

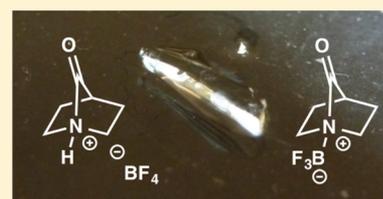
Total Synthesis and Characterization of 7-Hypoquinuclidonium Tetrafluoroborate and 7-Hypoquinuclidone BF₃ Complex

Marc Liniger,[†] David G. VanderVelde, Michael K. Takase, Mona Shahgholi, and Brian M. Stoltz*

Division of Chemistry and Chemical Engineering, California Institute of Technology, Pasadena, California 91125, United States

S Supporting Information

ABSTRACT: Derivatives of the fully twisted bicyclic amide 7-hypoquinuclidone are synthesized using a Schmidt–Aubé reaction. Their structures were unambiguously confirmed by X-ray diffraction analysis and extensive spectroscopic characterization. Furthermore, the stability and chemical reactivity of these anti-Bredt amides are investigated. 7-Hypoquinuclidonium tetrafluoroborate is shown to decompose to a unique nitrogen bound amide–BF₃ complex of 7-hypoquinuclidone under anhydrous conditions and to react instantaneously with water making it one of the most reactive amides known to date.



INTRODUCTION

The importance of the amide bond cannot be overstated.¹ Typical amides are planar structures,² however, amide bonds can be highly twisted such as in bicyclic bridgehead lactams.³ The distortion of the orbitals from planarity and the pyramidalization of the nitrogen from sp² toward sp³ dramatically affect the stability and reactivity^{3,4} of anti-Bredt amides.⁵ In 2006, our group published the first unambiguous synthesis and characterization of 2-quinuclidonium tetrafluoroborate **1** (Figure 1).⁶ Most recently Kirby and co-workers

energetics, and protonation of 7-hypoquinuclidone **4** were investigated by DFT calculations¹⁰ and the molecule has been suggested to be too strained to be isolated.^{10c}

RESULTS AND DISCUSSION

Based on the knowledge and experience in our research group with the synthesis of 2-quinuclidonium tetrafluoroborate **1**, we proposed a synthesis of 7-hypoquinuclidone **4** using an intramolecular Schmidt–Aubé reaction¹¹ leading to ketoazide **8** as the key fragment (Scheme 1).

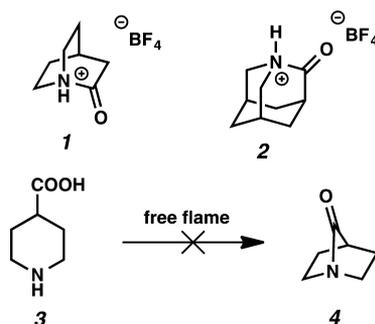
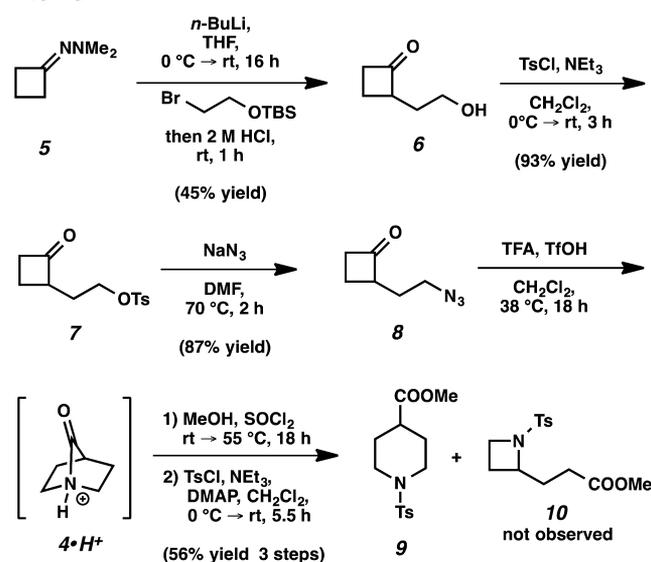


Figure 1. Stoltz's 2-quinuclidonium tetrafluoroborate (**1**), Kirby's "most reactive amide" **2**, and Hall's attempted synthesis of 7-hypoquinuclidone **4** from piperidine-4-carboxylic acid (**3**).

reported on the synthesis and characterization of the "most reactive" twisted amide, an 1-aza-2-adamantone HBF₄ salt **2**,⁷ which provoked us to explore the synthesis of an even more reactive amide.

Of interest to us was a 1958 paper, in which Hall failed to synthesize 7-hypoquinuclidone **4** by heating piperidine-4-carboxylic acid (**3**) in a free flame (Figure 1). Instead, sublimation of the amino acid was observed.⁸ The highly strained structure of a [2.2.1] bridged bicyclic lactam was also proposed as an intermediate in a model system toward the synthesis of perophoramidine.⁹ Most recently, the structure,

Scheme 1. Synthesis of Protected Piperidine 4-Carboxylic Acid Methyl ester **9**: First Proof for the Existence of 7-Hypoquinuclidone **4**



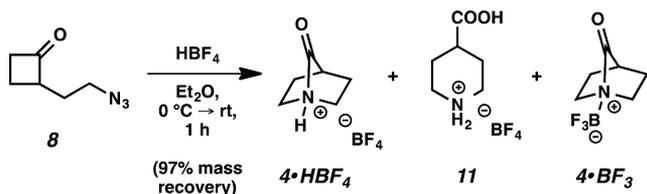
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Synthesis. The synthesis commenced from literature known cyclobutanone *N,N*-dimethylhydrazone **5**,¹² which was alkylated with TBS protected 2-bromoethanol (Scheme 1).^{13,14} The corresponding intermediate was fully deprotected under acidic conditions to afford hydroxy ketone **6** in 45% yield. Tosylation of the alcohol and substitution with sodium azide gave access to substrate **8** for the intramolecular Schmidt–Aubé reaction. Since it was uncertain if this highly strained and fully twisted lactam **4·H⁺** would even exist, we decided to solvolyze this hypothetical intermediate **4·H⁺** *in situ* with methanol as the nucleophile. Moreover, the reaction was performed under Fischer esterification conditions to ensure protection of the corresponding amino acid, in case **4·H⁺** would have been hydrolyzed with traces of water. Thus, treatment of ketoazide **8** with triflic acid¹⁵ followed by solvolysis/esterification with methanol and tosyl protection of the amine furnished *N*-tosyl piperidine 4-carboxylic acid methyl ester (**9**) in 56% yield over three steps after column chromatography.¹⁶ It should be noted that the corresponding protected azetidione **10** was not observed at all (it would originate from migration of the other single bond in the Schmidt–Aubé reaction).¹⁷

With a first proof for the existence of 7-hypoquinclidone in hand, ketoazide **8** was treated with tetrafluoroboric acid in diethyl ether, which led to immediate gas evolution and precipitation of a colorless solid (97% mass recovery). NMR experiments revealed the presence of three species in a 77:15:12 ratio: the protonated amide 7-hypoquinclidonium tetrafluoroborate **4·HBF₄**, the hydrolysis product **11**, and, unexpectedly, the BF₃ complex of 7-hypoquinclidone **4·BF₃** (Scheme 2).

Scheme 2. Total Synthesis of 7-Hypoquinclidonium Tetrafluoroborate **4·HBF₄ and 7-Hypoquinclidone BF₃ Complex **4·BF₃****



Since the formation of **4·BF₃** was at first mysterious and somehow unexpected, we wondered if traces of BF₃ etherate are present in our commercial 50–54% HBF₄ solution, which would catalyze the Schmidt–Aubé reaction.¹⁸ The inherent

instability of HBF₄ in acidic solutions was further supported by voltammetric investigations, which indicated decomposition of HBF₄ to a BF₃–solvent complex and HF.¹⁹ To check this hypothesis, ketoazide **8** was subjected to 2 equiv of BF₃ etherate instead of HBF₄ with the ultimate goal of selectively preparing **4·BF₃**. However, neither gas evolution nor consumption of the starting material was observed, even at room temperature. Subsequently, a catalytic amount of HBF₄ was added with the idea that the proton of the Brønsted acid would be formally released after formation of product **4·BF₃**. In contrast, the catalytic amount of acid was consumed instantaneously with concomitant gas evolution and precipitation of a solid. Thereafter, the reaction did not proceed any further without adding a stoichiometric amount of HBF₄ (2 equiv in total). After stirring overnight, we isolated instead of **4·BF₃** the hydrolyzed amino acid **11** as the major product (73%) along with 15% of **4·HBF₄** and a third unknown species (ca. 12%) according to ¹H NMR spectroscopy.²⁰ When the spectrum was recorded again the next day, the later two species had converted to **11** in a quantitative fashion. At this point, it was still unclear how **4·BF₃** was formed, but we gained first evidence for the inherent instability of **4·HBF₄** toward hydrolysis in dry CD₃CN leading to the expected hydrolysis product isonipecotic acid tetrafluoroborate (**11**).

Proof of Structure and Spectroscopic Data. 7-Hypoquinclidonium tetrafluoroborate (**4·HBF₄**) was isolated as a stable, colorless solid, which can be stored in a –40 °C freezer of a nitrogen filled glovebox for several weeks without decomposition. However, as soon as the solid is dissolved in any rigorously dried solvent, decomposition starts immediately, even upon handling in the dry atmosphere of a glovebox (N₂). For this reason, all of our attempts failed to grow single crystals of **4·HBF₄** via precipitation, recrystallization, or vapor diffusion method between –40 and 23 °C. Fortunately, decomposition was slow enough to characterize **4·HBF₄** spectroscopically in CD₃CN solution by multinuclear ¹H, ¹¹B, ¹⁹F, ¹³C, ¹⁴N, ¹⁵N NMR spectroscopy in a J. Young NMR tube and as a solid by attenuated total reflectance infrared spectroscopy (ATR-IR, Table 1). By contrast, **4·HBF₄** was hydrolyzed instantaneously in the matrix of the fast atom bombardment high-resolution mass spectrometer (FAB-HRMS) and in the electrospray ionization chamber (ESI) of a linear ion trap mass spectrometer (LTQ-CID-MS). The mass spectra for **4·HBF₄** were identical to those recorded for the hydrolysis product **11**. A very characteristic 1:1:1 triplet at 7.76 ppm was observed for the NH⁺ group in the ¹H NMR spectrum of **4·HBF₄** (Figure 2)

Table 1. Selected Spectroscopic Properties for Twisted Amides **4·HBF₄ and **4·BF₃** and for the Hydrolysis Product Isonipecotic Acid Tetrafluoroborate (**11**)**

compound ^a	4·HBF₄	4·BF₃	11
δ ¹ H of NH _x	7.76 (t, ¹ J _{1H14N} = 63 Hz)	–	6.90–6.12 (m, ¹ J _{1H14N} = ~55 Hz)
δ ¹³ C of C=O	174.7	179.8	169.7
δ ¹¹ B	–1.2 (s)	–0.3 (q, ¹ J _{11B19F} = 13.8 Hz)	–1.2 (s)
δ ¹⁹ F	–151.3 (s)	–154.9 (q, ¹ J _{19F11B} = 13.9 Hz)	–151.2 (s)
δ ¹⁴ N ^b	34.8 (d, ¹ J _{14N1H} = 63 Hz)	39.3 (s)	–4.9 (m, ¹ J _{14N1H} = not resolved)
δ ¹⁵ N ^b	78.6 (¹ J _{15N1H} = ~88 Hz)	–	38.8 (¹ J _{15N1H} = ~77 Hz) ^c
IR, ν _{max} C=O, cm ^{–1}	1877 ^d	1860 ^d	1814 ^e

^aAll NMR spectra were recorded in CD₃CN. ^b¹⁴N shifts referenced to tetramethylammonium iodide and ¹⁵N shifts to external liquid ammonia. Due to the low abundance of ¹⁵N, the chemical shifts and coupling constants were determined by ¹H–¹⁵N and ¹H{¹⁵N}–¹⁵N correlation experiments. ^cA vicinal proton coupling constant of ²J_{1H1H} = 10.8 Hz was observed. ^dMeasured using an ATR-IR in an argon filled glovebox. ^eNeat film on a NaCl plate.

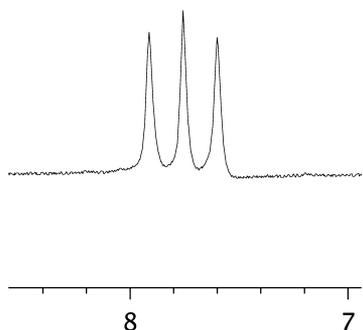


Figure 2. Detail of the ^1H NMR spectrum of $4\cdot\text{HBF}_4$ showing the distinctive 1:1:1 triplet of the protonated amide.

showing a ^1H – ^{14}N coupling ($J = 63$ Hz, $I = 1$, Table 1). This indicated a highly symmetric environment around the nitrogen, since otherwise the ^1H – ^{14}N splitting pattern would not be resolved due to significant quadrupolar line broadening.²¹

These findings for $4\cdot\text{HBF}_4$ were further confirmed by the observed doublets in the ^{14}N and ^{15}N NMR spectra (Table 1). The carbonyl infrared absorption band of $4\cdot\text{HBF}_4$ was observed at 1877 cm^{-1} (ATR), which is the highest value we have ever observed for an organic molecule, even higher than acid chlorides or anhydrides. This value suggests a rather short and strong C=O bond in a highly strained molecule. These conclusions were in line with our DFT calculations for the structure of $4\cdot\text{HBF}_4$ (see Table 21 in the SI).²² Moreover, since we did not observe any other C=O bands nor overlapping IR signals originating from the other two species ($4\cdot\text{BF}_3$ and **11**), the recorded IR spectrum of $4\cdot\text{HBF}_4$ was evidence for high purity of the isolated crude solid after the reaction. The observed mixture in the ^1H NMR spectrum of $4\cdot\text{HBF}_4$, $4\cdot\text{BF}_3$, and **11** (Scheme 2) most likely resulted from decomposition by dissolving the solid in CD_3CN and in the time until the NMR spectra were recorded.

A single crystal of $4\cdot\text{BF}_3$ suitable for X-ray diffraction analysis was grown over 4 weeks by slow diffusion of diethyl ether into a solution of the crude twisted amide $4\cdot\text{HBF}_4$ in acetonitrile at $-40\text{ }^\circ\text{C}$ in the glovebox (N_2). The crystal structure of $4\cdot\text{BF}_3$ is depicted in Figure 3.

In all our attempts to crystallize the protonated twisted amide $4\cdot\text{HBF}_4$, we could only isolate crystals of the BF_3 complex $4\cdot\text{BF}_3$, which apparently is the more stable compound of the two amides (Figure 3). To our knowledge, the BF_3 complex of 7-hypoquinclidone $4\cdot\text{BF}_3$ is the first and only nitrogen bound BF_3 –amide complex reported to date. A single

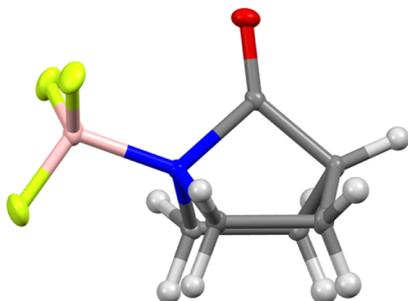


Figure 3. X-ray structure of 7-hypoquinclidone BF_3 complex $4\cdot\text{BF}_3$ (ellipsoids at the 50% probability level, oxygen = red, nitrogen = blue, boron = pink, fluorine = yellow, carbon = dark gray, hydrogen = white).

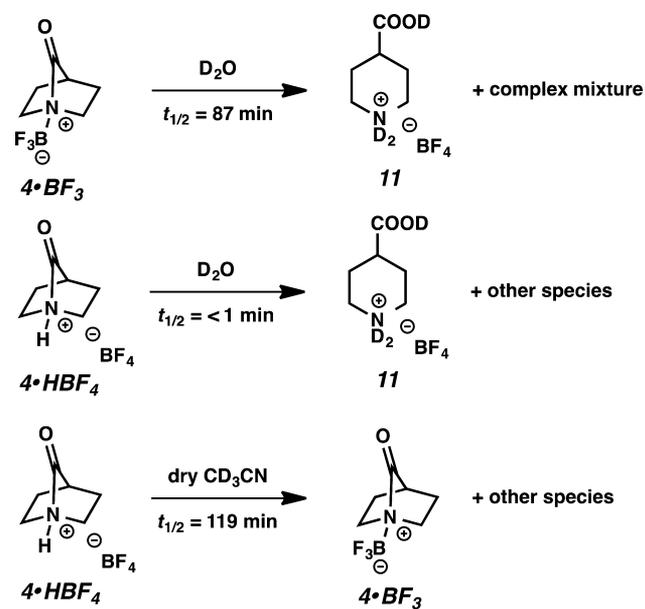
molecule of $4\cdot\text{BF}_3$ was observed in the unit cell of the crystal with a high degree of symmetry (mirror plane through the F–B–N–C=O axis). The compound clearly belongs among the most twisted amides with a torsion angle τ of 90.0° . The nitrogen is highly pyramidalized with an out-of-plane parameter χ_{N} of 69.8° , while the carbonyl carbon is exactly planar and sp^2 hybridized ($\chi_{\text{C}} = 0.0^\circ$). The observed length of the N–C(O) bond is 1.526 \AA , 1.186 \AA for the C=O bond and 1.606 \AA for the N–B bond, respectively. These parameters were all in close agreement to the calculated structure of $4\cdot\text{BF}_3$ (see Table 21 in the SI and compare with parameters of other twisted amides and more calculated structures). Selected spectroscopic parameters of $4\cdot\text{BF}_3$ are summarized in Table 1. The ^{13}C chemical shift of the carbonyl group in $4\cdot\text{BF}_3$ is 5 ppm more downfield than in $4\cdot\text{HBF}_4$, which is also true for the ^{19}F chemical shift at -154.9 ppm. In the latter case, the 1J coupling to ^{11}B ($I = 3/2$) was observed as a 1:1:1:1 quartet with a coupling constant of 14 Hz.²³ The reverse coupling to ^{19}F ($I = 1/2$) was visible at -0.3 ppm as a 1:3:3:1 quartet in the ^{11}B NMR spectrum, however without any coupling to ^{14}N .²⁴ The carbonyl stretching vibration for $4\cdot\text{BF}_3$ was observed at 1860 cm^{-1} , which is a slightly lower frequency than that for $4\cdot\text{HBF}_4$. This trend is in line with a slightly longer C=O bond for $4\cdot\text{BF}_3$ than for $4\cdot\text{HBF}_4$ according to our DFT calculations (see Table 21 in the SI).

The formal hydrolysis product of $4\cdot\text{HBF}_4$, isonipecotic acid tetrafluoroborate (**11**), was fully characterized by spectroscopic methods (Table 1), and the structure was unambiguously confirmed by X-ray diffraction analysis (see the SI). As for the protonated twisted amide $4\cdot\text{HBF}_4$, spin couplings of ^1H – ^{14}N and ^1H – ^{15}N were observed with coupling constants of 55 and 77 Hz, respectively. Remarkably, the C=O IR stretching frequency at 1814 cm^{-1} (NaCl) was rather high for a carboxylic acid.

Chemical Behavior. As described earlier in this paper, the protonated amide $4\cdot\text{HBF}_4$ was much more sensitive to nucleophiles than the BF_3 complex $4\cdot\text{BF}_3$. $4\cdot\text{HBF}_4$ decomposed very quickly in solution, even in rigorously dried solvents and with careful handling in the glovebox. For this reason, the NMR spectra of dissolved $4\cdot\text{HBF}_4$ had to be recorded as fast as possible, since the signals corresponding to $4\cdot\text{HBF}_4$ disappeared very quickly and several new species were formed over time. In contrast, solutions of the corresponding BF_3 complex $4\cdot\text{BF}_3$ were fairly stable according to NMR spectroscopy. This raised the question if the BF_3 complex $4\cdot\text{BF}_3$ is the decomposition product of the very labile amide $4\cdot\text{HBF}_4$ in dry solution, which would also explain why we could grow crystals of $4\cdot\text{BF}_3$ out of a solution of $4\cdot\text{HBF}_4$.

To answer these questions, we studied the decomposition and reactivity of both twisted amides $4\cdot\text{BF}_3$ and $4\cdot\text{HBF}_4$ in CD_3CN in the presence or absence of D_2O over time using a series of ^1H NMR measurements with 1,3,5-trichlorobenzene as the internal standard (Scheme 3; see the SI for more details).

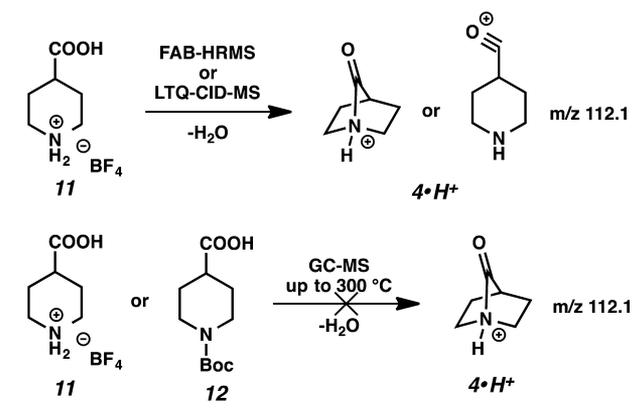
$4\cdot\text{BF}_3$ was fairly stable in wet CD_3CN with a half-life of 87 min (9.6 equiv of D_2O , $10.6\text{ }\mu\text{M}$) yielding a complex mixture of products along with amino acid **11** (Scheme 3). By contrast, the protonated amide $4\cdot\text{HBF}_4$ was hydrolyzed instantaneously upon addition of 5 equiv of D_2O ($t_{1/2} = <1$ min, $87.4\text{ }\mu\text{M}$) to give amino acid **11** as the major product. Compared to the half-lives of 2-quinuclidonium tetrafluoroborate **1** ($t_{1/2} = 135$ min, $84\text{ }\mu\text{M}$, 5 equiv)^{6a} and Kirby's "most reactive amide" **2** ($t_{1/2} = 8.4$ min, $84\text{ }\mu\text{M}$, 5 equiv D_2O , Figure 1),⁷ 7-hypoquinclidonium tetrafluoroborate $4\cdot\text{HBF}_4$ is now the most reactive

Scheme 3. Reactivity for $4\cdot\text{HBF}_4$ and $4\cdot\text{BF}_3$ in Solution and Determination of Their Half-Lives

twisted amide prepared to date. In addition, $4\cdot\text{HBF}_4$ decomposed in dry CD_3CN with a half-life of 119 min (117 μM). At the same time, saturation growth of the BF_3 complex $4\cdot\text{BF}_3$ was observed over time, which strongly indicated that $4\cdot\text{BF}_3$ is indeed formed from $4\cdot\text{HBF}_4$ in dry CD_3CN solution. It should be noted that several other unidentified species were observed together with $4\cdot\text{BF}_3$. However, amino acid **11** was not detected at all due to the absence of water.

When the twisted amides $4\cdot\text{HBF}_4$ and $4\cdot\text{BF}_3$ and the amino acid **11** were characterized by FAB-HRMS, we found identical spectra due to fast hydrolysis in the matrix, but also a common dehydration fragment with m/z 112.1 corresponding to the protonated twisted amide $4\cdot\text{H}^+$ or its ring-chain tautomer as an oxocarbenium ion (Scheme 4). Since we previously

Scheme 4. Gas Phase and Thermal Reactivity of Isonipectotic Acid Derivatives

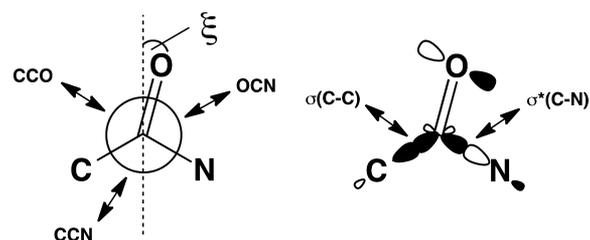


observed dehydration of the hydrolyzed twisted amide **1** (Figure 1) via collision induced dissociation (CID),^{6b} this raised the question if **11** was dehydrated to $4\cdot\text{H}^+$ by FAB ionization in the matrix or in the gas phase. To investigate this, we isolated the ammonium ion of **11** with m/z 130.1 in the ion trap of the LTQ-MS. Upon collisional excitation (MS^2 -CID), we did indeed observe dehydration giving an ion $4\cdot\text{H}^+$ with m/z

112.1 in the mass spectrum (see the SI for the spectra). When isolation and excitation of $4\cdot\text{H}^+$ was continued in a multistage MS experiment (MS^3), a formal loss of CO ($M-28$) corresponding to an ion with m/z 81.4 was observed.

Inspired by Kirby's observation for thermal cyclization to adamantane type twisted amides in the gas phase,⁷ we attempted to cyclize amino acid **11** and the commercially available Boc protected derivative **12** by gas chromatography (Scheme 4). However, all attempts failed and no ions were observed at all.

Definition of Bending Angle ξ . We observed significant bending of the carbonyl oxygen toward the nitrogen in the crystal structure of $4\cdot\text{BF}_3$ (Figure 3), and we found that this phenomenon was significantly underestimated in our calculated structure of $4\cdot\text{BF}_3$ (see Table 21 in the SI). Since there was no parameter available in the literature to describe $\text{C}=\text{O}$ bending, we introduced a $\text{C}=\text{O}$ bending angle ξ , which is defined as the deviation of the imaginary CCN angle bisector (Figure 4).

Figure 4. Definition of the bending angle ξ and the dominant orbital interactions of the p-type lone pair of the $\text{C}=\text{O}$ oxygen.

Mathematically, ξ can be calculated with the bond path angles CCN , CCO , and OCN :²⁵ $\xi = ((360^\circ - \text{CCN})/2 - \text{OCN})$. A positive value means bending toward the nitrogen, and a negative one, bending into the opposite direction. For the crystal and the calculated structure of $4\cdot\text{BF}_3$, we observed ξ values of 5.8° and 4.5° , respectively.

In 1985, Bürgi and Schmidt investigated $\text{C}=\text{O}$ bending in lactones and lactams for the first time based on X-ray structures and molecular orbital calculations.²⁶ An anomeric effect was proposed to explain this phenomenon, which involves destabilizing interactions of the p-type lone pair at oxygen with the bonding $\sigma(\text{C}-\text{C})$ orbital and favorable overlap with the antibonding $\sigma^*(\text{C}-\text{N})$ orbital (Figure 4). Thus, $\text{C}=\text{O}$ bending will reduce the former interaction and increase the latter one.²⁶ At the same time, $\text{C}=\text{O}$ bending is an early sign of $\text{C}-\text{N}$ bond breakage leading to an oxocarbenium ion similar to $4\cdot\text{H}^+$ (Scheme 4) with concomitant $\text{C}-\text{N}$ bond elongation.²⁶ In line with our own data (see Table 21 in the SI), significant deviations of calculated ξ values were observed compared to X-ray structures by Bürgi²⁶ and others.^{10c,27}

Since $\text{C}=\text{O}$ bending is a significant deformation of the amide bond in anti-Bredt lactams and an additional measure for their stability, we suggest using the Bürgi–Dunitz–Winkler parameters (χ_{C} , χ_{N} , τ , ξ) to describe twisted amides in the future.

CONCLUSIONS

Almost 60 years after Hall's first attempt to prepare 7-hypoquinclidone **4**,⁸ we have successfully accomplished the first total synthesis and complete characterization of the protonated twisted amide $4\cdot\text{HBF}_4$ and its BF_3 complex $4\cdot\text{BF}_3$. The use of a Schmidt–Aubé reaction proved again to be

key for success.^{6a} Moreover, the stability and reactivity of both **4**·HBF₄ and **4**·BF₃ were thoroughly investigated in solution and in the gas phase. These studies revealed that **4**·HBF₄ is, to our knowledge, the most reactive amide prepared to date with a half-life of less than 1 min in the presence of water. The reverse reaction to **4**·H⁺ was rendered possible in the gas phase by formal dehydration of isonipecotic acid **11** using FAB or CID excitation. Since C=O bending contributes to the stability of twisted amides²⁶ and is still difficult to predict by DFT calculations,^{10c,26,27} a novel bending angle ξ was defined as an addition to the already existing Dunitz–Winkler parameters.⁵ Looking ahead, the limits are still open for the synthesis of more or less reactive but structurally unique twisted amides.

METHODS

Standard methods were used for the preparation, isolation, and analysis of all new compounds (for experimental details and complete characterization, see the SI).

Preparation of **4·HBF₄ and Crystallization of **4**·BF₃ from Keto Azide **8**.** To a solution of **8** (52.0 mg, 0.37 mmol, 1.0 equiv) in Et₂O (0.75 mL) was added, at 0 °C, HBF₄ (0.10 mL, 0.71 mmol, 1.9 equiv, 50–54 wt %/wt in Et₂O). Gas evolution was observed immediately. After the mixture was stirred for 1 h at room temperature, the starting material was fully consumed and a colorless precipitate had been formed. The solvent was decanted off with a syringe under argon. The solids were washed with Et₂O (3 × 0.8 mL) and dried under high vacuum to afford crude **4**·HBF₄ (72.0 mg, 97% mass recovery) as a colorless solid. Slow diffusion of Et₂O into a solution of the crude product in acetonitrile at –40 °C over 4 weeks yielded one single crystal of **4**·BF₃ (2.0 mg, 3%) as a colorless needle.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.5b11750.

Crystallographic data for **9** (CIF)

Crystallographic data for **4**·BF₃ (CIF)

Crystallographic data for **11** (CIF)

Experimental procedures, characterization data, crystal and structure refinement data, calculated geometries, and details of kinetic measurements (PDF)

AUTHOR INFORMATION

Corresponding Author

*stoltz@caltech.edu

Present Address

†Givaudan Schweiz AG, Fragrances S&T/Ingredients Research, Ueberlandstrasse 138, CH-8600 Dübendorf, Switzerland.

Notes

The authors declare no competing financial interest.

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- (15) Neither gas evolution nor conversion was observed when 1.5 equiv of trifluoroacetic acid were used without any triflic acid.
- (16) Traces of the protected dimer and trimer of **9** were detected by LC-MS in the crude reaction mixture (see the SI for the spectra), which was evidence for the polymerizability of **4**. Compare with ref 8.
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overlapping with the more intense peak originating from ^{11}B coupling (ca. 1/3 intensity of the major peak).

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