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Activation of Electrophilicity of Stable Y-Delocalized Carbamate Cations in Intramolecular Aromatic Substitution Reaction: Evidence for Formation of Diprotonated Carbamates Leading to Generation of Isocyanates

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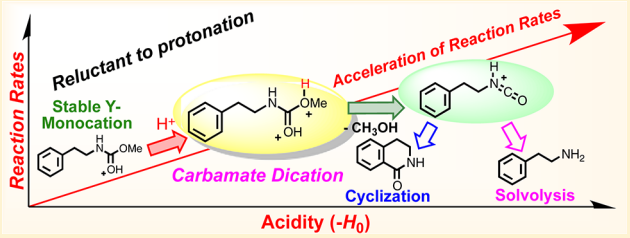
Supporting Information

ABSTRACT: Although cations with three heteroatoms, such as monoprotonated guanidine and urea, are stabilized by Y-shaped conjugation and such Y-conjugated cations are sufficiently basic to be further protonated (or protosolvated) to dications in strongly acid media, only O-monoprotonated species have been detected in the case of carbamates even in magic acid. We found that the trifluoromethanesulfonic acid-catalyzed cyclization of arylethylcarbamates proceeds to afford dihydroisoquinolones in high yield. In strong acids, methyl carbamates are fully O-monoprotonated, and these monocations do not undergo cyclization even under heating. But, as the acidity of the reaction medium is further increased, the cyclization reaction of methyl phenethylcarbamates starts to proceed as a first-order reaction, with a linear relationship between rate and acidity. The sign and magnitude of the entropy of activation $\Delta S^{\ddagger}$ were found to be similar to those of other $A_{Ac}1$ reactions. These results strongly support the idea that further protonation of the O-protonated carbamates is involved in the cyclization, but the concentration of the dications is very low and suggests that the rate-determining step is dissociation of methanol from the diprotonated carbamate to generate protonated isocyanate, which reacts with the aromatic ring. Therefore, O-protonated carbamates are weak bases in sharp contrast to other Y-shaped monocations.



INTRODUCTION

Y-Shaped Conjugate Cations. Cations with three heteroatoms, such as N-protonated guanidine and O-protonated urea, are stabilized by Y-shaped conjugation (Scheme 1).[1,2]

Such Y-conjugated cations are sufficiently basic to be further protonated (or protosolvated) in strongly acid media to afford dications. For example, guanidine (Scheme 1),[3,4] urea (Scheme 1),[3] thiourea,[5] allophanic acid (urea-1-carboxylate)[6] and tetrachloromethane[7] all afford discrete dications in strong acid. However, most Y-shaped cations, and even dications, do not show reactivity as electrophiles for aromatic compounds, and consequently there has been little exploration of the use of trisubstituted carbon electrophiles for aromatic functionalization. There have been several studies on the protonation of carbamates in acids. Armstrong et al. showed that the basicities of carbamates are intermediate between those of amides and esters[8] (H_0 values for half-protonation: for butylamide, $pK_{BH^+} = -1.19$; for ethyl acetate, $pK_{BH^+} = -6.93$). Thus, carbamates are essentially fully O-protonated in strong acid. Olah et al. attempted to observe diprotonated carbamic acid and ester derivatives (carbamates) in superacid media (FSO_3H in SO_2ClF) but could detect only O-monoprotonated carbamic acid and its ester derivatives even in magic acid (FSO_3H:SbF_5),[9] possibly because of the different basicities of amine nitrogen and ether oxygen atoms, notwithstanding the very similar structure of the putative Y-conjugated system (Scheme 1). Therefore, it has remained an open question whether diprotonated carbamates are really formed in strong acids.

Carbamates (carbamic acid esters) have been extensively used as protective groups in organic synthesis. However, chemical transformations of carbamates into other functionalities have been rather limited. Cyclizations of arylethylcarbamates to dihydroisoquinolinone derivatives in the presence of $POCl_3$,[10] Tf_2O,[11] PPA[12] and PCl_5[13] have been reported, but only in the context of total syntheses of a few natural products and medicinal compounds, particularly those containing an electron-rich dimethoxybenzene moiety. Recently, Wang et al improved the reaction conditions for cyclization of phenethylcarbamates by employing a combination of P_2O_5/$POCl_3$.[14] Using this modification, we were able to synthesize some dihydroisoquinolinone derivatives. However, the starting carbamates are restricted to N-methyl-substituted compounds: N-unsubstituted carbamates afforded the corresponding N−H dihydroisoquinolinone derivatives in low yields. The reaction mechanisms of these $POCl_3$-promoted reactions were not

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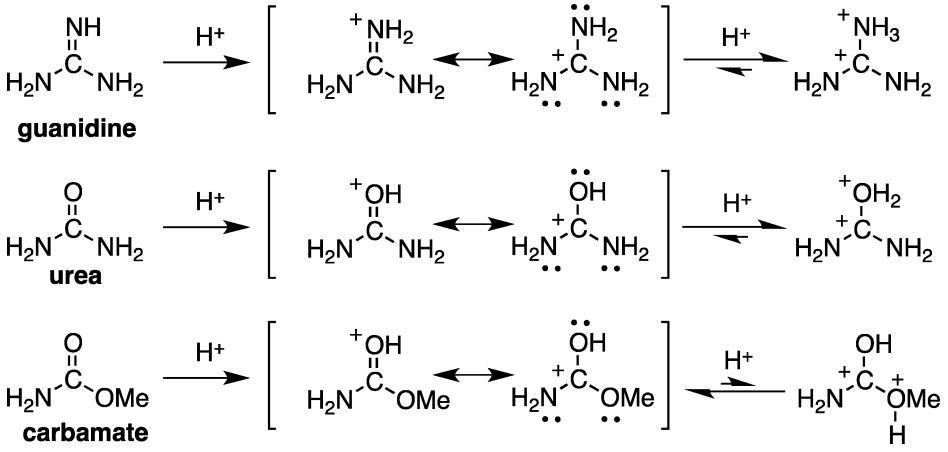
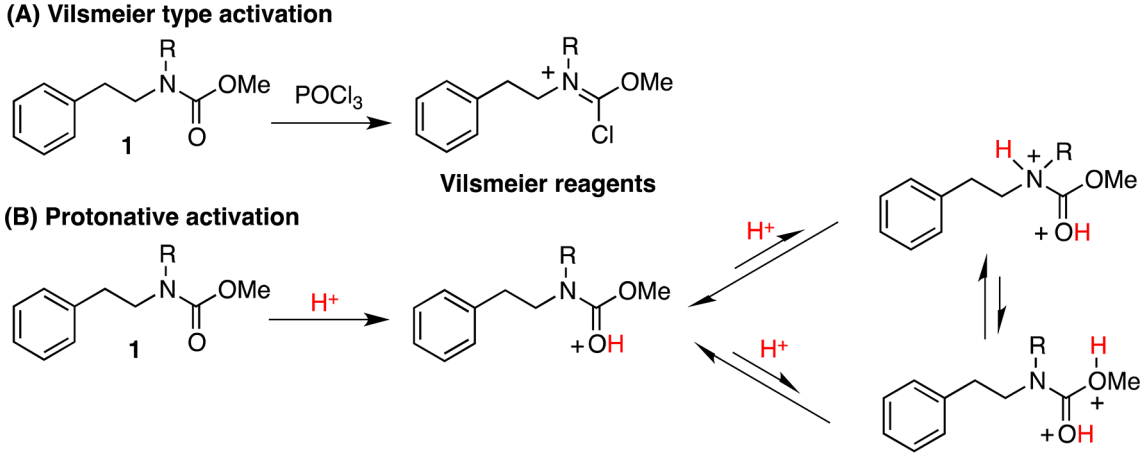
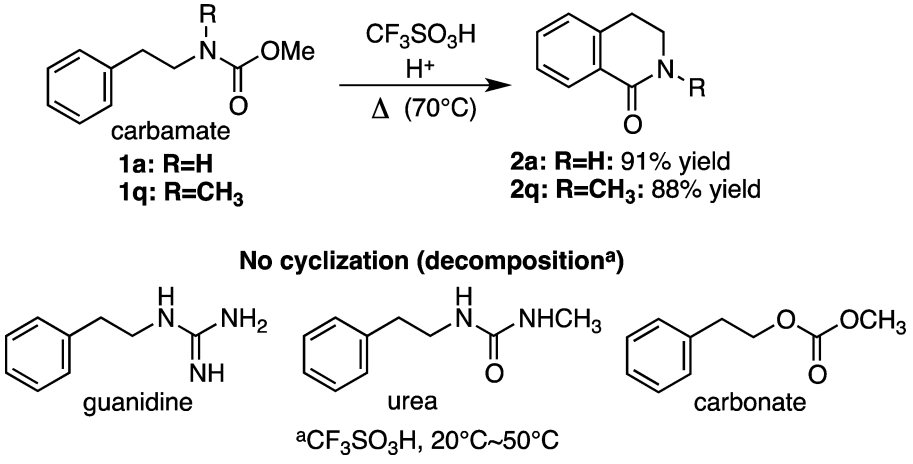
Scheme 1. Protonation of Y-Conjugated Cations



Scheme 2. Different Activation Pathways of Carbamates, Leading to Different Reactive Intermediates



Scheme 3. Aromatic Cyclization of Carbamates



studied in detail, but they are different from protonative activation, instead involving Vilsmeier-type reagents (Scheme 2A). This is consistent with the limited substrate range of these $POCl_3$-promoted reactions, which arises from the instability of the Vilsmeier reagents in the case of R = H (N−H). However, protonative activation is not subject to such limitations of carbamate substrate structure, that is, dependency of the reaction on the substituent (R) on the nitrogen atom (Scheme 2B).

Here, we found that trifluoromethanesulfonic acid (TFSA)-catalyzed cyclizations of arylethylcarbamates proceed to afford dihydroisoquinolone derivatives in high yields independently of N-substitution (Scheme 2). Based on our mechanistic studies, we propose that further protonated O-protonated carbamates, i.e., the dications, are indeed formed in a strong acid, though, in sharp contrast to other Y-shaped dications, the concentration of the formed diprotonated carbamates is too low for them to be observed directly, for example, by NMR spectroscopy.[9] Our

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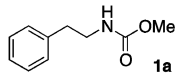
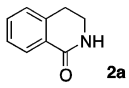
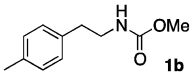
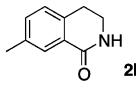
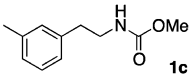
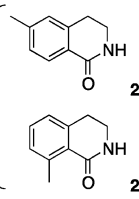
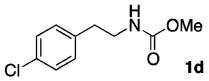
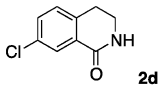
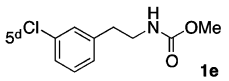
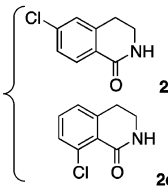
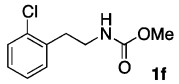
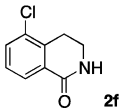
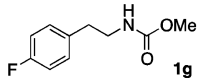
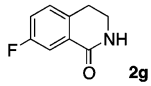
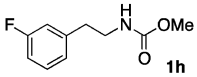
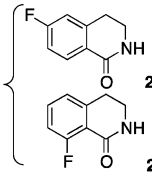
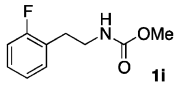
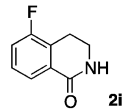
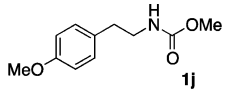
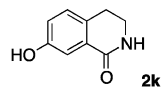
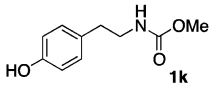
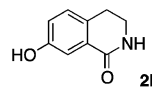
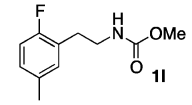
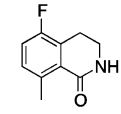
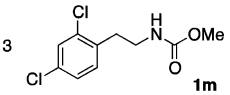
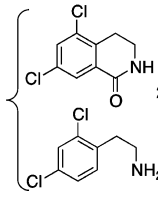
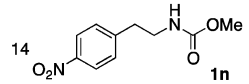
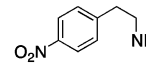
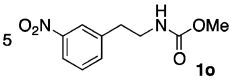
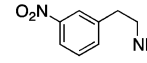
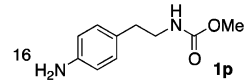
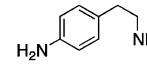
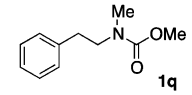
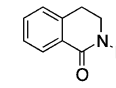
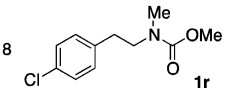
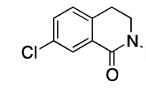
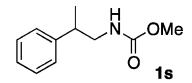
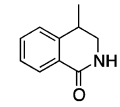
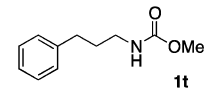
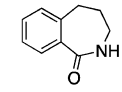
Table 1. Substrate Generality of the Reaction

Entry[a]	Substrate	Time (hr)	Product	Yield (%)[b]
1	 **1a**	24 24[c]	 **2a**	91 0[c]
2	 **1b**	16	 **2b**	97
3[d]	 **1c**	9	 **2c-1** **2c-2**	58 40
4	 **1d**	23 3[e] 3[f]	 **2d**	96 78[e] 0[f]
5[d]	 **1e**	16	 **2e-1** **2e-2**	70 28
6	 **1f**	24	 **2f**	98
7	 **1g**	28	 **2g**	91
8[d]	 **1h**	25	 **2h-1** **2h-2**	89 8
9	 **1i**	39	 **2i**	85
10	 **1j**	29	 **2k**	82
11	 **1k**	28	 **2k**	84
12	 **1l**	24	 **2l**	97
13	 **1m**	45	 **2m** **3m**	40 44
14	 **1n**	143	 **3n**	72
15	 **1o**	156	 **3o**	94
16	 **1p**	144	 **3p**	84
17	 **1q**	72	 **2q**	88
18	 **1r**	2[g]	 **2r**	78[g]
19	 **1s**	19	 **2s**	88
20	 **1t**	21	 **2t**	80
21	**1u**	48	**2u** **3u**	9 40

[a]Typical reaction conditions: A solution of the substrate (1.0 mmol) in TFSA (50 equiv) was heated at 70 °C for a specified time. [b]Isolation yield. [c]With 50 equiv of TFA instead of TFSA. Recovery **1a** was obtained in 90% yield. [d]The product ratio was determined by ^{1}H NMR spectroscopy. [e]With 50 equiv of TFSA, under microwave heating at 80 °C. [f]With 50 equiv of TFA instead of TFSA, under microwave heating at 80 °C. Recovery **1d** was obtained in 96% yield. [g]With 50 equiv of TFSA, under microwave heating at 100 °C.

conclusion is consistent with the previous observations by Olah's group[9] and also provides a rational interpretation of the previous results. We suggest that the diprotonated carbamate leads to generation of more reactive protonated isocyanates via dissociation of methanol, and this process is involved in the rate-determining step of the strong Brønsted acid-catalyzed aromatic cyclization or amine formation reactions of arylethylcarbamates. The idea that the diprotonated carbamates are formed at very low concentrations, too low to be observed directly, is also supported by the calculated differences of proton affinities. The present work has also validated the concept of activation of electrophiles: facile *in situ* selective cleavage of a carbon−heteroatom bond in a strongly acidic environment converts stable Y-conjugated cations substituted with different heteroatoms into activated carbon electrophiles

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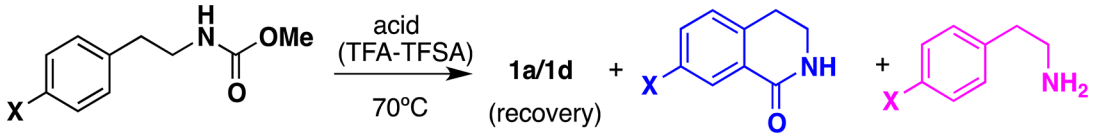
Table 2. Reaction of 1a and 1d in Media of Various Acidity Levels



1a (X = H)
1d (X = Cl)

2a (X = H)
2d (X = Cl)

3a (X = H)
3d (X = Cl)

entry	substrate	ratio of the acids (TFSA:TFA, 50 equiv)	$-H_0$	time (h)	recovery (**1**, %)	cyclization (**2**, %)	amine (**3**, %)
1	**1a**	0:100	2.7	3.5	89	0	0
2	**1a**	5:95	8.9	3.5	86	4	0
3	**1a**	91:9	13.0	3.5	42	53	0
4	**1a**	100:0	14.1	3.5	42	56	0
5	**1a**	100:0	14.1	24	0	91	0
6	**1d**	0:100	2.7	23	98	0	0
7	**1d**	5:95	8.9	23	40	0	54
8	**1d**	91:9	13.0	23	0	84	15
9	**1d**	100:0	14.1	23	0	96	0

(such as protonated isocyanates) with potential for aromatic functionalization.

RESULTS AND DISCUSSION

Reaction of Arylethylcarbamates in Superacid Media. Trifluoromethanesulfonic acid catalyzed the cyclization reaction of methyl phenethylcarbamate (**1a**) to give dihydroisoquinolone (**2a**) in high yield (Scheme 3 and Table 1). This is in sharp contrast to the inertness of the related guanidine, urea and carbonate compounds: only decomposition occurred without formation of cyclization products (Scheme 3). The reaction of the carbamate **1a** required heating at 70 °C and very high acidity, because **1a** did not afford **2a** in TFA (trifluoroacetic acid) (50 equiv) even at 70 °C (Table 1, entry 1). The N-methyl carbamate (**1q**) also provided the cyclization product (**2q**) in high yield under similar reaction conditions (Scheme 3 and Table 1).

An examination of substrate generality indicated that the present reaction is suitable for high-yield synthesis of dihydroisoquinolone derivatives, irrespective of N-substitution of the carbamates (Table 1 and Scheme 3). In the case of the cyclization reaction, substituents bearing a methyl (entries 2, 3), chloro (entries 4–6), or fluoro group (entries 7–9) gave cyclized products **2a–i** in high yields (83–98%).

When the aromatic ring is *meta*-substituted (entries 3, 5, 8), two regioisomers of the cyclized products were obtained. *Para*-methoxy-substituted substrate **1j** (entry 10) afforded the phenol derivative, which is the same as the product obtained in the reaction of *para*-hydroxy-substituted **1k** (entry 11). A plausible mechanism involves initial transformation of the methoxy group to a hydroxyl group, followed by cyclization reaction.[15] When the methyl group was introduced on the carbamate-nitrogen atom (entries 17, 18) or the benzyl carbon atom (entry 19), the cyclization proceeded in high yield. Phenylpropylcarbamate **1t** also gave the seven-membered cyclized product in high yield (entry 20), but in the case of **1u**, bearing a fluoro substituent, amine formation (vide infra) predominated over the cyclization (entry 21). Heating of the TFSA solution of **1d** under microwave irradiation at 80 °C accelerated the reaction very efficiently (78% yield, after 3 h). On the other hand, microwave heating of a TFA solution of **1d** at 80 °C did not promote the cyclization reaction, and the carbamate was recovered in 96% yield.

It was also found that when an electron-withdrawing substituent is present on the benzene ring, the cyclization is retarded, and the corresponding amine is formed instead (Table 1). An NMR study of the reaction solution in acids showed that the amine product was formed directly from the carbamate in the acidic medium, that is, before aqueous workup; thus, transformation of the carbamates to the amines occurs without the involvement of water, instead involving reaction of the intermediate (*vide infra*) with conjugate bases of acids such as $CF_3SO_3^-$ and/or $CF_3CO_2^-$. In the case of the *o,p*-dichlorophenyl-substituted carbamate (entry 13), **1m** gave the cyclized product **2m** together with the amine product **3m**. When electron-withdrawing substituents such as a nitro group (entries 14, 15) were present, the cyclization reaction did not proceed, but fragmentation of the carbamate occurred to give amine. Interestingly, the substrate bearing an amino group **1p** (entry 16) did not cyclize, despite the strong electron-donating ability of the amino group. That is probably because the amino group is fully protonated in the superacid medium, forming an ammonium group ($-NH_3^+$), which is a strongly electron-withdrawing group equivalent to a nitro group.

Acidity Dependence of the Reactions. The reactions showed apparent acidity dependence. To investigate the effect of the acidity of the medium on this reaction, we used a mixed acid of TFSA and TFA (50 equiv). The acidity function (H_0) of mixtures of TFSA and TFA has been reported in detail,[16] and such mixtures are frequently employed to investigate the acidity dependence of organic reactions.[17] In this experiment, the reactions were conducted at 70 °C, and the yields of the substrate **1** (recovery), cyclized product **2** and amine product **3** were examined in various acidic media (Table 2).

For substrate **1a**, recovered **1a** or/and cyclized product **2a** were obtained in media at four levels of acidity (entries 1–4). In each case, the reaction solution was heated at 70 °C for 3.5 h and quenched with ice–water. No cyclized product was obtained in TFA ($-H_0$ = 2.7, entry 1). When the acidity of the system was increased by addition of TFSA, the cyclization reaction began to proceed. In TFSA: TFA = 5:95 (w/w)($-H_0$ = 8.9, entry 2), the cyclization reaction proceeded only slightly, but at $-H_0$ = 13.0, the yield of the cyclized product reached 53%, and prolonged reaction (24 h) in TFSA ($-H_0$ = 14.1, entry 5) resulted in 91% yield. For substrate **1d**, a similar acidity dependence was observed: the cyclization reaction did not

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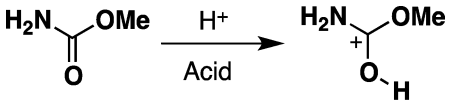
proceed in TFA ($-H_0$ = 2.7, entry 6) or in TFSA:TFA = 5:95 (w/w)($-H_0$ = 8.9, entry 7). In the latter case, the amine product **3d** was obtained in 54% yield after 23 h. As the acidity of the system was further increased by addition of TFSA, the cyclized product **2d** began to appear (entry 8). In TFSA ($-H_0$ = 14.1, entry 9), only the cyclized product was produced in high yield and no amine formation was observed. Thus, the reaction rate and the product yield (**2**+**3**) both increased with increasing acidity of the reaction medium.

Protonation of Carbamates. We evaluated the basicity of the carbamates in the present acid system. Because phenylethylcarbamate (**1a**) has several conformers, we chose the simplest carbamate, methyl carbamate **1v**, in order to simplify the NMR spectra. In the substituted carbamate (**1a**), the carbamate functionality is segregated from the phenyl group, so the nonaromatic carbamate (**1v**) is expected to be suitable as a minimal model for protonation study.

We monitored the protonation of methyl carbamate **1v** by following the ^{13}C NMR chemical shifts in TFSA-TFA at the acidity values of $-H_0$ = 2.7, 10.9, and 14.1 (Table 3). In TFA,

Table 3. Monitoring of Protonation of Methyl Carbamate 1v



1v **1v-H$^+$**

$-H_0$	^{13}C NMR chemical shift (δ)[a]	acid
15	162.7, 59.5	HSO_3F in SO_2ClF[b]
14.1	163.5, 59.5	TFSA[c]
10.9	163.8, 58.7	TFSA:TFA = 1:3 (w/w)[c]
2.7	162.1, 53.2	TFA[c]
	157.9, 52.3	$CDCl_3$[c]

[a]$CHCl_3$ in acetone-d_6 was used as an external calibrant (79.2 ppm). [b]Reference 9; observed at −78 °C. [c]Observed at 27 °C.

O-monoprotonation occurs at least partially, as judged from a comparison of the chemical shifts with those in $CDCl_3$. In acid stronger than $-H_0$ = 10.9, O-protonation of the carbamate was complete, resulting in ^{13}C chemical shifts close to those observed in FSO_3H/SO_2ClF solution.

Kinetic Studies of Superacid-Catalyzed Cyclization Reaction/Amine Formation. To clarify the mechanism of the cyclization, we measured the rate constants of cyclization and amine formation of the arylethylcarbamates, **1a**, **1b**, **1d**, **1g**, **1p** and nonaromatic **1w** in strong acids of defined acidity (Table 4). The reactions were carried out in the presence of 200 equiv. of the acid in NMR tubes, with heating at 70 °C, and the concentration of the starting material, arylethylcarbamate **1**, was monitored in terms of the integration values in the ^1H NMR spectra at 25 °C (at this temperature the reaction was slow enough to be quenched) (for details, see Supporting Information). All of the reactions were found to follow first-order kinetics (r > 0.99) (Figure 1).

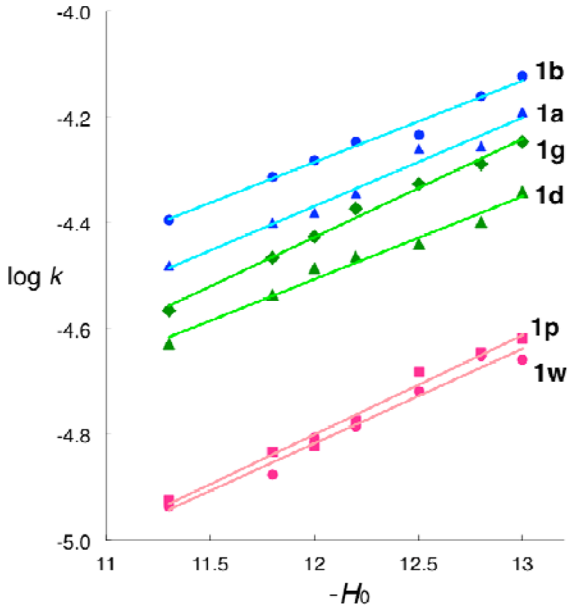


Figure 1. Acidity-rate profiles of cyclization reaction/amine formation of arylethylcarbamates. Slope and correlation coefficient (r) values are as follows: **1a**, slope = 0.17, r = 0.99; **1b**, slope = 0.15, r = 0.99; **1d**, slope = 0.16, r = 0.98; **1g**, slope = 0.19, r = 0.99; **1p**, slope = 0.19, r = 0.99; **1w**, slope = 0.18, r = 0.99.

The order of the rate constants was **1b** > **1a** > **1g** > **1d** > **1p** > **1w**. In the media of acidity between $-H_0$ = 11.3 and 13.0, **1a** and **1b** underwent only the cyclization reaction, whereas **1p** and **1w** afforded only the amine **3p** and **3w**, respectively (Scheme 4). Compounds **1d** and **1g** underwent both cyclization and amine formation. As shown in Figure 1, the reaction rates of **1a** and **1b** are correlated to the acidity of the media. According to the rate-acidity relationship (Zucker-Hammett hypothesis[18]), a linear dependency of the rate on the acidity can be interpreted in terms of the postulate that a cationic species formed by protonation is the reactive species and such protonation is involved in the rate-determining step of the reaction. Also, the concentration of the protonated species is low. This idea has been applied to several strong acid-catalyzed reactions.[19]

Table 4. Pseudo First-order Rate Constants for Cyclization Reaction/Amine Formation at Various Acidity Levels

	1a → **2a**	**1b** → **2b**	**1d** → **2d**/**3d**		**1g** → **2g**/**3g**		**1p** → **3p**	**1w** → **3w**
$-H_0$	10^5k (s^{-1})	10^5k (s^{-1})	10^5k (s^{-1})	(**2d**: **3d**)[a]	10^5k (s^{-1})	(**2g**:**3g**)[a]	10^5k (s^{-1})	10^5k (s^{-1})
11.3	3.31	4.03	2.35	49:51	2.71	48:52	1.19	1.16
11.8	3.99	4.87	2.91	46:54	3.42	68:32	1.47	1.33
12.0	4.15	5.23	3.26	71:29	3.75	68:32	1.51	1.56
12.2	4.53	5.67	3.43	87:13	4.23	82:18	1.68	1.64
12.5	5.48	5.84	3.63	85:15	4.71	89:11	2.08	1.91
12.8	5.54	6.91	4.00	94:6	5.14	94:6	2.26	2.23
13.0	6.45	7.54	4.55	97:3	5.66	96:4	2.40	2.19

[a]Product distributions: the ratio was determined by ^1H-NMR spectroscopy.

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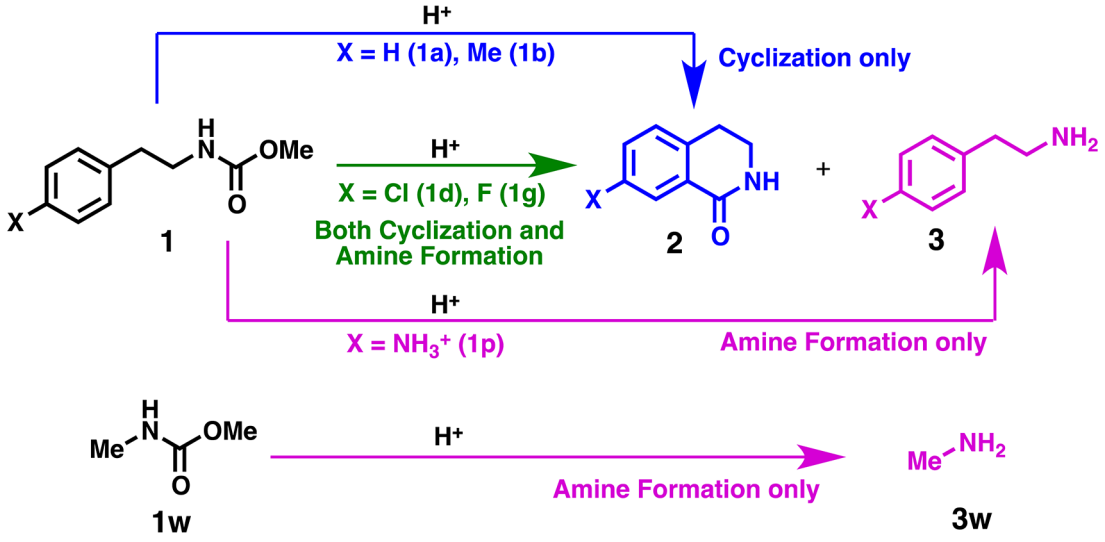
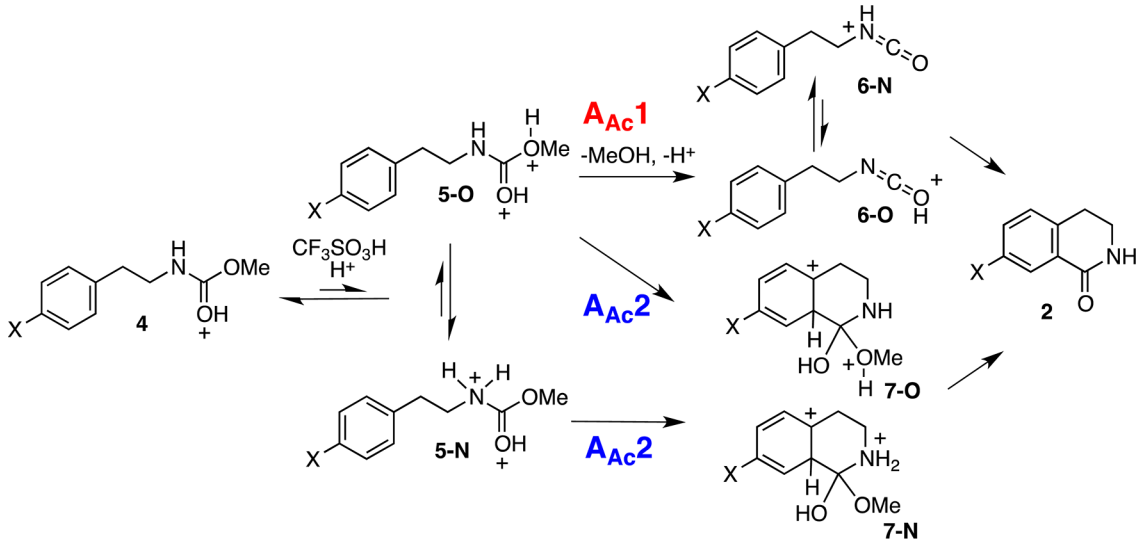
Scheme 4. Two Reaction Products, Depending on the Aromatic Substituent



Scheme 5. $A_{Ac}1$ and $A_{Ac}2$ Mechanisms for Cyclization of Diprotonated Carbamates



The estimated pK_{BH}^{+} value of carbamates is larger than −11.3 (at around −3 to −7), and substrate **1** is fully monoprotonated. Therefore, the observed correlation between the rate and the acidity (Figure 1) indicates that O-monoprotonated carbamate is not a reactive intermediate in the cyclization reactions observed in the acid region between $-H_0$ = 11.3 and 13.0, and suggests that further protonation is involved in the rate-determining step of the cyclization. A similar idea can be applied to amine formation of **3p** and **3w**, that is, O-monoprotonated carbamate is not a reactive intermediate for amine formation in the acid region between $-H_0$ = 11.3 and 13.0, and further protonation is suggested to be involved in the rate-determining step of amine formation.

Therefore, our kinetic data provide supporting evidence for the generation of diprotonated carbamates in strong acid, but at a concentration that is too low to be directly observed. Reluctance to undergo the second protonation is also consistent with the observed small effect of H_0 on the reaction rates (Figure 1). Therefore, the present result is consistent with Olah's report that only O-monoprotonated carbamic acid and its ester derivatives could be detected by NMR spectroscopy, even in magic acid.[9]

The observed relationships between acidity and rate are similar for these six substrates, that is, the relationships are linear with similar slopes (the reaction rates of **1d** and **1g** are the overall rates for formation of a mixture of the cyclization and amine products). Based on these results, it is reasonable to assume that the rate-determining step of these two types of reactions, that is, cyclization reaction and amine formation, is common.[20] Hydrolysis of carbamates in sulfuric acid to give amines has been studied previously and the mechanism was proposed to involve both $A_{Ac}1$ (production of isocyanate) and $A_{Ac}2$ (nucleophilic attack at carbonyl carbon by water) mechanisms.[21] Therefore, the present formation of cyclized product and amine can be postulated to involve the $A_{Ac}1$ (to form isocyanate **6**) or $A_{Ac}2$ (to form a tetrahedral intermediate **7**) mechanism (Scheme 5). The $A_{Ac}1$ mechanism was shown to be predominant in the high acidity region in the case of hydrolysis of carbamates in sulfuric acid to give amines.[21,22]

Substituent Effect on the Reaction Rates: Hammett Plot. The effects of aromatic substituents on the reaction rate

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were also studied by means of rate measurements with ^{1}H NMR spectroscopy (Table 5, Figure 2). The unsubstituted

Table 5. Substituent Effects: Pseudo-first-order Rate Constants for the Reactions of Arylethylcarbamates at $-H_0$ = 11.3 (at 70 °C)

substituent	substrate	σ	10^5 k (s^{-1})	product ratio (**2**:**3**)
p-Me	**1b**	−0.14	4.03	100:0
m-Me	**1c**	−0.06	3.90	100:0
H	**1a**	0	3.31	100:0
p-F	**1g**	0.06	2.71	48:52
p-Cl	**1d**	0.22	2.35	49:51[a]
m-F	**1h**	0.34	2.15	96:4
m-Cl	**1e**	0.37	2.12	92:8
p-NH_3^+	**1p**	0.60	1.19	0:100
m-NO_2	**1o**	0.71	0.970	0:100
p-NO_2	**1n**	0.78	0.892	0:100
m-NH_3^+	**1x**	0.86	0.795	0:100

[a]The product ratio (**2d**/**3d**) did not change significantly at different reaction temperatures (**2d**:**3d** = 41:59 at 65 °C; 41:59 at 80 °C).

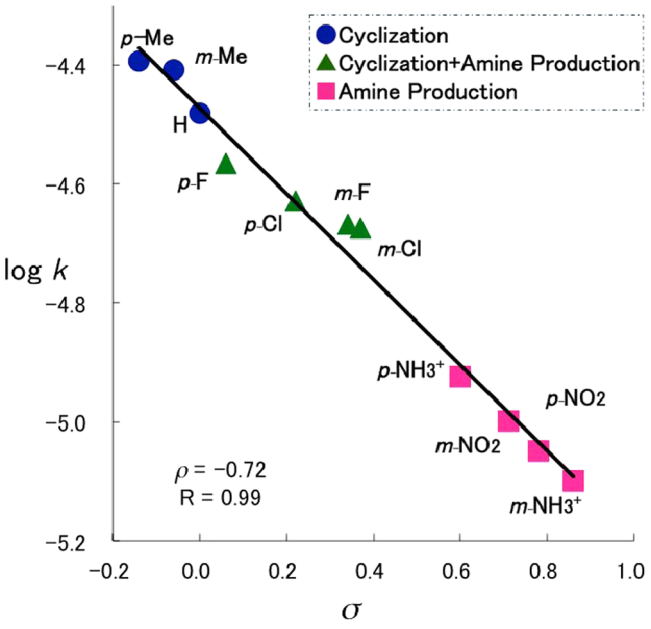


Figure 2. Hammett plot of reactions of carbamates.

substrate **1a** and the *p*-Me (**1b**), *m*-Me (**1c**), *p*-Cl (**1d**), *m*-Cl (**1e**), *p*-F (**1g**), *m*-F (**1h**), *p*-NO_2 (**1n**), *m*-NO_2 (**1o**), *p*-NH_3^+ (**1p**), and *m*-NH_3^+ (**1x**) substituted substrates were subjected to the reaction at 70 °C in the presence of a large excess of TFSA:TFA (43:57 (w/w), $-H_0$ = 11.3), and consumption of the starting materials was monitored in terms of the ^{1}H NMR integration values.

In this acid medium, substrates bearing a methyl group (**1b** and **1c**) and unsubstituted substrate **1a** underwent only the cyclization reaction (Scheme 4). Substrates bearing a halogen group (**1d**, **e**, **g** and **h**) underwent both cyclization reaction and amine formation. Substrates bearing a strong electron-withdrawing group, **1n**−**p** and **1x**, underwent only amine formation. The observed linear correlation in the Hammett plot (Figure 2) strongly supports the idea that the rate-determining step of these two types of reactions, cyclization reaction and amine formation, is common (see Scheme 6). In the case of **1d**, the product ratio (**2d**/**3d**) did not change significantly at three different reaction temperatures (**2d**:**3d** = 41:59 at 65 °C, 49:51 at 70 °C; 41:59 at 80 °C) (see Table 5 footnote).

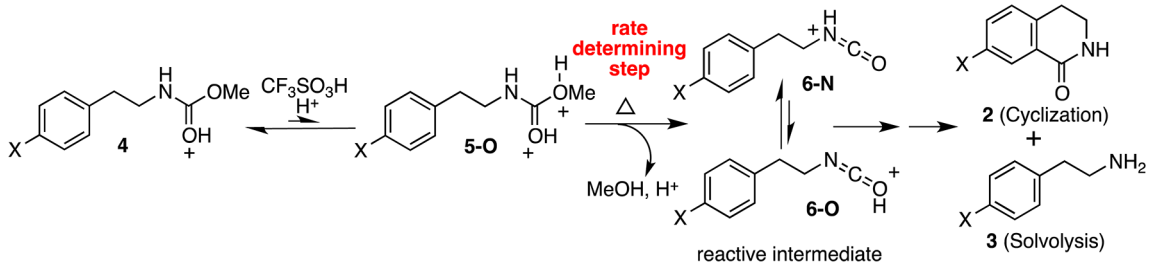
Thermodynamic Study of the Dissociation of Carbamates in Strong Acid. The activation parameters for the cyclization/amine formation of **1a**, **1b**, **1d** and **1p** were obtained from the rate constants of cyclization at five temperatures (60, 65, 70, 75, and 80 °C) (Table 6). The

Table 6. Rate Constants and Thermodynamic Parameters for the Cyclization Reaction (1a, 1b, and 1d) and Amine Formation Reaction (1p) in TFSA

temp (°C)	10^5k (s^{-1})	substrate	$\Delta H^{\ddagger}$ (kJ mol^{-1})[a]	$\Delta G^{\ddagger}$ (70 °C) (kJ mol^{-1})[b]	$\Delta S^{\ddagger}$ (J mol^{-1} K^{-1})[c]
80.0	22.9				
75.0	13.9				
70.0	7.82	**1a**	121.6	111.6	28.9
65.0	3.95				
60.0	1.80				
80.0	24.6				
75.0	15.1				
70.0	7.96	**1b**	121.4	111.5	28.8
65.0	4.24				
60.0	1.94				
80.0	17.6				
75.0	9.91				
70.0	5.35	**1d**	121.1	112.5	24.9
65.0	2.82				
60.0	1.39				
80.0	9.13				
75.0	4.38				
70.0	2.57	**1p**	120.2	114.6	16.4
65.0	1.44				
60.0	0.688				

[a]Errors: ±3.1 kJ mol^{-1}. [b]Errors: ±0.1 kJ mol^{-1}. [c]Errors: ±9.1 J mol^{-1} K^{-1} (343.15 K).

Scheme 6. Involvement of Diprotonation of Arylethylcarbamates in Strong Acids, Leading to Generation of Isocyanate Species



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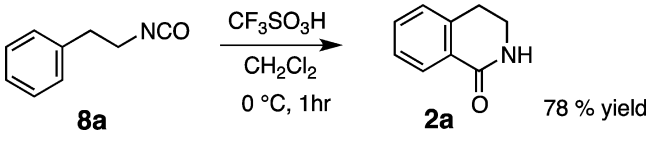
entropies of activation of these four compounds are consistently positive, which is considerably different from the case of intramolecular aromatic electrophilic substitution reactions in strong acid media, for example, Pictet-Spengler reaction of *N*-methylene-2-phenylethanamines in TFSA ($\Delta S^{\ddagger}$ = −141 J mol^{-1} K^{-1}).[23]

The observed positive values of $\Delta S^{\ddagger}$ are consistent with a dissociative nature of the transition state, that is, an $A_{Ac}1$ mechanism (Scheme 5).[24] Therefore, the rate-determining step of this reaction likely involves generation of the isocyanate intermediate **6-N** or **6-O** through cleavage of the C−O bond of the diprotonated methyl carbamate **5-O** (Scheme 6). This mechanism is similar to C−O (ether) bond cleavage of ester compounds[25] and C−N bond cleavage of amide compounds[26] through dicationic species.

After generation of the protonated isocyanate intermediate (**6-N** or **6-O**),[27] bifurcation of the reaction pathway takes place, depending on the aromatic nucleophilicity and concentrations of conjugate bases, and cyclized products (**2**) and amines (**3**) are generated (Scheme 6).[28] Transformation of isocyanates to amines through the nucleophilic addition of oxygen bases (such as solvents and conjugate bases) has been well documented.[29] Conversely, dependence of the amine formation on the aromatic substituent (X in Scheme 6, i.e., aromatic nucleophilicity) is suggestive of the intervention of the isocyanate intermediate (Tables 1 and 2), not direct C−N bond cleavage of N,O-diprotonated carbamate (**5-N**, Scheme 5). If the amine were formed by direct C−N bond cleavage, the amine would be formed from all carbamate substrates shown in Table 1, that is, it would be independent of the aromatic substituent X, distal from the carbamate functionality (see Scheme 8 in the section "Computational study"). In the cases of the NH_2 substituents (**1p** and **1x**), tricationic may be involved in the amine formation reaction (X = NH_3^+ in Scheme 6).

When a solution of phenethylisocyanate **8a** in CH_2Cl_2 was added to 200 equiv of TFSA at 0 °C and the solution was quenched with ice water after 1 h, we obtained the cyclized product **2a** in 78% yield (Scheme 7). In the absence of the acid

Scheme 7. Strong Acid-catalyzed Cyclization of Phenylethylisocyanate



(i.e., in only CH_2Cl_2) or in TFA, phenethylisocyanate **8a** did not provide the cyclized product at all. This finding that the cyclization reaction of phenethylisocyanate **8a** requires a strong acid catalyst and is much faster than that of phenethylcarbamate **1a** is consistent with the idea that the reactive species is the protonated isocyanate, not protonated carbamate. Thus, it is reasonable to consider that the concentration of the isocyanate, generated from the carbamate in the acid, is very low. The Friedel−Crafts type reaction of isocyanate with an aromatic ring has been reported.[30]

Computational Study. Since the novelty of the system lies in the roles of the diprotonated intermediates, it would be interesting to calculate the relative stabilities and bond strengths of the proposed intermediates. Calculations were carried out using the Gaussian03 and 09 suites of programs.[31] All the structures were fully optimized with B3LYP/6-31G** and MP2/6-31G**, and the energy calculations were performed with M06−2X/6-311++G(d,p) and MP4/6-311++G(d,p) on the basis of the optimized structures (see Supporting Information). We used methyl N-methylcarbamate (**1w**) as a model carbamate, since it was the smallest real substrate studied in the experiments (Scheme 4 and Table 4). In the case of O-protonated carbamate, the second protonation can occur on any of the three heteroatoms to produce three types of dications (**5w-N**, **5w-O1**, **5w-O2**, Scheme 8 and Table S2, Supporting Information). We calculated all possible conformers with respect to each of the dications (data not shown). The most stable conformer in each case and the relative energies are shown in Scheme 8. The N,O-dication (**5w-N**) is the most stable, while the O^1,O^2-dication (**5w-O1**) is second most stable, and the energy difference is 61.2 kJ/mol (48.7 kJ/mol) (Scheme 8B). This result is consistent with previous calculations.[9] The O^1,O^1-dication (**5w-O2**) was the most unstable. Thus, the nitrogen atom of O-protonated carbamate (**4w**) is the thermodynamic site of protonation, and O(ether)-protonation is in equilibrium with the N-protonation as a minor contributor (see Scheme 8C). Intriguingly, the HOMO of the O-protonated monocation (**4w**) has a large orbital coefficient distributed on the ether oxygen atom, not on the nitrogen atom (HOMO-2) (Scheme 8A, natural bond orbital analysis[32]). Thus, O(ether)-protonation of **4w** to yield dication **5w-O1** can be kinetically favored.

The relative easiness of bond dissociation of the diprotonated carbamates was also evaluated computationally (Scheme 8B and Table S3, Supporting Information). Among several possible modes of bond cleavage, C−O bond dissociation of the O^1,O^2-diprotonated cation **5w-O1** with elimination of methanol to generate N-protonated isocyanate **6w-N** is the lowest energy process, while C−N bond dissociation of N,O-diprotonated carbamate (**5w-N**) with elimination of methylamine is highly unfavorable, with an energy difference of 137.5 (129.6) kJ/mol as compared to the former process. While the N,O-diprotonated carbamate (**5w-N**) is more stable than the O^1,O^2-diprotonated cation (**5w-O1**), the C−O bond of the dication **5w-O1** is more labile than the C−N bond of the dication **5w-N**. Thus, C−O bond cleavage of the O^1,O^2-diprotonated cation **5w-O1** to give the protonated isocyanate (**6**) is likely to occur, in accordance with the experimentally based proposal (Scheme 6). Furthermore, these calculations exclude the possibility that C−N bond cleavage of the diprotonated carbamate (**5w-N**) would directly give the amine product (**3w**), because of the very high energy requirement of C−N bond dissociation, as described above. This supports the experimentally based proposal that the amine is formed through the intervention of the isocyanate (Scheme 6). Calculations of isocyanate (**6w-N**) formation through C−N bond dissociation of diprotonated urea (**12-N**) is also highly energy-demanding (Scheme 8B),[33] with an energy difference of 155.8 (147.7) kJ/mol as compared to the reference C−O bond cleavage of the diprotonated carbamates. This is consistent with the experimental finding of the inertness of the urea derivative to aromatic cyclization under similar conditions (Scheme 3).

Upon C−O bond cleavage of the O^1,O^2-protonated carbamate (**5w-O1**), two forms of protonated isocyanates, N-protonated (**6w-N**) and O-protonated (**6w-O**) species, are possible (Schemes 6 and 8), and they may be in equilibrium through deprotonation/protonation processes. Computationally, the N-protonated isocyanate (**6w-N**) is more stable than the O-protonated counterpart (**6w-O**), with an energy

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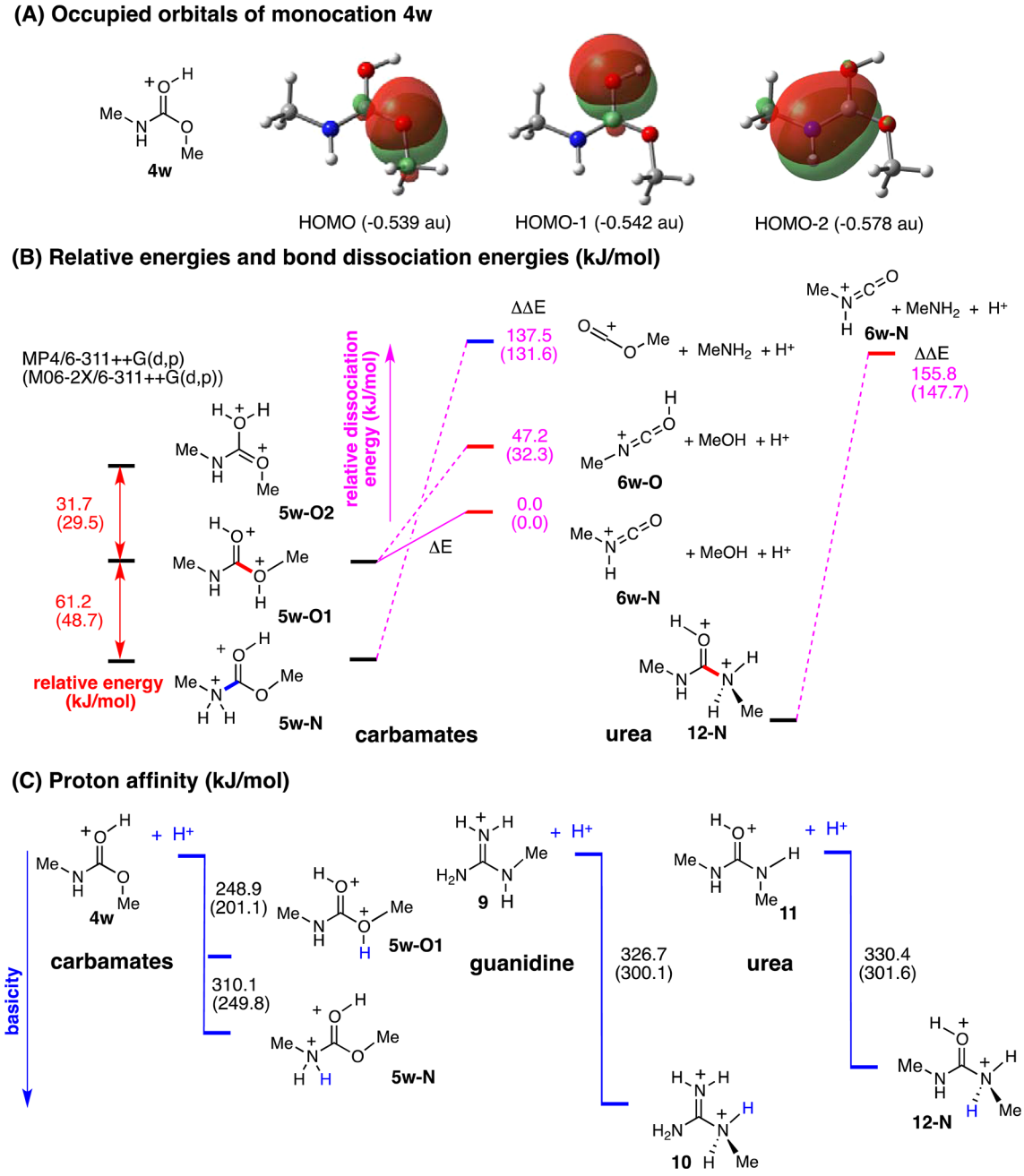
Scheme 8. Computed Properties of Protonated Species



difference of 47.2 (32.3) kJ/mol (see Table S4, Supporting Information). Furthermore, the LUMO of N-protonated species **6w-N** has orbital coefficients localized on the C═O group and the LUMO level (−0.253 au) is energetically low-lying compared to that of **6w-O** (−0.186 au) (see Figure S2). In this context, the N-protonated isocyanate (**6w-N**) is more likely to be formed and to work as a reactive intermediate than the O-protonated species (**6w-O**) (Scheme 6).

The calculated proton affinities are also consistent with less basic nature of O-protonated carbamates (monocation) as compared with other Y-conjugated monocations, such as N-protonated guanidine (guanidinium cation) and O-protonated urea (Scheme 8C and Table S5, Supporting Information). The proton affinities of O-protonated methyl *N*-methycarbamate (**4w**) with respect to N-protonation (to **5w-N**) and O-protonation (to **5w-O1**) were calculated. They were found to be smaller than those of N-protonation of *N*-methylguanidinium cation (**7** to **9**) and N-protonation of O-protonated *N*,*N*-dimethylurea (**10** to **11-N**). Thus, the order of basicity is predicted to be as follows: N-methylguanidinium cation (**9**) = O-protonated *N*,*N*-dimethylurea (**11**) > O-protonated methyl *N*-methycarbamate (**4w**) (as an N-base) > O-protonated methyl *N*-methycarbamate (**4w**) (as a O-base). This order is again consistent with our postulate that monoprotonated carbamates showed reluctance to undergo second protonation, in contrast to guanidines and ureas (Scheme 1).[3,4,9]

■ CONCLUSION

In summary, we found that strong Brønsted acid catalyzed the cyclization reaction of aromatic ring-containing methyl carbamates (arylethylcarbamates) to afford dihydroisoquinolone derivatives in high yield. This cyclization is promoted by

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protonation of carbamates and is not influenced by the substituent group on the nitrogen atom, that is, N−H and N−CH_3 do not affect the reaction yields (Scheme 3 and Table 1). Thus, the present reactions are different from the reported Vilsmeier-type cyclization reactions (Scheme 2). When the aromatic ring carried an electron-withdrawing group, cyclization did not proceed and amine formation occurred exclusively. While diprotonated carbamates have not been directly detected in previous studies, and their existence has been questioned, these chemical reactions provide clear evidence for the formation of diprotonated carbamates in strong acid, though in very low concentrations. In strong acid, carbamates are O-protonated and generate stable Y-shaped conjugated monocations. But, these cations showed little electrophilicity toward aromatic compounds. The acidity-rate relationship in strongly acid regions was found to be linear, supporting the idea that dicationic intermediates are involved in the activation of carbamates in superacid media. This kinetic relationship also indicated that the concentration of the dications formed remains low even in strong acid. Therefore, diprotonation of the carbamates does occur, but is a low-probability event even in strong acid, in sharp contrast to other Y-conjugated cations (Scheme 1). The present results are thus consistent with the previous observation that only O-monoprotonated carbamic acid and its ester derivatives could be detected by NMR spectroscopy, even in magic acid.[9] Calculated differences in the proton affinities of Y-conjugate cations are also consistent with this idea.

The acidity-rate relationship and the Hammett plot suggested that the cyclization reaction and amine formation have a common rate-determining step, that is, they occur via generation of isocyanate. Our thermodynamic studies also supported the idea that the rate-determining step is C−O bond dissociation of doubly protonated carbamate to generate isocyanate. The observed selective bond dissociation is also consistent with the computed bond dissociation energies. The present work has also validated the concept of activation of electrophiles:[21,22] facile *in situ* selective cleavage of a carbon-heteroatom bond in a strongly acidic environment converts stable Y-conjugated cations substituted with different heteroatoms into activated carbon electrophiles (such as protonated isocyanates) with potential for high-yield aromatic functionalization.

EXPERIMENTAL SECTION

General Methods. Melting points were determined without correction. In the ^{1}H (400 MHz) and ^{13}C (100 MHz) NMR spectra chemical shifts were calibrated with 1% tetramethylsilane as an internal standard or with the solvent peak and are shown in ppm (δ) values, and coupling constants are shown in hertz (Hz). The following abbreviations are used: s = singlet, d = doublet, t = triplet, q = quartet, dd = double doublet, dt = double triplet, dq = double quartet, h = hextet, m = multiplet, and brs = broad singlet. Electron spray ionization time-of-flight mass spectra (ESI-TOF MS) were recorded to give low-resolution mass spectra (LRMS) and high-resolution mass spectra (HRMS).

Synthesis of Methyl 2-Aryl-ethyl/3-Aryl-propyl-carbamate. *A Typical Procedure: Synthesis of Phenetylcarbamic Acid Methyl Ester* ***1a.*** To a solution of phenethylamine (1.0 mL, 8.0 mmol) and triethylamine (1.2 mL, 8.8 mmol, 1.1 equiv) in DMF (30 mL), methyl chloroformate (0.68 mL, 8.8 mmol, 1.1 equiv) were slowly added at 0 °C, and the reaction mixture was stirred at 25 °C for 1 h. Then, water (100 mL) was added, and the whole was extracted with AcOEt. The organic phase was washed with brine, dried over Na_2SO_4, and the solvent was evaporated under reduced pressure to give a residue, which was column-chromatographed on silica gel (eluent/AcOEt-*n*-hexane (1:3)) to afford phenetylcarbamic acid methyl ester **1a** as colorless oil (1.36 g, 7.59 mmol, 95% Yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.32−7.18 (m, 5H), 4.89 (brs, 1H), 3.64 (s, 3H), 3.43 (q, J = 6.8 Hz, 2H), 2.81 (t, J = 6.8 Hz, 2H). ^{13}C NMR ($CDCl_3$) δ: 156.9, 138.7, 128.6, 128.4, 126.3, 51.8, 42.1, 36.0. Anal. Calcd for $C_{10}H_{13}NO_2$: C, 67.02; H, 7.31; N, 7.82. Found: C, 66.73; H, 7.37; N, 7.82. MS (ESI$^+$): 202 ([M + Na]$^+$).

Synthesis of 2−4-Tolylethylcarbamic Acid Methyl Ester ***1b.*** Yield 93%. Mp: 37.5−39.5 °C (colorless needles, recrystallized from hexane and dichloromethane). ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.12 (d, J = 8.0 Hz, 2H), 7.08 (d, J = 8.0 Hz, 2H), 4.67 (brs, 1H), 3.65 (s, 3H), 3.42 (q, J = 6.4 Hz, 2H), 2.77 (t, J = 6.8 Hz, 2H), 2.32 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 156.8, 135.7, 135.5, 129.0, 128.4, 51.7, 42.1, 35.5, 20.8. Anal. Calcd for $C_{11}H_{15}NO_2$: C, 68.37; H, 7.82; N, 7.25. Found: C, 68.56; H, 7.87; N, 7.17. MS (ESI$^+$): 216 ([M + Na]$^+$).

Synthesis of 2−3-Tolyl-ethyl-carbamic Acid Methyl Ester ***1c.*** Yield 67%. Colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.22 (t, J = 7.6 Hz, 1H), 7.07−7.01 (m, total 3H) 4.99 (brs, 1H), 3.67 (s, 3H), 3.45 (q, J = 6.8 Hz, 2H), 2.80 (t, J = 6.8 Hz, 2H), 2.36 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 156.8, 138.5, 137.9, 129.3, 128.3, 127.0, 125.5, 51.7, 42.0, 35.8, 21.1. ESI-HRMS: Calcd. for $C_{11}H_{15}NNaO_2^+$ ([M + Na]$^+$): 216.1001. Found: 216.0995.

Synthesis of 2−4-Chloro-phenethyl-carbamic Acid Methyl Ester ***1d.*** Yield 92%. Mp. 50−51 °C (colorless plates, recrystallized from n-hexane/$CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$/TMS) δ (ppm): 7.28 (d, J = 8.4 Hz, 2H), 7.13 (d, J = 8.4 Hz, 2H), 4.82 (brs, 1H), 3.66 (s, 3H), 3,41 (q, J = 6.8 Hz, 2H), 2.79 (t, J = 6.8 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 157.0, 137.3, 132.3, 130.1, 128.7, 52.1, 42.1, 35.5. Anal. Calcd for $C_{10}H_{12}ClNO_2$: C, 56.21; H, 5.66; N, 6.56. Found: C, 56.22; H, 5.37; N, 6.52. ESI-HRMS: Calcd for $C_{10}H_{12}ClNNaO_2^+$ ([M + Na]$^+$): 236.0454. Found: 236.0455.

Synthesis of 2−3-Chloro-phenethylcarbamic Acid Methyl Ester ***1e.*** Yield 91%. Mp: 36.0−37.0 (recrystallized from hexane and dichlorometane). ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.24−7.08 (m, 3H), 7.07 (d, J = 6.8 Hz, 1H), 4.67 (brs, 1H), 3.67 (s, 3H), 3.43 (q, J = 6.8 Hz, 2H), 2.79 (t, J = 6.8 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 156.9, 140.7, 134.0, 129.6, 128.6, 126.8, 126.4, 51.8, 41.8, 35.6. Anal. Calcd for $C_{10}H_{12}ClNO_2$: C, 56.21; H, 5.66; N, 6.56. Found: C, 56.19; H, 5.72; N, 6.58. MS (ESI$^+$): 236 ([M + Na]$^+$) (M: $C_{10}H_{12}ClNO_2$).

Synthesis of 2−2-Chlorophenylethylcarbamic Acid Methyl Ester ***1f.*** Yield 90%. Colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.12−7.36 (m, 4H), 4.74 (brs, 1H), 3.66 (s, 3H), 3.45 (m, total 2H), 2.95 (t, J = 7.0 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 157.0, 136.4, 134.1, 131.0, 129.6, 128.0, 126.9, 52.1, 40.6, 33.9. Anal. Calcd for $C_{11}H_{15}NO_2$: C, 56.21; H, 5.66; N, 6.56. Found: C, 56.00; H, 5.62; N, 6.55. MS (ESI$^+$): 236 ([M + Na]$^+$) (M: $C_{11}H_{15}NO_2$).

Synthesis of 2−4-Fluoro-phenethylcarbamic Acid Methyl Ester ***1g.*** Yield 96%. Mp: 54.5−55.5 (recrystallized from hexane and dichloromethane). ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.14 (dd, J = 5.2 Hz, 2H), 6.99 (tt, J = 8.8, 2.0 Hz, 2H), 4.70 (brs, 1H), 3.65 (s, 3H), 3.41 (q, J = 6.8 Hz, 2H), 2.78 (t, J = 6.8 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 161.5 (d, J = 243 Hz), 156.8, 134.3, 130.0 (d, J = 8 Hz), 115.2 (d, J = 21 Hz), 51.9, 42.1, 35.2. Anal. Calcd for $C_{10}H_{12}FNO_2$: C, 60.90; H, 6.13; N, 7.10. Found: C, 60.91; H, 6.04; N, 7.06. ESI-HRMS: Calcd for $C_{10}H_{12}FNNaO_2^+$ ([M + Na]$^+$): 220.0750. Found: 220.0774.

Synthesis of 2−3-Fluoro-phenethylcarbamic Acid Methyl Ester ***1h.*** Yield 65%. Colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$/TMS) δ (ppm): 7.22−6.99 (m, total 4H), 4.89 (s, 1H), 3.63 (s, 3H), 3.41 (q, J = 6.4 Hz, 2H), 2.84 (t, J = 6.4 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 162.9 (d, J = 234 Hz), 157.0, 141.3 (d, J = 8 Hz), 130.1 (d, J = 8 Hz), 124.4 (d, J = 3 Hz), 115.6 (d, J = 20 Hz), 113.4 (d, J = 21 Hz), 52.1, 42.0, 35.9. ESI-HRMS: Calcd for $C_{10}H_{12}FNNaO_2^+$ ([M + Na]$^+$): 220.0750. Found: 220.0747.

Synthesis of 2−2-Fluoro-phenethylcarbamic Acid Methyl Ester ***1i.*** Yield 78%. Colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$/TMS) δ (ppm): 7.19−7.13 (m, total 2H), 7.22 (dt, J = 7.6, 1.2 Hz, 1H), 6.97

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(dt, J = 8.4, 1.2 Hz, 1H), 5.10 (s, 1H), 3.59 (s, 3H), 3.38 (q, J = 6.4 Hz, 2H), 2.82 (t, J = 6.8 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 160.9 (d, J = 234 Hz), 156.9, 130.9 (d, J = 4 Hz), 128.0 (d, J = 8 Hz), 125.6 (d, J = 16 Hz), 123.9 (d, J = 3 Hz), 115.1 (J = 22 Hz), 51.7, 40.9, 29.4. ESI-HRMS: Calcd for $C_{10}H_{12}FNNaO_2^+$ ([M + Na]$^+$): 220.0750. Found: 220.0745.

Synthesis of 2−4-Methoxyphenylethylcarbamic Acid Methyl Ester ***1j.*** Yield 65%. Mp: 60.0−62.0 (recrystallized from hexane and dichloromethane) ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.26 (s, 1H), 7.10 (d, J = 8.4 Hz, 2H), 6.85 (d, J = 8.4 Hz, 2H), 4.66 (brs, 1H), 3.79 (s, 3H), 3.65 (s, 3H), 3.39 (q, J = 6.4 Hz, 2H), 2.75 (t, J = 6.8 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 158.1, 156.9, 130.6, 129.5, 113.8, 55.0, 51.8, 42.2, 35.0. Anal. Calcd for $C_{11}H_{15}NO_3$: C, 63.14; H, 7.23; N, 6.69. Found: C, 63.00; H, 7.19; N, 6.55. MS (ESI+): 232 ([M + Na]$^+$). (M: $C_{11}H_{15}NO_3$).

Synthesis of [2-(2-Fluoro-5-methyl-phenyl)-ethyl]-carbamic Acid Methyl Ester ***1l.*** Yield 78%. Colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 6.98−6.85 (m, total 3H), 4.89 (brs, 1H), 3.63 (s, 3H), 3.39 (q, J = 6.4 Hz, 2H), 2.79 (t, J = 6.8 Hz, 2H), 2.27 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 159.5 (d, J = 241 Hz), 157.0, 133.5 (d, J = 3 Hz), 131.5 (d, J = 5 Hz), 128.6 (d, J = 8 Hz), 125.2 (d, J = 16 Hz), 114.9 (d, J = 22 Hz), 51.9, 41.1, 29.6, 20.5. ESI-HRMS: Calcd for $C_{11}H_{14}FNNaO_2^+$ ([M + Na]$^+$): 234.0906. Found: 234.0914.

Synthesis of 2,4-Dichlorophenethylcarbamic Acid Methyl Ester ***1m.*** Yield 54%. Colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.37 (d, J = 2.0 Hz, 1H), 7.20- 7.14 (m, total 2H), 4.72 (brs, 1H), 3.66 (s, 3H), 3.42 (q, J = 6.4 Hz, 2H), 2.92 (t, J = 6.8 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 156.9, 134.9, 134.6, 132.7, 131.5, 129.1, 126.9, 51.9, 40.2, 33.1. Anal. Calcd for $C_{10}H_{11}Cl_2NO_2$: C, 48.41; H, 4.47; N, 5.65. Found: C, 48.39; H, 4.57; N, 5.50. MS(ESI+): 270 ([M + Na]) (M: $C_{10}H_{11}Cl_2NO_2$).

Synthesis of 2−4-Nitro-phenylethylcarbamic Acid Methyl Ester ***1n.*** Yield 94%. Mp: 116.5−117.5 °C (colorless plates, recrystallized from CH_2Cl_2-*n*-hexane). ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 8.19 (d, J = 8.8 Hz, 2H), 7.38 (d, J = 8.4 Hz, 2H), 4.75 (brs, 1H), 3.69 (s, 3H), 3.50 (q, J = 6.8 Hz, 2H), 2.96 (t, J = 6.8 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 156.9, 146.9, 146.6, 129.7, 123.8, 52.2, 41.7, 36.2. Anal. Calcd for $C_{10}H_{12}N_2O_4$: C, 53.57; H, 5.39; N, 12.49. Found: C, 53.36; H, 5.34; N, 12.49. ESI-HRMS: Calcd for $C_{10}H_{12}N_2NaO_4^+$ ([M + Na]$^+$): 247.0695. Found: 247.0691.

Synthesis of 2−3-Nitro-phenylethylcarbamic Acid Methyl Ester ***1o.*** Yield 68%. Mp: 87.5−88.0 °C (colorless plates, recrystallized from CH_2Cl_2-*n*-hexane). ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 8.10 (dd, J = 8.0, 0.8 Hz, 1H), 8.08 (d, J = 0.8 Hz, 1H), 7.56 (d, J = 7.6 Hz, 1H), 7.50 (t, J = 7.6 Hz, 1H), 4.81 (brs, 1H), 3.68 (s, 3H), 3.49 (q, J = 6.8 Hz, 2H), 2.96 (t, J = 7.6 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 156.9, 148.4, 140.9, 135.1, 129.5, 123.6, 121.7, 52.2, 41.9, 35.9. Anal. Calcd for $C_{10}H_{12}NO_4$: C, 53.57; H, 5.39; N, 12.49. Found: C, 53.72; H, 5.29; N, 12.41. ESI-HRMS: Calcd for $C_{10}H_{12}N_2NaO_4^+$ ([M + Na]$^+$): 247.0695. Found: 247.0681.

Synthesis of (2-Phenyl-propyl)-carbamic Acid Methyl Ester ***1s.*** Yield 92%. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.34−7.19 (m, 5H), 4.56 (brs, 1H), 3.63 (s, 3H), 3.52−3.45 (m, 1H), 3.30−3.23 (m, 1H), 3.00−2.93 (m, 1H), 1.27 (d, J = 6.8 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 157.0, 144.0, 128.6, 127.1, 126.6, 51.9, 47.7, 40.0, 19.1. ESI-HRMS: Calcd for $C_{11}H_{15}NNaO_2^+$ ([M + Na]$^+$): 216.1001. Found: 216.0999.

Synthesis of Methyl (3-Phenylpropyl)carbamate ***1t.*** Yield 87%. Colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$/TMS) δ (ppm): 7.33−7.29 (m, total 2H), 7.23−7.19 (m, total 3H), 4.85 (brs, 1H), 3.68 (s, 3H), 3.26−3.21 (m, total 2H), 2.67 (t, J = 7.6 Hz, 2H), 1.89 −1.82 (m, total 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 157.1, 141.5, 128.5, 128.4, 126.0, 52.0, 40.6, 33.0, 31.6. Anal. Calcd for $C_{11}H_{15}NO_2$: C, 68.37; H, 7.82; N, 7.25. Found: C, 68.17; H, 7.86; N, 7.26. ESI-HRMS: Calcd for $C_{11}H_{15}NNaO_2^+$ ([M + Na]$^+$): 216.1001. Found: 216.1002.

Synthesis of Methyl Methylcarbamate ***1w.*** Yield 46%. Colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$/TMS) δ (ppm): 4.67 (brs, 1H), 3.65 (s, 3H), 2.78 (t, J = 4.0 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 157.7, 52.0, 27.5.

Synthesis of 2−4-Hydroxy-phenethylcarbamic Acid Methyl Ester ***1k.*** To a solution of [2-(4-Methoxy-phenyl)-ethyl]-carbamic acid methyl ester (628.1 mg, 3.0 mmol) in DCM (dichloromethane, 5.0 mL), a solution of BBr_3 in DCM (1M, 9.0 mL, 3 equiv) was slowly added and the mixture was stirred at 0 to 20 °C for 4 h. To quench the reaction mixture, methanol (5 mL) was added, and then water (30 mL) was added and the whole was extracted with DCM (100 mL). The organic phase was washed with brine, dried over Na_2SO_4, and the solvent was evaporated under reduced pressure to give a residue, which was column-chromatographed on silica-gel (eluent:AcOEt-*n*-hexane (1:8 to 1:3)) to afford [2-(4-Hydroxy-phenyl)-ethyl]-carbamic acid methyl ester (545.0 mg, 2.79 mmol, 93% yield). Mp. 91.0 - 91.5 °C (white powder, recrystallized from n-hexane and $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ(ppm): 7.03 (d, J = 8.4 Hz, 2H), 6.81 (dt, J = 8.8, 2.4 Hz, 2H), 6.56 (brs, 1H), 4.85 (brs, 1H), 3.68 (s, 3H), 3.41 (q, J = 6.8 Hz, 2H), 2.74 (t, J = 7.2 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 157.3, 154.7, 130.1, 129.8, 115.5, 52.2, 42.4, 35.2. Anal. Calcd. for $C_{10}H_{13}NO_3$: C, 61.53; H, 6.71; N, 7.18. Found: C, 61.71; H, 6.83; N, 7.07. ESI-HRMS: Calcd for $C_{10}H_{13}NNaO_3^+$ ([M + Na]$^+$): 218.0793. Found: 218.0763.

Synthesis of 2−3/4-Amino-phenylethylcarbamic Acid Methyl Ester ***1p*** *and* ***1x.*** *A Typical Procedure: Synthesis of 2−4-Amino-phenylethylcarbamic Acid Methyl Ester* ***1p.*** A solution of 2−4-amino-phenylethylcarbamic acid methyl ester (621 mg 2.76 mmol) and palladium on carbon (5% w/w, wet, 33.5 mg) in methanol (20 mL) was stirred at 20 °C for 4 h under H_2 atmosphere. Then, the solvent was filtered and evaporated under reduced pressure to give a residue, which was column-chromatographed on silica gel (eluent: $CHCl_3$) to afford 2−4-amino-phenylethylcarbamic acid methyl ester **1p** as colorless oil (558.9 mg, 2.88 mmol, quantitative yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 6.97 (d, J = 8.4 Hz, 2H), 6.64 (dd, J = 8.8, 2.4 Hz, 2H), 4.84 (brs, 1H), 3.66 (s, 3H), 3.51 (s, 2H), 3.37 (q, J = 6.8 Hz, 2H), 2.69 (t, J = 6.8 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 156.9, 144.8, 129.5, 128.5, 115.3, 51.9, 42.4, 35.1. ESI-HRMS: Calcd for $C_{10}H_{14}N_2NaO_2^+$ ([M + Na]$^+$): 217.0953. Found: 217.0937.

Synthesis of 2−3-Amino-Phenylethylcarbamic Acid Methyl Ester ***1x.*** Quantitative Yield. Colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.07 (t, J = 8.0 Hz, 1H), 6.58−6.52 (m, 2H), 6.49 (s, 1H), 5.06 (brs, 1H), 3.71 (s, 2H), 3.65 (s, 3H), 3.39 (q, J = 6.8 Hz, 2H), 2.69 (t, J = 6.8 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 156.8, 146.6, 139.8, 129.2, 118.5, 115.2, 113.0, 51.7, 41.9, 35.8. ESI-HRMS: Calcd for $C_{10}H_{14}N_2NaO_2^+$ ([M + Na]$^+$): 217.0953. Found: 217.0954.

Synthesis of N-Methylated Arylphenethyl Carbamates ***1q*** *and* ***1r.*** *A Typical Procedure: Synthesis of Methyl N-Methyl-phenethylcarbamate* ***1q.*** To a suspension of NaH (60 mg of a 60% dispersion in mineral oil) in DMF (10 mL) were added phenethyl carbamate **1a** (400 mg, 2.23 mmol) and triethyl amine (0.34 mL) at room temperature (20 °C) and the mixture was stirred for 5 min. MeI (0.42 mL) was then added in a dropwise manner. The whole was stirred at 20 °C for 16 h. The reaction was quenched with water and the whole was extracted with AcOEt. The combined organic extracts were washed with brine and dried (Na_2SO_4), and the solvent was evaporated under reduced pressure to give a residue, which was column-chromatographed on silica-gel (eluent: AcOEt−hexane (1:5)) to afford the title compound (362 mg, 1.87 mmol). Yield 84%. Colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$), two rotamers with respect to the amide bond were observed (approximately 1:1 ratio) δ (ppm): 7.34−7.19 (m, total 5H), 3.75 (s, 3H, rotamer A), 3.65 (s, 3H, rotamer B), 3.51−3.46 (m, total 2H), 2.89 (s, 2H), 2.84 (s, 3H). ^{13}C NMR (100 MHz, CDCl3) δ (ppm): 156.7, 138.9, 128.7, 128.4, 126.2, 52.3, 51.0, 50.4, 34.8, 34.5, 34.0. ESI-HRMS: Calcd for $C_{11}H_{15}NNaO_2^+$ ([M + Na]$^+$): 216.1001. Found: 216.0993.

Synthesis of Methyl-(2-p-chloro-phenyl-ethyl)-carbamic acid methyl ester ***1r.*** Yield 83%. Colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$), two rotamers with respect to the amide bond were observed (approximately 1:1 ratio), δ (ppm): 7.30−7.26 (m, total 2H, rotamer A and B), 7.14 (brs, 2H, rotamer A and B), 3.71 (s, 3H, rotamer A), 3.65 (m, total 3H, rotamer B), 3.47 (brs, 2H, rotamers A and B), 2.88 (s, 2H, rotamers A and B), 2.83 (s,3H, rotamers A and B). ^{13}C NMR (100 MHz, $CDCl_3$), a mixture of two rotamers, δ (ppm): 156.8, 137.4,

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132.1, 130.15, 130.11, 128.7, 128.6, 52.5, 50.8, 50.3, 35.0, 34.6, 34.0, 33.4. ESI-HRMS: Calcd for $C_{11}H_{14}ClNNaO_2^+$ ([M + Na]$^+$): 250.0611. Found: 250.0598.

Synthesis of 3-(4-Fluorophenyl)-propyl Carbamic Acid Methyl Ester ***1u.*** To a solution of 4-fluorophenethyl bromide (2072 mg, 10.2 mmol) in CH_3CN (10 mL), TMSCN (1507 mg, 15.2 mmol, 1.5 equiv) and tetrabutylammonium fluoride (TBAF) in THF (1 M solution, 15 mL, 15 mmol.) were added at 0 °C, and the reaction mixture was stirred at 70 °C for 40 min. Then the solvent was evaporated under reduced pressure to give a residue, which was column-chromatographed on silica gel (eluent: AcOEt−*n*-hexane (1:6)) to afford to 3-(4-fluoro-phenyl)-propionitrile as colorless oil (1298 mg, 8.70 mmol, 85%). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.16−7.10 (m, 4H), 2.92 (t, J = 7.6 Hz, 2H), 2.59 (t, J = 7.6 Hz, 2H).

To a solution of $LiAlH_4$ (920.4 mg) in dry ether (30 mL), the above product, 3-(4-fluorophenyl)propionitrile (1298 mg, 8.70 mmol) was added in a dropwise manner at 0 °C, and the reaction mixture was heated at reflux for 2 h with stirring. Then, cooled to 0 °C and quenched by sodium sulfate hydrate, and the whole was filtered. Then, the solution was dried over Na_2SO_4, and the solvent was evaporated under reduced pressure to afford crude mixture contains 3-(4-methyl-phenyl)-1-propanamine as colorless oil.

To a solution of above obtained 3-(4-fluorophenyl)-1-propanamine in DMF (10 mL), methyl chloroformate (0.58 mL, 7.5 mmol, 1.5 equiv) and triethylamine (0.98 mL, 7.5 mmol, 1.5 equiv) were added at 0 °C, and the reaction mixture was stirred at 0 °C to room temperature for 2 h. Then, water (15 mL) was added, and the whole was extracted with Et_2O (100 mL × 2). The organic phase was washed with brine, dried over Na_2SO_4, and the solvent was evaporated under reduced pressure to give a residue, which was column-chromatographed on silica gel (eluent: AcOEt−*n*-hexane (1:3)) to afford to compound **1u** as colorless oil (354.8 mg, 1.68 mmol, 19% over 2 steps). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.14−7.11 (m, 2H), 6.99−6.94 (m, 2H), 4.67 (brs, 1H), 3.67 (s, 3H), 3.23−3.18 (q, J = 6.4 Hz, 2H), 2.62 (t, J = 8.0 Hz, 2H), 1.84−1.77 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 161.3 (d, J = 242 Hz), 157.1, 137.0, 129.6 (d, J = 7 Hz), 115.2 (d, J = 21 Hz), 52.0, 40.5, 32.2, 31.8. Anal. Calcd for $C_{11}H_{14}FNO_2$: C, 62.55; H, 6.68; N, 6.63. Found: C, 62.60; H, 6.69; N, 6.51. ESI-HRMS: Calcd for $C_{11}H_{14}FNNaO_2^+$ ([M + Na]$^+$): 234.0906. Found: 234.0949.

Acid-catalyzed Cyclization Reaction of Methyl 2-Aryl-ethyl/3-Aryl-propyl-carbamate. A Typical Procedure: Synthesis of 3,4-Dihydro-2H-isoquinolin-1-one ***2a.*** To phenethylcarbamic acid methyl ester (183.6 mg, 1.02 mmol), trifluoromethanesulfonic acid (4.56 mL, 50 equiv) was slowly added at 0 °C. The whole was heated at 70 °C for 24 h with stirring, then the whole was poured into ice−water (50 mL), and extracted with dichloromethane (50 mL × 3). The organic phase was washed with brine, dried over Na_2SO_4, and the solvent was evaporated under reduced pressure to give a residue, which was column-chromatographed on silica-gel (eluent: AcOEt−Hexane (1:1)) to afford 3,4-dihydro-2*H*-isoquinolin-1-one as colorless plates (136.8 mg, 0.930 mmol, 91%).

Mp: 56.0−58.0 (white powder, recrystallized from hexane and dichloromethane). ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 8.06 (d, J = 7.6 Hz, 1H), 7.45 (t, The following use of keep-together tags is outside the context of a table.J = 7.6 Hz, 1H), 7.35 (t, J = 7.6 Hz, 1H), 7.23 (d, J = 7.6 Hz, 1H), 3.57 (dt, J = 6.4, 2.8 Hz, 2H), 3.00 (t, J = 6.4 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 166.6, 138.9, 132.2, 128.9, 127.9, 127.2, 127.1, 40.2, 28.3. Anal. Calcd for C_9H_9NO +1/4H_2O: C, 71.27; H, 6.31; N, 9.23. Found: C, 71.13; H, 6.12; N, 9.27. ESI-HRMS: Calcd for $C_9H_9NNaO^+$ ([M + Na]$^+$): 170.0576. Found: 170.0570.

Synthesis of 7-Methyl-3,4-dihydro-2H-isoquinolin-1-one ***2b.*** Yield 97% (113 mg, 0.701 mmol, from 0.723 mmol of **1b**). Mp: 107−108.5 °C (colorless needles, recrystallized from hexane and dichloromethane). ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.87 (s, 1H), 7.26 (d, J = 2.2 Hz, 1H), 7.20 (brs, 1H), 7.10 (d, J = 7.6 Hz, 1H), 3.54 (dt, J = 6.7, 2.9 Hz, 2H), 2.93 (t, J = 6.6 Hz, 2H), 2.36 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 166.8, 136.7, 135.8, 132.8, 128.6, 128.2, 127.1, 40.1, 27.8, 20.9. Anal. Calcd for $C_{10}H_{11}NO$+1/4 H_2O: C, 72.48; H, 7.00; N, 8.45. Found: C, 72.65; H, 7.00; N, 8.45. MS (ESI$^+$): 184 ([M + Na]$^+$) (M: $C_{10}H_{11}NO$).

*Synthesis of 6-Methyl-3,4-dihydro-2H-isoquinolin-1-one (***2c-1***) and 8-Methyl-3,4-dihydro-2H-isoquinolin-1-one (***2c-2***).* Mixture of **2c-1** and **2c-2** (157 mg, 0.972 mmol, from 0.991 mmol of **1c**) (**2c-1**:**2c-2** = 59:41, the ratio was determined by ^{1}H NMR) was obtained after column chromatography (MeOH/$CHCl_3$ = 1:20). The mixture was separated roughly (column chromatography with less polar solvent, MeOH/$CHCl_3$ = 1:80) and pure products were obtained after recrystallization.

2c-1: 58% Yield. Mp.: 106.0−106.5 °C (colorless needles, recrystallized from n-hexane and diethylether). ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.94 (d, J = 7.6 Hz, 1H), 7.57 (brs, 1H), 7.14 (dd, J = 8.0, 0.8 Hz, 1H), 7.01 (s, 1H), 3.54 (dt, J = 6.4, 2.8 Hz, 2H), 2.92 (t, J = 6.8 Hz, 2H), 2.36 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 166.8, 142.4, 138.8, 127.7, 127.6, 126.2, 39.9, 28.1, 21.4. ESI-HRMS: Calcd for $C_{10}H_{11}NNaO^+$ ([M + Na]$^+$): 184.0738. Found: 184.0737.

2c-2: 40% Yield. Mp. 98.0−98.5 °C (colorless flakes, recrystallized from *n*-hexane and diethylether). ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.28 (t, J = 7.6 Hz, 1H), 7.14 (d, J = 7.6 Hz, 1H), 7.05 (d, 7.6 Hz, 1H), 6.97 (brs, 1H), 3.47 (dt, J = 6.8, 3.6 Hz, 2H), 2.94 (t, J = 6.4 Hz, 2H), 2.72 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 167.1, 140.8, 140.1, 130.8, 130.7, 127.3, 125.0, 39.7, 29.9, 22.0. ESI-HRMS: Calcd for $C_{10}H_{11}NNaO^+$ ([M + Na]$^+$): 184.0738. Found: 184.0756.

Synthesis of 7-Chloro-3,4-dihydro-2H-isoquinolin-1-one ***2d.*** Yield 96% (152 mg, 0.837 mmol, from 0.871 mmol of **1d**). Mp.: 152−154 °C (colorless needles, recrystallized from *n*-hexane and $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$/TMS) δ (ppm): 8.05 (d, J = 2.0 Hz, 1H), 7.41 (dd, J = 8.0, 2.0 Hz, 1H), 7.28 (br, 1H), 7.18 (d, J = 8.0 Hz, 1H), 3.61−3.57 (m, total 2H), 2.98 (t, J = 6.8 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 165.5, 137.2, 133.1, 132.1, 130.5, 128.8, 127.9, 40.0, 27.7. ESI-HRMS: Calcd for $C_9H_8ClNNaO^+$ ([M + Na]$^+$): 204.0187. Found: 204.0192.

*Synthesis of 6-Chloro-3,4-dihydro-2H-isoquinolin-1-one (***2e-1***) and 8-Chloro-3,4-dihydro-2H-isoquinolin-1-one (***2e-2***).* To 2−3-chlorophenylethylcarbamic acid methyl ester (254.4 mg, 1.19 mmol), trifluoromethanesulfonic acid (5.30 mL, 50 equiv) was slowly added at 20 °C. The whole was stirred at 70 °C for 16 h, then the whole was poured into ice−water (50 mL), and filtered to afford **2e-1** (65.2 mg, 0.359 mmol, 30% yield). The filtered water was extracted with $CHCl_3$. The organic phase was washed with brine, dried over Na_2SO_4, and the solvent was evaporated under reduced pressure to give a residue, which was column-chromatographed on silica gel (eluent: $CHCl_3$−MeOH (10:1)) to compound **2e-1** and **2e-2** as white powders (ratio, **2e-1**:**2e-2** = 59:41). (146.5 mg, 0.807 mmol, 68% yield).

2e-1: 70% Yield. Mp: 148.0 − 150.0 °C. (colorless needles, recrystallized from water). ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 8.00 (d, J = 8.0 Hz, 1H), 7.28 (m, 2H), 6.04 (brs, 1H), 3.58 (dt, J = 6.8, 2.4 Hz, 2H), 2.99 (t, J = 6.4 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 165.9, 140.6, 138.5, 129.6, 127.5, 127.3, 126.9, 40.0, 28.0. HRMS: Calcd for $C_9H_8ClNNaO^+$ ([M + Na]$^+$): 204.0187. Found: 204.0189.

2e-2: 28% Yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.38 (d, J = 7.2 Hz, 1H), 7.31 (t, J = 7.8 Hz, 1H), 7.13 (d, J = 7.8 Hz, 1H), 6.02 (brs, 1H), 3.49 (dt, J = 6.4, 3.6 Hz, 2H), 2.99 (t, J = 6.4 Hz, 2H).^{13}C NMR (100 MHz, $CDCl_3$) δ:164.3, 142.1, 134.7, 131.7, 130.6, 126.5, 126.0, 39.5, 30.1.

A mixture of **2e-1** and **2e-2**: Anal. Calcd for C_9H_8ClNO: C, 59.52; H, 4.44; N, 7.71. Found: C, 59.78; H, 4.31; N, 7.64. MS (ESI$^+$): 204 ([M + Na]$^+$) (M: C_9H_8ClNO).

Synthesis of 5-Chloro-3,4-dihydro-2H-isoquinolin-1-one ***2f.*** Yield 98% (106 mg, 0.583 mmol, from 0.600 mmol of **1f**). Mp: 166.0−167.0 (colorless plates, recrystallized from CH_2Cl_2-*n*-hexane). ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 8.00 (d, J = 7.6 Hz, 1H), 7.51 (d, J = 8.0 Hz, 1H), 7.29 (m, 1H), 7.07 (brs, 1H), 3.59 (dt, J = 6.6, 2.8 Hz, 2H), 3.10 (t, J = 6.6 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 165.6, 136.7, 132.7, 132.5, 130.8, 127.7, 126.6, 39.4, 25.4. Anal. Calcd for C_9H_8ClNO: C, 59.52; H, 4.44; N, 7.71. Found: C, 59.23; H, 4.72; N, 7.53. MS (ESI$^+$): 204 ([M + Na]$^+$) (M: C_9H_8ClNO).

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Synthesis of 7-Fluoro-3,4-dihydro-2H-isoquinolin-1-one ***2g***. Yield 91% (145 mg, 0.877 mmol, from 0.962 mmol of **1g**). Mp: 117.5−118.5 (colorless needles, recrystallized from CH_2Cl_2 and n-hexane). ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.76 (dd, J = 9.2, 2.8 Hz, 1H), 7.14−7.20 (m, 2H), 6.17 (brs, 1H), 3.57 (dt, J = 6.8, 3.2 Hz, 2H), 2.98 (t, J = 6.0 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 165.7, 161.6 (d, J = 244 Hz), 134.4 (d, J = 3 Hz), 130.7 (d, J = 7 Hz), 128.8 (d, J = 7 Hz), 118.9 (d, J = 22 Hz), 114.2 (d, J = 22 Hz), 39.9, 27.3. Anal. Calcd for C_9H_8FNO: C, 65.45; H, 4.88; N, 8.48. Found: C, 65.24; H, 5.03; N, 8.37. MS (ESI+): 188 ([M + Na]$^+$).

*6-Fluoro-3,4-dihydro-2H-isoquinolin-1-one (***2h-1***) and 8-Fluoro-3,4-dihydro-2H-isoquinolin-1-one (***2h-2***).* Mixture of **2h-1** and **2h-2** (199.6 mg, 1.21 mmol, from 1.25 mmol of **1h**) (**2c-1**:**2c-2** = 92:8, the ratio was determined by ^{1}H NMR) was obtained after column chromatography (MeOH/$CHCl_3$ = 1:10). The mixture was separated roughly (column chromatography with less polar solvent) and pure products were obtained after recrystallization.

2h-1: 89% Yield. Mp.: 111.0−112.0 °C (colorless needles, recrystallized from *n*-hexane and diethylether). ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 8.08 (dd, J = 8.8, 5.6 Hz, 1H), 7.21 (brs, 1H), 7.03 (dt, J = 8.8, 2.8 Hz, 1H), 6.92 (dd, J = 8.8, 2.8 Hz, 1H), 3.59 (dt, J = 6.4, 2.8 Hz, 2H), 2.99 (t, J = 6.4 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 166.1, 164.7 (d, J = 219 Hz), 141.7 (d, J = 9 Hz), 130.7 (d, J = 10 Hz), 125.3, 114.2 (d, J = 19 Hz), 114.0 (d, J = 19 Hz), 40.0, 28.4 (d, J = 1 Hz). ESI-HRMS: Calcd for $C_9H_8FNNaO^+$ ([M + Na]$^+$): 188.0488. Found: 188.0490.

2h-2: 8% Yield. Mp.: 127.0−128.0 °C (colorless needles, recrystallized from *n*-hexane/diethylether). ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.43−7.38 (m, total 1H), 7.08−7.03 (m, total 2H), 6.79 (brs, 1H), 3.54 (dt, J = 6.8, 3.2 Hz, 2H), 3.00 (t, J = 6.4 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 163.6, 162.3 (d, J = 257 Hz), 141,8, 133.2 (d, J = 10 Hz), 123.0 (d, J = 4 Hz), 117.3 (d, J = 7 Hz), 115.8 (d, J = 23 Hz), 39.8, 29.2 (d, J = 2 Hz). ESI-HRMS: Calcd for $C_9H_8FNNaO^+$ ([M + Na]$^+$): 188.0488. Found: 188.0499.

Synthesis of 5-Fluoro-3,4-dihydro-2H-isoquinolin-1-one ***2i***. Yield 85% (158 mg, 0.959 mmol, from 1.13 mmol of **1i**). Mp.: 151.0−152.0 °C (colorless needles, recrystallized from n-hexane and diethylether). ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.88 (dd, J = 8.0, 0.8 Hz, 1H), 7.35−7.18 (m, total 2H), 6.53 (s, 1H), 3.59 (dt, J = 6.4, 2.8 Hz, 2H), 3.03 (t, J = 6.8 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 165.3, 159.4 (d, J = 245 Hz), 130.8 (d, J = 3 Hz), 127.8 (d, J = 7 Hz), 125.7, 123.6 (d, J = 3 Hz), 118.8 (d, J = 21 Hz), 39.7, 20.9. ESI-HRMS: Calcd for $C_9H_8FNNaO^+$ ([M + Na]$^+$): 188.0488. Found: 188.0498.

Synthesis of 7-Hydroxy-3,4-dihydro-2H-isoquinolin-1-one ***2k***. Yield 82% (138 mg, 0.701 mmol, from 1.03 mmol of **1j**), 84% Yield (133 mg, 0.816 mmol, from 0.968 mmol of **1k**). Mp. 204.0−206.0 °C (white powder, recrystallized from AcOEt/$CHCl_3$). ^{1}H NMR (400 MHz,DMSO-d_6) δ (ppm): 9.49 (s, 1H), 7.85 (s, 1H), 7.25 (d, J = 2.8 Hz, 1H), 7.09 (d, J = 8.4 Hz, 1H), 6.85 (dd, J = 7.6, 2.8 Hz, 1H), 3.32 (dt, J = 6.8, 2.8 Hz, 2H), 2.76 (t, J = 6.8 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 165.1, 156.5, 130.8, 129.9, 128.9, 119.3, 113.7, 39.9, 27.3. ESI-HRMS: Calcd for $C_9H_9NNaO_2^+$ ([M + Na]$^+$): 186.0531. Found: 186.0542.

Synthesis of 5-Fluoro-8-methyl-3,4-dihydro-2H-isoquinolin-1-one ***2l***. Yield 97% (195 mg, 1.09 mmol, from 1.12 mmol of **1l**). Mp.: 115.5−116.0 °C (white powder, recrystallized from *n*-hexane/diethylether). ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.11−7.03 (m, total 2H), 6.17 (brs, 1H), 3.48 (dt, J = 6.4, 3.2 Hz, 2H), 2.96 (t, J = 6.4 Hz, 2H), 2.65 (3H, s). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 166.4 (d, J = 3 Hz), 157.1 (d, J = 241 Hz), 136.4 (d, J = 4 Hz), 131.1 (d, J = 7 Hz), 128.5 (d, J = 3 Hz), 126.7 (d, J = 8 Hz), 117.7 (d, J = 22 Hz), 39.4, 22.0 (d, J = 4 Hz), 21.5. ESI-HRMS: Calcd for $C_{10}H_{10}FNNaO^+$([M + Na]$^+$): 202.0644. Found: 202.0655.

Synthesis of 5,7-dichloro-3,4-dihydro-2H-isoquinolin-1-one ***2m***. Yield 40% (87.0 mg, 0.403 mmol, from 1.00 mmol of **1m**). Mp.: 195.0−195.5 °C (white powder, recrystallized from *n*-hexane/dichloromethane). ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 8.02 (d, J = 2.0 Hz, 1H), 7.54 (d, J = 2.4 Hz, 1H), 6.04 (brs, 1H), 3.59 (dt, J = 6.7, 2.9 Hz, 2H), 2.93 (t, J = 6.8 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 164.6, 135.2, 133.4, 133.3, 132.3, 131.8, 126.8, 39.2. 25.0. ESI-HRMS: Calcd for $C_9H_7Cl_2NNaO^+$ ([M + Na]$^+$): 237.9797. Found: 237.9796.

Synthesis of 2-Methyl-3,4-dihydro-2H-isoquinolin-1-one ***2q***. Yield 88% (120 mg, 0.744 mmol, from 0.845 mmol of **1q**). Colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$/TMS) δ (ppm): 8.10 (d, J = 7.6 Hz, 1H), 7.42 (dd, J = 7.6, 7.2 Hz, 1H), 7.37 (dd, J = 7.6, 7.2 Hz, 1H), 7.19 (dd, J = 7.2 Hz, 1H), 3.59 (t, J = 6.8 Hz, 2H), 3.18 (s, 3H), 3.03 (t, J = 6.8 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 164.8, 137.9, 131.5, 129.4, 128.1, 127.0, 126.9, 48.1, 35.2, 27.9. ESI-HRMS: Calcd for $C_{10}H_{11}NNaO^+$ ([M + Na]$^+$): 184.0738. Found: 184.0737.

Synthesis of 7-Chloro-2-methyl-3,4-dihydro-2H-isoquinolin-1-one ***2r***. Yield 78% (156 mg, 0.799 mmol, from 1.03 mmol of **1r**). Colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$/TMS) δ (ppm): 8.06 (d, J = 2.0 Hz, 1H), 7.42 (dd, J = 8.0, 2.4 Hz, 1H), 7.12 (d, J = 8.0, 7.2 Hz, 1H), 3.57 (t, J = 6.8 Hz, 2H), 3.16 (s, 3H), 2.99 (t, J = 6.8 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 163.6, 136.2, 133.1, 131.4, 130.9, 128.4, 128.1, 48.0, 35.2, 27.3. ESI-HRMS: Calcd for $C_{10}H_{10}ClNNaO^+$ ([M + Na]$^+$): 218.0349. Found: 218.0337.

Synthesis of 4-Methyl-3,4-dihydro-2H-isoquinolin-1-one ***2s***. Yield 88% (138 mg, 0.855 mmol, from 0.977 mmol of **1s**). Colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$/TMS) δ (ppm): 8.08 (dd, J = 8.0, 1.6 Hz, 1H), 7.49 (dt, J = 7.6, 1.6 Hz, 1H), 7.36 (dt, J = 7.6, 0.8 Hz, 1H), 7.26 (d, J = 7.6 Hz, 1H), 7.11 (1H, brs), 3.66 (dq, J = 8.4, 2.4 Hz, 1H), 3.31 (dq, J = 8.0, 3.2 Hz, 1H), 3.12 (h, J = 6.8 Hz, 1H), 1.36 (d, J = 6.8 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 166.4, 143.9, 132.3, 128.1, 128.0, 126.9, 125.8, 46.4, 32.3, 18.4. ESI-HRMS: Calcd for $C_{10}H_{11}NNaO^+$ ([M + Na]$^+$): 184.0738. Found: 184.0737.

Synthesis of 2,3,4,5-Tetrahydro-benzo[c]azepin-1-one ***2t***. 80% Yield (156.3 mg, 0.970 mmol, from 1.22 mmol of **1t**). Mp.: 94−95 °C (white powder, recrystallized from n-hexane and $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$/TMS) δ (ppm): 7.73 (d, J = 7.2 Hz, 1H), 7.43 (dd, J = 7.2, 7.2 Hz, 1H), 7.36 (dd, J = 7.6, 7.2 Hz, 1H), 7.21 (d, J = 7.6 Hz, 1H), 6.69 (br, 1H), 3.15 (q, J = 6.4 Hz, 2H), 2.89 (t, J = 7.2 Hz, 2H), 2.08 - 2.01 (m, total 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 173.9, 138.3, 135.0, 131.3, 128.8, 128.6, 127.0, 39.6, 30.5, 30.3. Anal. Calcd for $C_{10}H_{11}NO$: C, 74.51; H, 6.88 N, 8.69. Found: C, 74.21; H, 6.99; N, 8.54. MS (ESI+): 184 ([M + Na]$^+$) (M: $C_{10}H_{11}NO$)

Synthesis of 8-Fluoro-2,3,4,5-tetrahydro-benzo[c]azepin-1-one ***2u***. Yield 9% (16.2 mg, 0.090 mmol, from 1.06 mmol of **1u**). Mp.: 166.0−167.0 °C (colorless needles, recrystallized from *n*-hexane and diethylether). ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.44 (dd, J = 8.8, 2.8 Hz, 1H), 7.20−7.11 (m, total 2H), 6.47 (brs, 1H), 3.16 (q, J = 6.4 Hz, 2H), 2.86 (t, J = 7.2 Hz, 2H), 2.03 (m, total 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 172.7 (d, J = 2 Hz), 162.2 (d, J = 245 Hz), 136.7 (d, J = 8 Hz), 134.0, 130.3 (d, J = 8 Hz), 118.0 (d, J = 21 Hz), 115.7 (d, 21 Hz), 39.5, 30.3 (d, J = 1 Hz), 29.5. ESI-HRMS: Calcd for $C_{10}H_{10}FNNaO^+$ ([M + Na]$^+$): 202.0644. Found: 202.0645.

2-(4-Chlorophenyl)ethanamine ***3d***. Colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.25 (d, J = 6.4 Hz, 2H), 7.11 (d, J = 6.4 Hz, 2H), 2.93 (t, J = 6.8 Hz, 2H), 2.70 (t, J = 6.8 Hz, 2H), 1.30 (brs, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 138.3, 131.9, 130.2, 128.5, 43.4, 39.4. ESI-HRMS: Calcd for $C_8H_{11}ClN^+$ ([M + H]$^+$): 156.0575. Found: 156.0564.

2-(4-Fluorophenyl)ethanamine ***3g***. Colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.16−7.12 (m, 2H), 7.00−6.95 (m, 2H), 2.93 (t, J = 6.8 Hz, 2H), 2.71 (t, J = 6.8 Hz, 2H), 1.51 (brs, 2H).^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 162.3 (d, J = 43 Hz), 135.3 (d, J = 4 Hz), 130.0 (d, J = 8 Hz), 115.0 (d, J = 21 Hz), 43.4, 39.0. ESI-HRMS: Calcd. for $C_8H_{11}FN^+$ ([M+H]$^+$): 140.0870. Found: 140.0881.

2-(2,4-Dichlorophenyl)ethanamine ***3m***. Yield 44% (83.4 mg, 0.439 mmol, from 1.00 mmol of **1m**). Yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.37 (d, J = 1.6 Hz, 1H), 7.20−7.15 (m, 2H), 2.95 (dt, J = 8.0, 1.2 Hz, 2H), 2.85 (dt, J = 7.2, 0.8 Hz, 2H), 1.48 (brs, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 136.0, 134.8, 132.6, 131.6, 129.3, 127.0, 41.8, 37.2. ESI-HRMS: Calcd for $C_8H_{10}Cl_2N^+$ ([M + H]$^+$): 190.0185. Found: 190.0176.

2-(4-Nitrophenyl)ethanamine ***3n***. Yield 72% (35.7 mg, 0.215 mmol, from 0.297 mmol of **1n**). Yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 8.16 (dd, J = 6.8, 2.0 Hz, 2H), 7.37 (dd, J = 6.8, 2.0

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Hz, 2H), 3.03 (dt, J = 6.8, 0.4 Hz, 2H), 2.87 (t, J = 6.8 Hz, 2H), 1.30 (brs, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 147.9, 146.6, 129.6, 123.7, 43.1, 39.9. ESI-HRMS: Calcd for $C_8H_{11}N_2O_2^+$ ($[M + H]^+$): 167.0815. Found: 167.0816.

2-(3-Nitrophenyl)ethanamine ***3o***. Yield 85% (44.3 mg, 0.267 mmol, from 0.313 mmol of **1o**). Yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 8.09−8.06 (m, 2H), 7.55 (dt, J = 7.6, 1.2 Hz, 1H), 7.50−7.45 (m, 1H), 3.04 (t, J = 6.8 Hz, 2H), 2.87 (t, J = 6.4 Hz, 2H), 1.22 (brs, 2H).^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 148.4, 142.0, 135.1, 129.3, 123.6, 121.4, 43.2, 39.6. ESI-HRMS: Calcd for $C_8H_{11}N_2O_2^+$ ($[M + H]^+$): 167.0815. Found: 167.0803.

2-(4-Aminophenyl)ethanamine ***3p***. Yield 84% (25.5; mg, 0.187 mmol, from 0.224 mmol of **1p**). Yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 6.98 (dt, J = 8.4, 2.0 Hz, 2H), 6.63 (dt, J = 8.4, 2.0 Hz, 2H), 3.57 (brs, 2H), 2.89 (t, J = 6.8 Hz, 2H), 2.63 (t, J = 6.8 Hz, 2H), 1.15 (brs, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 144.6, 129.8, 129.6, 115.3, 43.8, 39.3. ESI-HRMS: Calcd for $C_8H_{11}N_2O_2^+$ ($[M + H]^+$): 167.0815. Found: 167.0803.

3-(4-Fluorophenyl)-propylamine ***3u***. Yield 40% (64.8 mg, 0.423 mmol, from 1.06 mmol of **1u**). Yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.16−7.11 (m, 2H), 6.99−6.93 (m, 2H), 2.72 (t, J = 7.2 Hz, 2H), 2.63 (t, J = 8.0 Hz, 2H), 1.79−1.71 (m, 2H), 1.50 (brs, 2H) ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 162.4, 148.9 (d, J = 223 Hz), 129.6 (d, J = 8 Hz), 115.0 (d, J = 21 Hz), 41.6, 35.4, 32.4. ESI-HRMS: Calcd for $C_9H_{13}FN^+$ ($[M + H]^+$): 154.1027. Found: 154.1037.

Experiments of Acidity-dependent Reactions (Table 2). Table 2, Entries 1−4. Mixtures of TFSA and TFA in specified weight ratios were made. To weighted **1a** (1.0 mmol) in a flask was added 50 equiv amount of the mixed acid at 0 °C. The whole was stirred at 70 °C for 3.5 h. Then the mixture was poured into 30 mL of ice−water and the whole was extracted with CH_2Cl_2. The organic phase was washed with brine and dried over Na_2SO_4, then the solvent was evaporated under reduced pressure to give a residue. The residue was column-chromatographed on silica gel (*n*-hexane: ethyl acetate as an eluent) to afford **1a**, and **2a** respectively.

Table 2, Entries 6−9. Mixtures of TFSA and TFA in specified weight ratios were made. To weighted **1d** (1.0 mmol) in a flask was added 50 equiv amount of the mixed acid at 0 °C. The whole was stirred at 70 °C for 23 h. Then the mixture was poured into 30 mL of ice−water and the whole was extracted with CH_2Cl_2. The organic phase was washed with brine and dried over Na_2SO_4, and then the solvent was evaporated under reduced pressure to give a residue. The residue was column-chromatographed on silica gel (*n*-hexane: ethyl acetate as an eluent) to afford **1d**, and **2d** respectively. The water layer was basified with powdered K_2CO_3 to be higher than 12 in terms of pH value, and the whole was extracted with CH_2Cl_2. The organic phase was washed with brine and dried over Na_2SO_4, then the solvent was evaporated under reduced pressure to give **3d**.

*^{13}C NMR Analysis of Methyl Methyl Carbamate (**1v**) in Strong Acid (Table 3).* Mixtures of TFSA and TFA in specified weight ratios were made. The acid solution (0.6 mL) was placed in a dried vial. This acid solution was added to weighted methyl methylcarbamate (**1v**) (10 mg). After mixing, the resulting solution was transferred to a dried NMR tube filled with Ar. The NMR spectra were obtained at 27 °C.

Kinetics Measurement (Tables 4 and 5). A Typical Procedure. Mixtures of TFSA and TFA in specified weight ratios were made. Each substrate **1** (0.05 mmol) was dissolved in the mixed acid (0.7 mL) and transferred into a dried NMR tube filled with argon and heated at 70 ± 0.01 °C in HAAKE DC30 circulator bath. At regular intervals, a tube was cooled in iced water and the NMR spectrum was recorded. Magnetic field locking was not used, but maximized the shimming with using acetone-d_6. The ^{1}H NMR spectra were obtained at 27 °C. The peak of TFSA was used as an internal standard of integration. The integration value of the benzyl protons of the substrate, as compared with that of TFSA, was obtained and concentrations are calculated (only for **1c**, aromatic methyl group proton was used because benzyl proton peak of substrate duplicates with benzyl peak of product). The ratios (in logarithm) of disappearance of the starting substrate against the initial amount of the substrate were plotted against time to give first-order kinetics (regression coefficient r > 0.99 in all cases). The rate constants were obtained on the basis of the first 5−10 data (before half-life of the substrates). For substrates that produce both cyclized product **2** and amine product **3**, the ratio of **2** and **3** was determined by ^{1}H NMR at the half time of half-life ($t_{1/2}$) of substrate.

Cyclization of Phenethylisocyanate ***8a*** *((2-Isocyanatoethyl)-benzene).* A solution of phenethylisocyanate **8a** (72.6 mg, 0.49 mmol) in CH_2Cl_2 (20 mL) was added into well-stirred trifluoromethanesulfonic acid (8.8 mL, 200 equiv) at 0 °C in a dropwise manner over 1 h under argon atmosphere. The whole was stirred at 0 °C for 1 h, then the whole was poured into ice−water (50 mL), and extracted with dichloromethane (50 mL × 2). The organic phase was dried over Na_2SO_4, and the solvent was evaporated to give a residue, which was column-chromatographed on silica-gel (eluent: AcOEt−Hexane (1:1)) to afford 3,4-dihydro-2*H*-isoquinolin-1-one **2a** as colorless plates (56.3 mg, 0.38 mmol, 78%).

COMPUTATIONAL METHODS

We carried out computational studies by using the Gaussian 03 and Gaussian 09 suites of programs. All the structures were fully optimized at the B3LYP/6-31G(d,p) and MP2/6-31G(d,p) levels. All the natural bond orbital (NBO) population analyses were carried out on the B3LYP/6-31G(d,p)-optimized structures. Single point energies were calculated with B3LYP/6-311++G(d,p)// B3LYP/6-31G(d,p), MP2/6-311++G(d,p)// MP2/6-31G(d,p) and MP4/6-311++G(d,p)// MP2/6-31G(d,p) levels.

Complete reference of (31) in the text. (31) Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Montogomery, J. A.; Jr., T. V.; Kudin, K. N.; Burant, J. C.; Millam, J. M.; Lyengar, S. S.; Tomasi, J.; Barone, V.; Mennucci, B.; Cossi, M.; Scalmani, G.; Rega, N.; Peterson, G. A.; Nakatsuji, H.; Hada, M.; Ehara, M.; Toyota, K.; Fukuda, R.; Hasegawa, J.; Ishida, M.; Nakajima, T.; Honda, Y.; Kitao, O.; Nakai, H.; Klene, M.; Li, X.; Knox, J. E.; Hratchian, H. P.; Cross, J. B.; Adamo, C.; Jaramillo, J.; Gomperts, R.; Stratmann, R. E.; Yazyev, O.; Austin, A. J.; Cammi, R.; Pomelli, C.; Ochterski, J. W.; Ayala, P. Y.; Morokuma, K.; Voth, G. A.; Salvador, P.; Dannenberg, J. J.; Zakrzewski, G.; Dapprich, S.; Daniels, A. K.; Foresman, J. B.; Ortiz, J. V.; Cui, Q.; Baboul, A. G.; Clifford, S.; Cioslowski, J.; Stefanov, B. B.; Liu, G.; Liashenko, A.; Piskorz, P.; Komaromi, I.; Martin, R. L.; Fox, D. J.; Keith, T.; Al-Laham, M. A.; Peng, C. Y.; Nanayakkara, A.; Challacombe, M.; Gill, P. M. W.; Johnson, B.; Chen, W.; Wong, M. W.; Gonzalez, C.; Pople, J. A. Gaussian 03, Gaussian, Inc.; Pittsburgh, PA, 2003.

ASSOCIATED CONTENT

Supporting Information

Supporting graphics and detailed calculations. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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REFERENCES

(1) Gunt, P. *J. Chem. Ed.* **1972**, *49*, 100−103.
(2) Minkwitz, R.; Neikes, F.; Lohmann, U. *Eur. J. Inorg. Chem.* **2002**, 27−30.
(3) (a) Olah, G. A.; White, A. M. *J. Am. Chem. Soc.* **1968**, *90*, 6087−6091. (b) Rasul, G.; Prakash, G. K. S.; Olah, G. A. *J. Org. Chem.* **1994**, *59*, 2552−2556.
(4) (a) Limatibul, S.; Watson, J. W. *J. Org. Chem.* **1971**, *36*, 3805−3807. (b) Ohwada, T. *Rev. Heteroatom Chem.* **1995**, *12*, 179−209. (c) Olah, G. A.; Burrichter, A.; Rasul, G.; Hachoumy, M.; Prakash, G. K. S. *J. Am. Chem. Soc.* **1997**, *119*, 12929−12933. (d) Olah, G. A.; Prakash, G. K. S.; Rasul, G. *J. Phys. Chem. C* **2008**, *112*, 7895−7899.
(5) Olah, G. A.; Burrichter, A.; Rasul, G.; Christe, K. O.; Prakash, G. K. S. *J. Am. Chem. Soc.* **1997**, *119*, 4345−4352.
(6) Olah, G. A.; Ku, A. T.; Olah, J. A. *J. Org. Chem.* **1971**, *36*, 3582−3584.
(7) Olah, G. A.; Rasul, G.; Yudin, A. K.; Burrichter, A.; Prakash, G. K. S.; Chistyakav, A. L.; Stankrvich, I. V.; Akhrem, I. S.; Gambaryan, N. P.; Vol'pin, M. E. *J. Am. Chem. Soc.* **1996**, *118*, 1446−1451.
(8) Armstrong, V. C.; Moodie, R. B. *J. Chem. Soc. B* **1968**, 275−277.
(9) Olah, G. A.; Heiner, T.; Rasul, G.; Prakash, G. K. S. *J. Org. Chem.* **1998**, *63*, 7993−7998.
(10) (a) Martin, S. F.; Tu, C. Y *J. Org. Chem.* **1981**, *46*, 3763−3764. (b) Pearson, W. H.; Schkeryantz, J. M. *J. Org. Chem.* **1992**, *57*, 6783−6789. (c) Angle, S. W.; Boyce, J. P. *Tetrahedron. Lett.* **1995**, *36*, 6185−6188. (d) Grunewald, G. L.; Caldwell, T. M.; Li, Q.; Dahanukar, V. H.; McNeil, B.; Criscione, K. R. *J. Med. Chem.* **1999**, *42*, 4351−4361.
(11) (a) Banwell, M. G.; Bissett, B. D.; Busato, S.; Cowden, C. J.; Hockless, D. C. R.; Holman, J. W.; Read, R. W.; Wu, A. W. *Chem. Soc. Chem. Commun.* **1995**, 2551−2553. (b) Shin, I.; Choi, E.; Cho, C. *Angew. Chem., Int. Ed.* **2007**, *46*, 2303−2305. (c) Szántó, G.; Hegedűs, L.; Mattyasovszky, L.; Simon, A.; Simon, Á.; SBitter, I.; Tóth, G.; Tőke, L.; Kádas, I. *Tetrahedron* **2009**, *65*, 8412−8417. (d) Manpadi, M.; Kireev, A. S.; Magedov, I. V.; Altig, J.; Tongwa, P.; Antipin, M. Y.; Evidente, A.; Otterlo, W. A. L.; Kornienko, A. *J. Org. Chem.* **2009**, *74*, 7122−7131.
(12) (a) Sall, D. J.; Grunewald, G. L. *J. Med. Chem.* **1987**, *30*, 2208−2216. (b) Grunewald, G. L.; Sall., D. J.; Monn, J. A. *J. Med. Chem.* **1988**, *31*, 433−444. (c) Grunewald, G. L.; Sall., D. J.; Monn, J. A. *J. Med. Chem.* **1988**, *31*, 824−830. (d) Norman, M. H; Rigdon, G. C.; NavasIII, F.; Cooper, B. R. *J. Med. Chem.* **1994**, *37*, 2552−2563. (e) Grunewald, G. L.; Seim, M. R.; Lu, J.; Makboul, M.; Criscione, K. R. *J. Med. Chem.* **2006**, *49*, 2939−2952. (f) Funke, U.; Fischer, S.; Hiller, A.; Scheunemann, M.; Deuther-Conrad, W.; Brust, P.; Steinbach, J. *Bioorg. Med. Chem. Lett.* **2008**, *18*, 4727−4730.
(13) Narasimhan, N. S.; Chandrachood, P. S.; Shete, N. R. *Tetrahedron* **1981**, *37*, 825−827.
(14) Wang, X. J; Tan, J.; Grozinger, K. *Tetrahedron Lett.* **1998**, *39*, 6609−6612.
(15) Decomposition of the methoxy group is faster than the cyclization reaction (see Supporting Information).
(16) Saito, S.; Saito, S.; Ohwada, T.; Shudo, K. *Chem. Pharm. Bull.* **1991**, *39*, 2718−2720.
(17) (a) Ohwada, T.; Yamazaki, T.; Suzuki, T; Saito, S.; Shudo, K. *J. Am. Chem. Soc.* **1996**, *118*, 6220−6224. (b) Klumpp, D. A.; Baek, D. N.; Prakash, G. K. S.; Olah, G. A. *J. Org. Chem.* **1997**, *62*, 6666−6671. (c) Klumpp, D. A.; Lau, S. *J. Org. Chem.* **1999**, *64*, 7309−7311. (d) Olah, G. A.; Mathew, T.; Marinez, E. R.; Esteves, P. M.; Etzkorn, M.; Rasul, G.; Prakash, G. K. S. *J. Am. Chem. Soc.* **2001**, *123*, 11556−11561. (e) Klumpp, D. A.; Zhang, Y.; Kindelin, P. J.; Lau, S. *Tetrahedron* **2006**, *62*, 5915−5921. (f) Nakamura, S.; Sugimoto, H.; Ohwada, T. *J. Am. Chem. Soc.* **2007**, *129*, 1724−1732. (g) Nakamura, S.; Sugimoto, H.; Ohwada, T. *J. Org. Chem.* **2008**, *73*, 4219−4224. (h) Kurouchi, H.; Sugimoto, H.; Otani, Y.; Ohwada, T. *J. Am. Chem. Soc.* **2010**, *132*, 807−815.
(18) Zucker, L.; Hammett, L. P. *J. Am. Chem. Soc.* **1939**, *61*, 2791−2798.
(19) For monocations: (a) Lucchini, V.; Modena, G.; Scorrano, G.; Tonellato, U. *J. Am. Chem. Soc.* **1977**, *99*, 3387−3392. (b) Baigrie, L. M.; Cox, R. A.; Slebocka-Tilk, H.; Tencer, M.; Tidwell, T. T. *J. Am. Chem. Soc.* **1985**, *107*, 3640−3645. For dications: (c) Saito, S.; Sato, Y.; Ohwada, T.; Shudo, K. *J. Am. Chem. Soc.* **1994**, *116*, 2312−2317. (d) Sato, Y.; Yato, M.; Ohwada, T.; Saito, S.; Shudo, K. *J. Am. Chem. Soc.* **1995**, *117*, 3037−3043. (e) Suzuki, T.; Ohwada, T.; Shudo, K. *J. Am. Chem. Soc.* **1997**, *119*, 6774−6780. (f) Ohwada, T.; Suzuki, T.; Shudo, K. *J. Am. Chem. Soc.* **1998**, *120*, 4629−4637. (g) Yokoyama, A.; Ohwada, T.; Shudo, K. *J. Org. Chem.* **1999**, *64*, 611−617. (h) Olah, G. A.; Mathew, T.; Marinez, E. R.; Esteves, P. M.; Etzkorn, M.; Rasul, G.; Prakash, G. K. S. *J. Am. Chem. Soc.* **2001**, *125*, 11556−11561.
(20) The relationship can be considered in another way. If the cyclization and amine formation reactions occur independently, both reaction rates should be linear functions of acidity. For substrates **1a**, **1b**, **1p** and **1w**, the reaction rates are linearly related to acidity. But, the reaction rate of amine formation decreased as the acidity of the medium was increased (Figure S1, Supporting Information), even though the reaction rates of **1d** and **1g** showed a linear dependency on acidity. Therefore, the figure indicates that the rate-determining step is common for the cyclization and amine formation.
(21) Armstrong, V. C.; Moodie, R. B. *J. Chem. Soc. B* **1969**, 934−939.
(22) Formation of isocyanates from hindered ureas was also reported recently: Hutchby, M.; Houlden, C. E.; Ford, J. G.; Tyler, S. N. G.; Gagné, M. R.; Jones, G. C. L.; Milburn, K. I. B. *Angew. Chem., Int. Ed.* **2009**, *48*, 8721−8724.
(23) Yokoyama, A.; Ohwada, T.; Shudo, K. *J. Org. Chem.* **1999**, *64*, 611−617.
(24) (a) Bender, M. L.; Ladenheim, H.; Chen, M. C. *J. Am. Chem. Soc.* **1961**, *83*, 123−127. (b) Yates, K. *Acc. Chem. Res.* **1971**, *4*, 136−144.
(25) Olah, G. A.; Hartz, N.; Rasul, G.; Burrichter, S.; Prakash, G. K. S. *J. Am. Chem. Soc.* **1995**, *117*, 6421−6427.
(26) (a) Cox, R. A. *Can. J. Chem.* **2005**, *83*, 1391−1399. (b) Cox, R. A. *Can. J. Chem.* **2008**, *86*, 290−297.
(27) (a) The crystal structure of isocyanate carbocation was recently reported. See: Uehara, K.; Fukaya, K.; Mizuno, N. *Angew. Chem., Int. Ed.* **2012**, *51*, 7715−7718. (b) Olah, G. A.; Nishimura, J.; Kreienbühl, P. *J. Am. Chem. Soc.* **1973**, *95*, 7672−7680.
(28) Bieber, T. I. *J. Am. Chem. Soc.* **1952**, *74*, 1405−1408.
(29) (a) Moodie, R. B.; Sansom, P. J. *J. Chem. Soc., Perkin Trans. 2* **1981**, 664. (b) Raspoet, G.; Nguyen, M. T. *J. Org. Chem.* **1998**, *63*, 6867−6877.
(30) (a) Leuckart, R. *J. Prakt. Chem.* **1890**, *41*, 301−329. (b) Effenberger, F.; Gleiter, R. *Chem. Ber.* **1964**, *97*, 472−479. (c) Hendrickson, J. B.; Bogard, T. L.; Fisch, B. M.; Grossert, S.; Yoshimura, N. *J. Am. Chem. Soc.* **1974**, *96*, 7781−7789. (d) Umezawa, B.; Hoshino, O.; Sawaki, S.; Mori, K. *Chem. Pharm. Bull.* **1980**, *28*, 1003−1005. (e) Sánchez, I. H.; Larraza, M. I.; Flores, H. J.; Martell, E. A.; Linzaga, I.; Carter, A. A. *Heterocycles* **1985**, *23*, 251−256.
(31) Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Montogomery, J. A., Jr.; Vreven, T.; Kudin, K. N.; Burant, J. C.; Millam, J. M.; Lyengar, S. S.; Tomasi, J.; Barone, V.; Mennucci, B.; Cossi, M.; Scalmani, G.; Rega, N.; Peterson, G. A.; Nakatsuji, H.; Hada, M.; Ehara, M.; Toyota, K.; Fukuda, R.; Hasegawa, J.; Ishida, M.; Nakajima, T.; Honda, Y.; Kitao, O.; Nakai, H.; Klene, M.; Li, X.; Knox, J. E.; Hratchian, H. P.; Cross, J. B.; Bakken, V.; Adamo, C.; Jaramillo, J.; Gomperts, R.; Stratmann, R. E.; Yazyev, O.; Austin, A. J.; Cammi, R.; Pomelli, C.; Ochterski, J. W.; Ayala, P. Y.; Morokuma, K.; Voth, G. A.; Salvador, P.; Dannenberg, J. J.; Zakrzewski, G.; Dapprich, S.; Daniels, A. K.; Strain, M. C.; Farkas, O.; Malick, D. K.; Rabuck, A. D.; Raghavachari, K.; Foresman, J. B.; Ortiz, J. V.; Cui, Q.; Baboul, A. G.; Clifford, S.; Cioslowski, J.; Stefanov, B. B.; Liu, G.; Liashenko, A.; Piskorz, P.; Komaromi, I.; Martin, R. L.; Fox, D. J.; Keith, T.; Al-Laham, M. A.; Peng, C. Y.; Nanayakkara, A.; Challacombe, M.; Gill, P. M. W.; Johnson, B.; Chen, W.; Wong, M. W.; Gonzalez, C.; Pople, J. A. *Gaussian 03*; Gaussian, Inc.: Pittsburgh, PA, 2003. Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Scalmani, G.; Barone, V.; Mennucci, B.; Petersson, G. A.; Nakatsuji, H.; Caricato, M.; Li, X.; Hratchian, H. P.; Izmaylov, A. F.; Bloino, J.; Zheng, G.; Sonnenberg, J.

L.; Hada, M.; Ehara, M.; Toyota, K.; Fukuda, R.; Hasegawa, J.; Ishida, M.; Nakajima, T.; Honda, Y.; Kitao, O.; Nakai, H.; Vreven, T.; Montgomery, J. A., Jr.; Peralta, J. E.; Ogliaro, F.; Bearpark, M.; Heyd, J. J.; Brothers, E.; Kudin, K. N.; Staroverov, V. N.; Kobayashi, R.; Normand, J.; Raghavachari, K.; Rendell, A.; Burant, J. C.; Iyengar, S. S.; Tomasi, J.; Cossi, M.; Rega, N.; Millam, J. M.; Klene, M.; Knox, J. E.; Cross, J. B.; Bakken, V.; Adamo, C.; Jaramillo, J.; Gomperts, R.; Stratmann, R. E.; Yazyev, O.; Austin, A. J.; Cammi, R.; Pomelli, C.; Ochterski, J. W.; Ayala, P. Y.; Strain, M. C.; Farkas, O.; Malick, D. K.; Rabuck, A. D.; Raghavachari, K.; Cui, Q.; Baboul, A. G.; Clifford, S.; Stefanov, B. B.; Liu, G.; Liashenko, A.; Piskorz, P.; Komaromi, I.; Keith, T.; Al-Laham, M. A.; Peng, C. Y.; Nanayakkara, A.; Challacombe, M.; Gill, P. M. W.; Johnson, B.; Chen, W.; Wong, M. W.; Pomelli, C.; Ochterski, J. W.; Martin, R. L.; Morokuma, K.; Zakrzewski, V. G.; Voth, G. A.; Salvador, P.; Dannenberg, J. J.; Dapprich, S.; Daniels, A. D.; Farkas, Ö.; Foresman, J. B.; Ortiz, J. V.; Cioslowski, J.; Fox, D. J. *Gaussian 09*; Gaussian, Inc.: Wallingford, CT, 2009.

(32) (a) Reed, A. E.; Curtiss, L. A.; Weinhold, F. *Chem. Rev.* **1988**, *88*, 899. (b) NBO version 3.

(33) During the preparation of this manuscript, a new method to enhance the dissociation of C-N bond of urea was reported. Raja, E. K.; Nilsson Lill, S. O.; Klumpp, D. A. *Chem. Commun.* **2012**, *48*, 8141−8143.