of the 2-phenethylamino moiety. Although the *C*,*N*-diprotonated species can be formed,[24,25] the phenyl group of the R_1 substituent is not essential for the dicationic cyclization, i.e., the cyclization reactions of the imines **1a** and **1b** can be promoted by TFSA. Thus, we can postulate that the dicationic superelectrophiles commonly involved in the superacid-catalyzed Pictet−Spengler reaction of **1a**−**1e** are the *N*,*N*-diprotonated imines, i.e., the ammonium−carbenium dications **4** (Scheme 2).[18,26] The carbenium center of the iminium moiety of **4** is activated by an electron-withdrawing ammonium group, restoring or increasing the electrophilicity intrinsic to the methylium center of the monocation **3a**. Involvement of relevant ammonium−carbenium dications has been shown in the acid-catalyzed stereoisomerization of olefin moieties of cinnamaldimines[27] and in the Friedel−Crafts type reactions of cinnamaldimines with benzene, catalyzed by TFSA.[28]

Substituent Effects in the Pictet−Spengler Reactions. We investigated the substituent effect of the electron-donating group on the cyclizing benzene ring of the relevant imines (Table 1). The imines **1f**−**1h**, *N*-benzilidene-2-arylethylamines, were prepared by the condensation of the corresponding 2-arylethylamine and benzaldehyde. The imine **1f**, *N*-benzylidene-2-(3-methylphenyl)ethylamine, which bears a monomethyl group on the cyclizing benzene ring, requires the superacid catalyst to undergo the facile cyclization. In TFA, the cyclization of **1f** was very slow: the yield of the cyclized product, 6-methyl-1-phenyl-1,2,3,4-tetrahydroisoquinoline (**2f**), was only 3% after 32 h at reflux (72 °C). In TFSA the reaction was accelerated to give a mixture of 6-methyl-1-phenyl-1,2,3,4-tetrahydroisoquinoline (**2f**) and 8-methyl-1-phenyl-1,2,3,4-tetrahydroisoquinoline (**2f′**) (ratio 3:1) in a total yield of 77% even at a lower reaction temperature (60 °C, 30 h). A double methyl substitution of the aromatic ring as in *N*-benzylidene-2-(3,5-dimethylphenyl)ethylamine **1g** activated the monocationic cyclization through the *N*-protonated imine **3g**: in TFA the imine **1g** undergoes cyclization to give the product **2g** in 50% yield after heating at reflux (72 °C) for 26 h. The cyclization reaction is significantly accelerated in TFSA: the yield of **2g** is 94% in TFSA, even at 60 °C after only 2 h. Acceleration of the cyclizations of the imines **1f** and **1g** by TFSA as compared with the reactions in TFA can be interpreted in terms of the intervention of the dicationic cyclization through the corresponding dications **4f** and **4g** (Scheme 2).[24,25] As estimated from the reaction time and reaction temperature, the cyclization reactions of **1f** and **1g** in TFA through the monocations **3f** and **3g** are slow as compared with those of **1f** and **1g** in TFSA, the rate ratio being evaluated to be on the order of 10^2;

(23) Sato, Y.; Yato, M.; Ohwada, T.; Saito, S.; Shudo, K. *J. Am. Chem. Soc.* **1995**, *117*, 3037−3043.

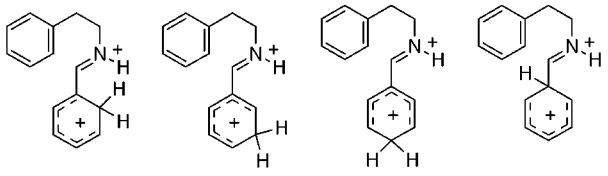
(24) The facile deuterium exchange of the phenyl protons of the 2-phenethylamine moiety of **1c** even at 23 °C indicates a facile formation of dicationic species such as **5i**−**5iii**



5i **5ii** **5iii** **5iv**

and probably *ipso*-protonated **5iv**. Nevertheless, they are not substrates for the cyclization due to positive charge repulsion between the benzenium cation and the iminium cation. A more facile ring protonation is expected in the imines **1f** and **1g**.

(25) Despite the lack of deuterium exchange of the phenyl ring protons of **1c** attached to the iminio carbon atom in TFSA-d_1 at 23 °C, we could not exclude as contribution of *C*,*N*-diprotonated species such as **6i**−**6iii**



6i **6ii** **6iii** **6iv**

as well as *ipso*-protonated **6iv** which might be activated electrophiles due to conjugate positive ion centers. Relevant dications can also be formed in the cases of the imines **1f** and **1g**.

(26) The electrophilic reactivity of imines is known to be increased by *N*-acylation or *N*-sulfonylation, so-called amidoalkylation. The proposed intermediates of the amidoalkylation are *N*-acyliminium ions or *N*-sulfonyliminium ions, which are activated to react with nitrobenzene. The ammonium group of the dication **4** acts as an acyl-nitrogen atom or a sulfonyl-nitrogen atom. (a) Venkov, A.; Lukanov, L. *Synthesis* **1989**, 59−61. (b) Lukanov, L.; Venkov, A. P.; Mollov, N. M. *Synthesis* **1987**, 204−206. (c) For reviews of amidoalkylations, see: Speckamp, W. N.; Hiemstra, H. *Tetrahedron* **1985**, *41*, 4367−4416. (d) Zaugg, H. E. *Synthesis* **1985**, 49. (e) Sisido, K.; Inada, H.; Isida, T. *Tetrahedron Lett.* **1968**, *50*, 5267−5269.

(27) Child, R. F.; Dickie, B. D. *J. Am. Chem. Soc.* **1983**, *105*, 5041−5046.

(28) (a) Ohwada, T.; Yamagata, N.; Shudo, K. *J. Am. Chem. Soc.* **1991**, *113*, 1364−1373. (b) Saito, S.; Sato, Y.; Ohwada, T.; Shudo, K. *J. Am. Chem. Soc.* **1994**, *116*, 2312−2317. (c) Saito, S.; Ohwada, T.; Shudo, K. *J. Am. Chem. Soc.* **1995**, *117*, 11081−11084. (d) Suzuki, T.; Ohwada, T.; Shudo, K. *J. Am. Chem. Soc.* **1997**, *119*, 6774−6780.

the magnitude corresponds well to that between the dicationic and monocationic cyclizations in the case of **1a**. Furthermore, the cyclization reactions of the methyl-substituted imines (**1f** and **1g**) in TFSA (at 60 °C) are faster than that of the unsubstituted imine **1c** in TFSA (at 60 °C, practically no reaction takes place). This result strongly supports the idea that the cyclization process is involved in the rate-determining step of the reaction, because the presence of one or more methyl substituent increases the electron-donating ability of the cyclizing benzene ring and the cyclization is accelerated. If rate-determining protonation were involved,[29] the cyclization reaction would be independent of the aromatic substituents of the phenethylamino moiety because these remote substituents would not modify the basicity of the common iminium moiety of the monocations **3c**, **3f**, and **3g**, which is relevant to the equilibrium with the dications **4**.[30] The large values of negative entropy of activation ($\Delta S^{\ddagger}$, −33.8 eu to −46.3 eu) of the cyclization of **1c**−**1e** (Table 3) are also consistent with the rate-determining cyclization.

Because a methoxy group on the aromatic ring is a much stronger electron-donating group than the methyl group, the imine **1h**, *N*-benzylidene-2-(3,5-dimethoxyphenyl)ethylamine, which bears two methoxy groups, can be regarded as a truly activated substrate. This imine **1h** readily undergoes cyclization in TFA even at 30 °C (62 h) to give the corresponding **2h** in a high yield (89% yield). When the reaction was carried out at reflux (72 °C) in TFA, the reaction is rapid (1.2 h), and the yield of **2h** is 89%. The imine **1h** is completely *N*-monoprotonated in TFA to give the iminium cation **3h** in a manner similar to the that for imine **1c**, since the basicities of the imino nitrogen atoms of **1c** and **1h** are identical. This facile reaction of **1h** confirms the intermediacy of the *N*-monoprotonated imine **3h** in the conventional Pictet−Spengler reaction, wherein strongly activated cyclizing benzenes are involved.[31]

Conclusion

Our study showed that the prototype Pictet−Spengler reaction of *N*-methylene-2-phenethylamine **1a** can be catalyzed by TFA to give 1,2,3,4-tetrahydroisoquinoline **2a** in good yield. This result shows that cyclization through the *N*-protonated iminium monocation **3a** can intervene in the prototype Pictet−Spengler reaction and also confirms the original observation of Pictet and Spengler, approximately 90 years after their publication. We also found that a superacid can catalyze the Pictet−Spengler reactions of the imines (**1a**−**1e**) of 2-phenethylamine, including **1a**. The acidity dependence of the reaction suggested that *N*-protonated imines **3b**−**3e** (except **3a**) are not reactive intermediates in the Pictet−Spengler reactions. Our kinetic studies of the cyclizations revealed that the true electrophiles are dicationic superelectrophiles, the *N*,*N*-diprotonated imines **4a**−**4e**, i.e., the ammonium−carbenium dications. These findings dispel the notion that the Pictet−Spengler reaction is restricted to activated substrates which bear strongly electron-donating groups on the cyclizing benzene ring. The present chemistry of the superelectrophiles will give a new impetus to synthetic applications of the Pictet−Spengler reaction, and the proposed reaction mechanisms also shed light on the mechanisms of biosynthesis of the endogenous tetrahydroisoquinolines, which are of great interest in neuroscience.[6,7]

Experimental Section

Materials Trifluoromethanesulfonic acid (TFSA) was purchased from Central Glass Co. (Japan) and was purified by distillation as described previously.[12] Great care was taken to obtain anhydrous TFSA, which has an acidity of $H_0 = -14.1$. Trifluoroacetic acid (TFA) was also purified by distillation as described previously.[12] Piperidine was purified by distillation and stored in glass ampules. The imines are prepared as previously described.[15,17,31−34]

Cyclization of 1a−1e in TFSA. General Procedure. The imine **1** (1.0 mmol) was dissolved in 100 equiv of TFSA (15.2 g, 100 mmol) at ambient temperature, and the mixture was stirred at a specified temperature for a specified time shown in Table 1. Then the solution was poured into ice−water (100 mL), and the mixture was basified with 5 N NaOH (30 mL) and extracted with CH_2Cl_2 (100, 50, and 50 mL). The combined organic layer was dried over anhydrous Na_2SO_4, and the solvent was evaporated. The residue was flash-chromatographed (CH_2Cl_2, then MeOH:CH_2Cl_2 = 1:20, or MeOH:ethyl acetate = 1:20) to give the cyclized product, the 1,2,3,4-tetrahydroisoquinoline derivative **2**.

Acid-Catalyzed Cyclization of *N*-Methylidene-2-phenethylamine 1a to 1,2,3,4-Tetrahydroisoquinoline 2a. (1) Direct Separation of 2a. TFSA. To well-stirred TFSA (15.11 g, 101 mmol) was added the imine (135 mg, 1.01 mmol) at ambient temperature. The solution was stirred at ambient temperature for 3 h. Then the acid solution was poured into 100 mL of ice and water, followed by addition of 30 mL of 5 N NaOH. The whole was extracted with methylene chloride, and the organic layer was dried over Na_2SO_4. The solvent was evaporated to give the residue, which was flash-chromatographed (aluminum oxide, acetonitrile/methylene chloride) to give 55 mg (41%) of **2a**. The amine **2a** obtained above was identical with authentic 1,2,3,4-tetrahydroisoquinoline in terms of the ^{1}H NMR spectrum.

(2) Separation after Benzoylation. In the case of the imine **1a**, the crude extract of the reaction mixture was subjected to benzoylation (benzoyl chloride in dry CH_2Cl_2 and triethylamine at 0 °C), followed by the separation. The benzoylation of authentic 1,2,3,4-tetrahydroisoquinoline proceeded quantitatively (98.2% yield).

TFSA−TFA. To a well-stirred solution of the imine **1a** (532.6 mg, 4 mmol) in TFA (5.86 g) was added weighed TFSA (52.7 g) at ambient temperature to give a 90% w/w TFSA−10% w/w TFA solution (100 equiv with respect to **1a**). The solution was heated at 50 °C with stirring for 1 h. After cooling in an ice−water bath, the whole was poured into 200 mL of ice and water, followed by basification with 5 N aqueous NaOH. The whole was extracted with methylene chloride and dried over Na_2SO_4. The solvent was evaporated to give the crude amine residue (455.8 mg). To a solution of the crude amine in 3 mL of dry CH_2Cl_2 and triethylamine (1 mL) was added a solution of benzoyl chloride (484.6 mg) in 1 mL of dry CH_2Cl_2 at 0 °C. After 1 h, water was added; then the whole was extracted with CH_2Cl_2 (200 mL), and the organic layer was washed with brine and dried over Na_2SO_4. The residue obtained after evaporation of the solvent was flash-chromatographed (silica gel, acetone/*n*-hexane 1:8) to give 705.2 mg (74%) of *N*-benzoyl-1,2,3,4-tetrahydroisoquinoline (the *N*-benzoyl form of **2a)** and 45.1 mg (5% yield) of *N*-benzoyl-2-phenethylamine.

(29) Ritchie, C. D.; Lu, S. *J. Am. Chem. Soc.* **1989**, *111*, 8542−8543.

(30) Even when the *N*,*C*-diprotonation to give the dication **6** is involved, the basicities of the benzene carbon atoms of the substituent R_1 of the monocations **3c**, **3f**,and **3g** would be similar to each other. If the *N*,*C*-protonation process is rate-determining, the cyclization rates of **1c**, **1f**, and **1g** would not be modified. This is in disagreement with the observed acceleration, **1g** > **1f** > **1c**.

(31) The reaction of **1h** in TFA at 72 °C is significantly faster than those of **1a**, **1f**, and **1g** under the same reaction conditions (Table 1). Thus, in the monocationic cyclization in TFA, the cyclization process is also involved in the rate-determining process.

Table 4. Corrected Values of Acidity Function of the Acid Media in the Presence of 1 mol % Piperidine

acid[a]	uncorrected H_0[b]	corrected H_0[c]
100% TFSA	−14.1	−12.66
89.0% TFSA−11.0% TFA	−13.3	−12.42
78.5% TFSA−21.5% TFA	−12.7	−12.10
59.9% TFSA−40.1% TFA	−12.2	−11.52
26.2% TFSA−73.8% TFA	−10.8	−10.54

[a] Weight percent of the composite acids. [b] Reference 12. [c] See also ref 13.

TFA. To 31 mL of TFA was added the imine **1a** (531.7 mg, 4 mmol) at ambient temperature. It was completely dissolved in 15 min at ambient temperature. The solution was heated at 50 °C with stirring for 20 h. After cooling in an ice−water bath, the whole was poured into 200 mL of ice and water, followed by basification with 5 N aqueous NaOH. The whole was extracted with methylene chloride (500 mL), washed with brine, and dried over Na_2SO_4. The solvent was evaporated to give the crude amine residue (445.1 mg). The residue was subjected to benzoylation as described in (2), and the residue obtained was flash-chromatographed (silica gel, acetone/*n*-hexane 1:8) to give 510.5 mg (54%) of the *N*-benzoyl form of **2a** and 183.2 mg (20% yield) of *N*-benzoyl-2-phenethylamine.

Acidity Values H_0 of TFSA−TFA in the Presence of 1 mol % of Piperidine. Acid mixtures, TFSA−TFA, used in the determination of the acidities (H_0) and in the kinetic studies were prepared in a polyethylene glovebox (AtmosBag, Aldrich) under a dry nitrogen atmosphere. UV spectra were recorded with a Shimadzu UV-200S using matched quartz glass 1-cm cells sealed with a Teflon stopper.

In strong acid of more than $H_0 = -10$, wherein the cyclization can take place, the imines **1** and the resultant cyclized product, 1,2,3,4-tetrahydroisoquinolines **2**, behave as strong nitrogen bases because of complete *N*-monoprotonation, thus reducing the acidity of the reaction medium. We therefore estimated the lowering of the acidity of the reaction medium by measuring the acidity of TFSA−TFA (100 equiv with respect to piperidine) in the presence of piperidine at acidity levels stronger than $H_0 \approx -10$ (Table 4).[12,13]

Determination of the acidity of the acid mixtures was conducted by means of the usual indicator method with UV spectroscopy at 25 °C.[12] Acid mixtures, TFSA−TFA, were prepared in an AtmosBag (Aldrich) under a dry nitrogen atmosphere at ambient temperature. The acidity of acids stronger than 59.9% w/w TFSA−40.1% w/w TFA, including 100% TFSA ($H_0 = -11.52$ to -12.66), was determined by using 4-fluoronitrobenzene as an indicator.[12] In the determination of the acidity of 26.2% w/w TFSA−73.8% w/w TFA acid, 2,4,6-trinitroaniline was used as an indicator.[12]

The corrected values of the acidity function were determined as follows. For example, 59.9% w/w TFSA−40.1% w/w TFA acid in the presence of 1 mol % piperidine: the acid mixture (59.9% w/w TFSA−40.1% w/w TFA) was prepared by mixing TFSA (30.052 g) and TFA (20.138 g) at ambient temperature. To the weighed acid mixture (50.190 g, 377 mmol, 102 equiv with respect to piperidine) was added piperidine (315 mg, 3.70 mmol). To an aliquot of the above acid solution (9.873 g) was added a weighed indicator, 4-fluoronitrobenzene (6.18 mg), to obtain a good solution. A small portion of this solution (0.819 g) was transferred into a 10-mL volumetric flask and diluted to 10 mL with the stock acid solution (the final concentration of 4-fluoronitrobenzene was 3.63×10^{-4} mol/L in this case). A portion of this solution was transferred into a 1-cm quartz cell, which was sealed tightly with a Teflon cap. The same acid, containing piperidine, but free from the indicator, was used as a reference in the UV measurements. The value of the acidity function was determined from the absorption of the indicator as described previously[12]

Kinetics of the Cyclization of 1c−1e and 1a. Samples of the imines **1c−1e** were prepared at ambient temperature. An imine (**1c−1e**) (1 mmol) and a trace amount of dry CH_2Cl_2 (2−3 mg, as an internal reference for the ^{1}H NMR measurements) were dissolved in a premixed TFSA−TFA acid (ca 1.0 g, 0.1 mol, 100 equiv) under a dry nitrogen atmosphere in an AtmosBag (Aldrich). A 0.5-mL aliquot of the solution was transferred into an NMR tube, which was then sealed. A dozen sealed samples were prepared similarly. A set of the samples sealed in the NMR tubes, containing the same acid solution of the imine **1**, was immersed in a silicon oil (KF-96-10, Shin-Etsu, Japan) bath heated at a specified temperature (100, 110, and 120 °C). The temperature was controlled by a thermostat-controlled circulator (DCS-B3, Haake, Germany). The error in temperature is within ±0.1 °C. At regular intervals, a tube was withdrawn from the heating bath and cooled in an ice−water bath to quench the reaction, and the process of the reaction was monitored by measuring in the ^{1}H NMR spectrum at 30 °C (at 30 °C practically no cyclization reaction takes place for the imines **1c−1e**). The disappearance of the starting material was monitored in terms of the integrated signal intensity with respect to the signal of the acid as an integration reference with a GX 400-MHz NMR spectrometer. We also measured the rates of the formation of the product and confirmed that the rate of disappearance of the starting imine (for example **1c**) is identical with the rate of appearance of the cylized product.

The solution of **1a** in the TFSA−TFA acid was prepared as follows: to the weighed imine **1a** was added weighed TFA at ambient temperature in an AtmosBag (Aldrich). This TFA solution was cooled to 0 °C in an ice−water bath after a good solution had been obtained. To this TFA solution was added a precooled weighed aliquot of TFSA under a dry nitrogen atmosphere in an AtmosBag (Aldrich). A portion of the final solution was transferred to an NMR tube, which was sealed. The ^{1}H NMR spectra were recorded at a specified temperature. The NMR probe temperature was controlled to within ±0.1. Rates of cyclization of **1a** in TFA were measured at 50.0, 60.0, and 70.0 °C, and those of **1a** in 90% w/w TFSA−10% w/w TFA were obtained at 0.0, 10.0, and 20.0 °C. Temperatures were calibrated with ethylene glycol (in the range of 50.0−70.0 °C) and with methanol (in the range of 0.0−20.0 °C) as usual.[36] The disappearance of the starting material was monitored at regular intervals. We obtained good first-order kinetics in the cyclization reactions of the imines **1a** and **1c−1d**. Errors of rates, derived from the signal integration, are within ±2%.

Supporting Information Available: General experimental details and compound characterization data (6 pages). Ordering information is given on any current masthead page.

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