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Mechanistic Pathways in CF_3COOH-Mediated Deacetalization Reactions†

Wei Li,* Jianchang Li, Yuchuan Wu, Nathan Fuller, and Michelle A. Markus

Chemical Sciences, Wyeth Research, 200 Cambridge Park Drive, Cambridge, Massachusetts 02140

weili@wyeth.com, publications.weili@gmail.com

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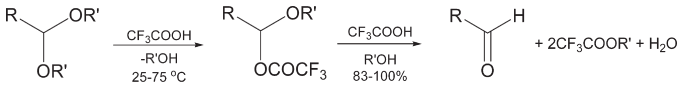

It has been widely accepted that both the protection of carbonyls and the deprotection of acetals and ketals involve the participation of a water molecule: formation of acetals and ketals is a dehydration process, whereas the deprotection is often referred to as hydrolysis, which, as implied by its name, always requires the presence of water. Herein, we report experimental evidence and mechanistic investigations that provide an alternative view to this process. We have demonstrated that water is not required to convert acetals and ketals to the corresponding carbonyls. The ^1H NMR experimental results revealed that the TFA-mediated transformation of acetal to aldehyde occurs via a hemiacetal TFA ester intermediate, which differentiates itself from the classic acid-catalyzed hydrolysis, where the hemiacetal is the putative intermediate responsible for the formation of the aldehyde. More interestingly, alcohols are not the final byproducts as they are in the classical hydrolysis, rather, the two alcohol molecules are converted to two TFA esters under the reaction conditions. On the basis of the NMR evidence, we have proposed that the two TFA esters are formed in two separate steps via a different mechanism along the reaction pathway. Formation of the TFA esters renders the reaction irreversible. To the best of our knowledge, the cascade reaction pathway presented by the TFA-mediated conversion of acetals and ketals to carbonyls has never been previously postulated.

Introduction

Acetals and ketals are a well-known class of compounds for protecting aldehydes and ketones in organic synthesis.[1] The chemistry of acetals and ketals, including their preparation, stabilities under different reaction conditions, and deprotection to recover the original carbonyls, has been well established in literature and is generally described in organic chemistry textbooks.[2] Recent reports describing methodologies that employ acetals and ketals directly for functional group transformations indicate the unmet need to explore the synthetic potential of these compounds.[3] As a result of the search for green chemistry and more efficient chemical transformations, new methodologies for both the formation[4] and deprotection[5] of acetals and ketals, as well as mechanistic studies,[6] are continuously emerging, reflecting the renewed interest in this field.

It has been widely accepted that the nature of both the protection and deprotection reactions involves the participation

† Dedicated to Professor William von Eggers Doering on the occasion of his 92nd birthday.

(1) (a) Kocienski, P. J. *Protecting Groups*, 1st ed.; Georg Thieme Verlag: Stuutgart, Germany, 1994. (b) Green, T. W.; Wuts, P. G. M. *Protective Groups in Organic Synthesis*, 3rd ed.; John Wiley & Sons: New York, 1999.

(2) Smith, B. M.; March, J. *Advanced Organic Chemistry*, 5th ed.; John Wiley & Sons, Inc.: New York, 2001; p 465.

(3) Selected references: (a) Singh, S.; Guiry, P. J. *J. Org. Chem.* **2009**, *74*, 5758. (b) Bates, R. W.; Lu, Y.; Cai, M. P. *Tetrahedron* **2009**, *65*, 7852. (c) Downey, C. W.; Johnson, M. W.; Tracy, K. J. *J. Org. Chem.* **2008**, *73*, 3299. (d) Barluenga, J.; Andina, F.; Aznar, F. *Org. Lett.* **2006**, *8*, 2703. (e) Gao, F.; Burnell, D. J. *J. Org. Chem.* **2006**, *71*, 356. (f) Surendra, K.; Krishnaveni, N. S.; Rao, K. R. *Tetrahedron Lett.* **2006**, *47*, 2133. (g) Berliner, M. A.; Belecki, K. *J. Org. Chem.* **2005**, *70*, 9618. (h) Hunt, K. W.; Grieco, P. A. *Org. Lett.* **2001**, *3*, 481. (i) Motherwell, W. B.; O'Mahony, D., Jr.; Popkin, M. E. *Tetrahedron Lett.* **1998**, *39*, 5285. (j) McCluskey, A.; Mayer, D. M.; David, J.; Young, D. J. *Tetrahedron Lett.* **1997**, *38*, 5217. (k) Goff, D. A.; Harris, R. N.; Bottaro, J. C.; Bedford, C. D. *J. Org. Chem.* **1986**, *51*, 4711.

(4) Selected references: (a) Ren, Y.-M.; Cai, C. *Tetrahedron Lett.* **2008**, *49*, 7110. (b) Robinson, M. W. C.; Graham, A. E. *Tetrahedron Lett.* **2007**, *48*, 4727.

(5) Selected references: (a) Mansilla, H.; Afonso, M. M. *Synth. Commun.* **2008**, *38*, 2607. (b) Gregg, B. T.; Golden, K. C.; Quinn, J. F. *J. Org. Chem.* **2007**, *72*, 5890. (c) Kumar, R.; Kumar, D.; Chakraborti, A. K. *Synthesis* **2007**, 299. (d) Fujioka, H.; Okitsu, T.; Sawama, Y.; Murata, N.; Li, R.; Kita, Y. *J. Org. Chem.* **2007**, *72*, 5930. (e) See ref 4b.

(6) (a) Pluth, M. D.; Bergman, R. G.; Raymond, K. N. *J. Org. Chem.* **2009**, *74*, 58. (b) Amyes, T. L.; Jencks, W. P. *J. Am. Chem. Soc.* **1988**, *110*, 3677.

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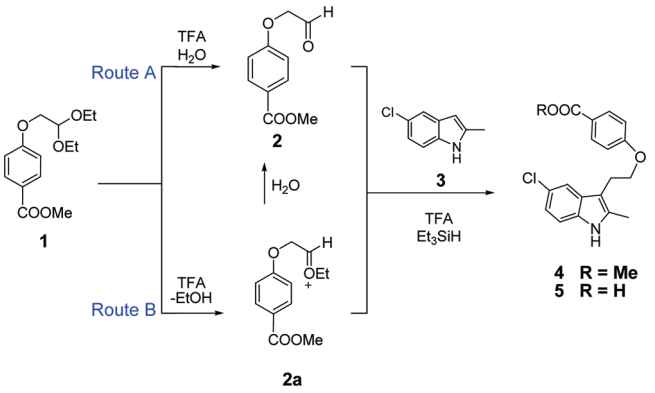
SCHEME 1. The Indole/Acetal C3-Reductive Alkylation

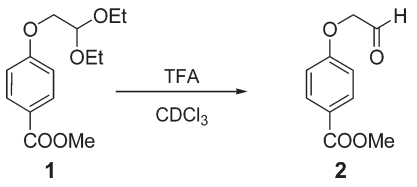


of a water molecule: formation of acetals and ketals is a dehydration process,[7] whereas the deprotection is often referred to as acid-catalyzed hydrolysis,[8] which, as implied by its name, involves the presence of water. Herein, we report our observations and experimental evidence that water is not required to accomplish the transformation of acetals and ketals to the corresponding carbonyls. Further ^{1}H NMR evidence suggests that the TFA-mediated deacetalization and deketalization represent an as yet unreported process in terms of reaction intermediates, product distributions, and the reaction mechanism involved.

As part of our ongoing research into developing new synthetic methodologies for the preparation of drug candidates,[9] we were interested in further exploration of the reaction mechanism of the indole C3 reductive alkylation using acetal/TFA/water/Et_3SiH (Route A, Scheme 1).[10] In this very efficient coupling reaction used to prepare the C3 alkyl substituted indole analogues, the acetal **1** is used directly in the presence of water to generate the aldehyde **2** in situ, initiating the reductive alkylation cascade.[11] However, the presence of water also leads to hydrolysis of the methyl ester group in **1** to result in the acid **5** as an impurity. To improve the synthetic efficiency, exploration of anhydrous reaction conditions became necessary to prevent this side reaction.

We modified the reaction by eliminating the use of water (Route B) and it worked remarkably well. In addition to the improved purity, the new reaction afforded the desired product in even higher yield than Route A. We hypothesized that, similar to the protonated aldehyde **2**, the active intermediate here is the alkyl oxonium species **2a** that captures the indole nucleophile to initiate the cascade reductive alkylation. To gain further insights into the reactivity of **2a**, we were prompted to see what happens if the other reagents, such as the indole nucleophile and the reducing agent Et_3SiH, were absent. Unlike deacetalization under aqueous conditions,[12] the mechanism of the water-free deacetalization reaction has been surprisingly neglected,[13] and we were thus encouraged to undertake this investigation.

TABLE 1. The TFA-Mediated Deacetalization of 1



entry	TFA (equiv)	temp (° C)	time (h)	conversion (%)[a]
1	4.0	25	4	30
2	4.0	25	20	95
3	6.0	25	20	100
4	10.0	25	14	100
5	20.0	25	5	100
6	4.0	75	1	84
7	4.0	75	2	100

[a]conversion to product, not including the amount converted to intermediate.

Results and Discussion

We set up the reaction in the NMR tube that contains the acetal **1** (0.25 mmol) and TFA in chloroform-*d* (1.0 mL) at ambient temperature without the addition of water. The reaction was monitored by ^{1}H NMR at different time points along the reaction course. Formation of the aldehyde **2** was observed with 4 equiv of TFA, but with a slow reaction rate—only 30% of the acetal was converted to **2** after 4 h. The reaction was 95% complete after 20 h (entries 1 and 2, Table 1).

The trends of the reaction rate are shown in Table 1. A higher reaction rate is associated with higher concentration of TFA (entries 1, 3, 4, and 5). For example, with 20 equiv of TFA, only 5 h were required to reach 100% conversion at ambient temperature (entry 5). Temperature also has a remarkable effect on the reaction rates (entries 6 and 7). Elevated reaction temperature not only allows the use of less TFA, but it also shortens the reaction time (entry 7, 2 h/75 °C/4 equiv of TFA).

However, what made the reaction more intriguing was the detection of transient intermediates and their conversions to the final products, all of which were clearly captured by the ^{1}H NMR spectra during the course of the reaction. Figure 1 shows the representative spectra at different time points.

(7) Smith, B. M.; March, J. *Advanced Organic Chemistry*, 5th ed.; John Wiley & Sons, Inc.: New York, 2001; p 1180.

(8) Selected recent references: (a) Duval, R. A.; Allmon, R. L.; Lever, J. R. *J. Med. Chem.* **2007**, *50*, 2144. (b) Douelle, F.; Capes, A. S.; Greaney, M. F. *Org. Lett.* **2007**, *9*, 931.

(9) (a) Li, W.; Li, J.; Lin, M.; Wacharasindhu, S.; Tabei, K.; Mansour, T. S. *J. Org. Chem.* **2007**, *72*, 6016. (b) Li, W.; Li, J.; Wan, Z.-K.; Wu, J.; Massefski, W. *Org. Lett.* **2007**, *9*, 4607. (c) Li, W.; Li, J.; DeVincentis, D.; Mansour, T. S. *Tetrahedron Lett.* **2004**, *45*, 1071.

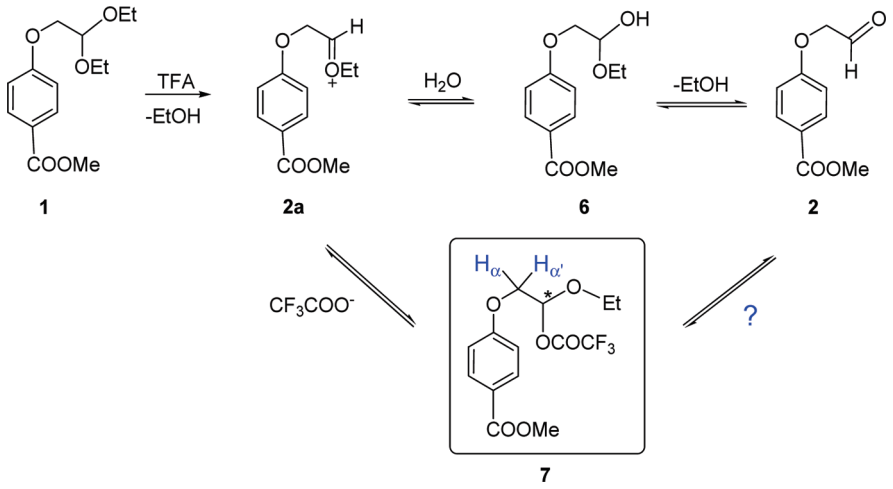
(10) Li, W.; Li, J.; DeVincentis, D.; Mansour, T. S. *Tetrahedron* **2008**, *64*, 7871.

(11) (a) Appleton, J. E.; Dack, K. N.; Green, A. D.; Steele, J. *Tetrahedron Lett.* **1993**, *34*, 1529. (b) Mahadevan, A.; Sard, H.; Gonzalez, M.; McKew, J. C. *Tetrahedron Lett.* **2003**, *44*, 4589.

(12) There are plenty of reports on TFA/water deacetalization and deketalization. Selected examples are: (a) Cysewski, R.; Kwit, M.; Warzajtis, B.; Rychlewska, U.; Gawronski, J. *J. Org. Chem.* **2009**, *74*, 4573. (b) Li, G.; Stamford, A. W.; Huang, Y.; Cheng, K.; Cook, J.; Farley, C.; Gao, J.; Ghibaudi, L.; Greenlee, W. J.; Guzzi, M.; van Heek, M.; Hwa, J. J.; Kelly, J.; Mullins, D.; Parker, E. M.; Wainhaus, S.; Zhang, X. *Bioorg. Med. Chem. Lett.* **2008**, *18*, 1146. (c) Biechy, A.; Hachisu, S.; Quiclet-Sire, B.; Ricard, L.; Zard, S. Z. *Angew. Chem., Int. Ed.* **2008**, *47*, 1436. (d) Reynolds, N. T.; Rovis, T. *Tetrahedron* **2005**, *61*, 6368.

(13) There have been scattered experimental reports on reactions of TFA deacetalization and deketalization without listing water as reagent, but the reports lack reaction details in general, and offer no mechanistic explorations or discussions. For example: Chakrabarti, S.; Liu, M.; Waldeck, D. H.; Oliver, A. M.; Paddon-Row, M. N. *J. Am. Chem. Soc.* **2007**, *129*, 3247.

SCHEME 2. Formation of the Hemiacetal TFA Ester 7



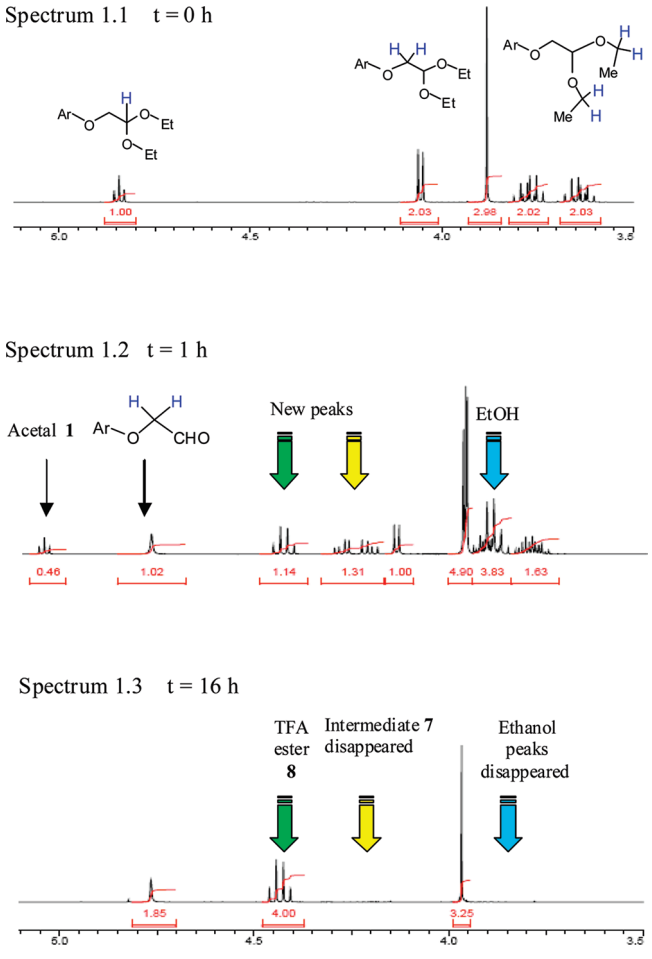


FIGURE 1. The reaction time course monitored by ^{1}H NMR in the 3.5− 5.2 ppm region.

Spectrum 1.1 represents the ^{1}H NMR of acetal **1** in the selected region between δ 5.1 and 3.5. The protons are assigned in blue above the corresponding peaks. The splitting pattern of the $-CH_2-$ protons in the ethyl acetals (δ 3.75 and 3.60) is quite complicated, characteristic for the methylene units of acetals and believed to be an AB-type rather than A_2-type spectra.[14]

Spectrum 1.2 shows the peaks of all species (starting material, intermediates, and final products) coexisting in the reaction mixture after 60 min. The peaks of all protons of the acetal **1** are shifted toward the low field after the introduction of TFA. In addition to aldehyde **2** and the anticipated ethanol, two new sets of peaks emerged as indicated by the green and yellow arrows (spectrum 1.2). The ^{1}H NMR evidence indicated that the aldehyde was detected at the inception and increased to be one of the final products at the end of the reaction. The existence of multiple methylene units (δ 4.43, 4.25, 3.90, and 3.55)[15] recorded in this region makes the assignment of the ethanol peak difficult, but it was eventually confirmed by spiking the proton ^{1}H NMR sample with authentic ethanol (cyan arrow). The following discussions are focused on the identification of the structures associated with these new peaks and the proposed pathways for their generation and transformation to the final products.

Capture of the Key Transition Intermediate. The peak at δ 4.25 with the seemingly complicated splitting pattern (the yellow arrow, spectrum 1.2) disappeared at the end of the reaction (spectrum 1.3) implicating its intermediate nature. This peak was assigned to be one of the methylene units of the hemiacetal TFA ester **7** (Scheme 2) based on the ABX splitting pattern.[16] The first-order coupling constants (J_{AX} and J_{BX}) for the doublets are slightly different with J_{AX} = 4.4 Hz (the left quartet) and J_{BX} = 5.8 Hz (the right quartet). After the first-order approximation, the AB coupling constant (J_{AB}) could be clearly seen as 10.4 Hz. For structural information, the AB quartet implicates the presence of a chiral center adjacent to the carbon bearing the AB protons, which makes the methylene protons diastereotopic.[17] The ABX nature further suggests that this stereogenic carbon should also bear a proton X, which splits

(14) Shafer, P. R.; Davis, D. R.; Vogel, M.; Nagarajan, K.; Roberta, J. D. *Proc. Natl. Acad. Sci. U.S.A.* **1961**, *47*, 49.

(15) Those are the $-CH_2-$ units not only from the starting material and final products, but also from the intermediates.

(16) The difference of the chemical shifts of the AB protons is 0.07 ppm (δ_A 4.28 − δ_B 4.21). This difference is equal to 28 Hz (400 MHz ^{1}H NMR) and is nearly three times larger than the biggest coupling constant (J_{AB}), which resulted in the anticipated ABX coupling pattern. See: Harwood, L. M.; Moody, C. J. *Experimental Organic Chemistry*, 1st ed.; Oxford: London, UK, 1992; p 345.

the AB proton with different coupling constants (J_{AX} and J_{BX}). All of these perfectly support the structure of the hemiacetal TFA ester **7**, formation of which is illustrated in Scheme 2.

On the basis of the known mechanism under acidic conditions, formation of the oxonium **2a** is predicted to be the first event, resulting in the release of an ethanol molecule.[18] As the first step of the deacetalization, formation of **2a** should happen regardless of the presence or absence of water. In the presence of water, the putative intermediate, hemiacetal **6**,[19] is generated via the addition of water to **2a**. Whereas in the absence of water, the potential nucleophiles in the reaction mixture are the CF_3COOH and the newly released EtOH, if the oxonium **2a** reacts with the ethanol, it goes back to the starting acetal **1**. However, if **2a** is trapped by CF_3COOH, it forms the hemiacetal trifluoroacetic ester **7**. Formation of **7** is also accompanied by the creation of a chiral center, which explains the ABX pattern of the ^{1}H NMR in discussion.

Although the hemiacetal acetic ester was first prepared more than a century ago,[20] this class of compounds is comparatively less known than alcohols, aldehydes, and acids, and therefore also less studied.[21] Hemiacetal TFA esters have been primarily prepared by reactions of vinyl ethers with TFA[22,23] and used for the preparation of end-functionalized polymers via living cationic polymerizations.[24] In addition to polymer chemistry, hemiacetal TFA esters have also found applications in sugar chemistry.[25] In contrast, research on hemiacetal TFA esters has lagged in basic organic chemistry. For example, acetals have been used for the preparation of hemiacetal TFA esters, but only limited to reactions with trifluoroacetic anhydride (TFAA)[26,27] or in the presence of base.[28] The ^{1}H NMR evidence of the formation and disappearance of **7** may imply that the hemiacetal TFA ester **7** acts as a transient intermediate to bridge the transformation of acetal to aldehyde. What remains to be revealed is the pathway by which **7** is degraded to the aldehyde **2** (Scheme 2).

Spectrum 1.3 shows that the reaction had gone to completion after 16 h. The neat spectrum reflects the cleanness of the reaction. The aldehyde **2** was formed completely, and all the other peaks associated with the starting material **1** and the key intermediate **7** have disappeared. However, it was surprising to note that the ethanol peaks also disappeared (the cyan arrow, spectrum 1.3). The disappearance of ethanol in the final reaction mixture suggests that it is consumed and transformed to other chemical(s) under the reaction conditions. This intriguing observation suggested that we had observed a new process that is fundamentally different from the classical acid hydrolysis, in which the ethanol is one of the final products. In contrast to the disappearance of ethanol, a set of quartet peaks at δ 4.43 stood out as one of the final products. Integration of the peak indicates it is composed of four protons as referenced to **2**. The early time-course ^{1}H NMR (spectrum 1.2, Figure 1) evidenced that this molecule is formed at the inception of the reaction, and coexisted with the ethanol molecule (δ 3.89) during the course of the reaction. We postulated that this new set of peaks was derived from the ethanol and we believed that identification of its structure would further reveal the mechanism of the TFA-mediated deacetalization.

Structure of the Second New Species. After the confirmation of the ethanol peaks at δ 3.89, the new quartet peaks at δ 4.43 (green arrow, spectrum 1.3) were quite perplexing. The downfield movements of these methylene protons suggest a strong electron-withdrawing group adjacent to the quartet proton carbon. The possibility of ester exchange in **2** with ethanol was ruled out due to the intact methyl ester indicated by the ^{1}H NMR. The number of protons for this peak also rules out the possibility that it is a part of the aldehyde **2** structurally. With these exclusions, there are two remaining possibilities for the unknown structure: diethyl ether or ethyl trifluoroacetate. The structure of this species was confirmed to be the TFA ethyl ester **8** (Scheme 3) after spiking with an authentic sample.

Reaction Mechanism and the Formation of the TFA Ethyl Ester. Detection of the TFA ethyl ester here was not anticipated. Like most esters, the TFA esters are commonly prepared by reaction of alcohols with anhydride (in this case TFAA) in the presence of base, and similar reagents were not present in the reaction mixture. The serendipitous detection of the TFA ethyl ester prompted us to explore the origin of its formation under such mild conditions.

(17) (a) Casarini, D.; Lunazzi, L.; Macciantelli, M.; Mazzanti, A.; Rosini, C. *J. Org. Chem.* **2007**, *72*, 7667. (b) Thiele, C. M. *J. Org. Chem.* **2004**, *69*, 7403. (c) Casarini, D.; Lunazzi, L.; Macciantelli, M. *J. Chem. Soc., Perkin Trans.* **1992**, *2*, 1363. (d) Eliel, E. L. *J. Chem. Educ.* **1980**, *57*, 52. (e) Jennings, W. B. *Chem. Rev.* **1975**, *75*, 307.

(18) (a) McClelland, R. A.; Ahmad, M. *J. Am. Chem. Soc.* **1978**, *100*, 7027. (b) Young, P. R.; Jencks, W. P. *J. Am. Chem. Soc.* **1977**, *99*, 8238.

(19) (a) Smith, B. M.; March, J. *Advanced Organic Chemistry*, 5th ed.; John Wiley & Sons, Inc.: New York, 2001; p 465. (b) Kresge, A. J.; Weeks, D. P. *J. Am. Chem. Soc.* **1984**, *106*, 7140. (c) Young, P. R.; Bogseth, R. C.; Rietz, E. G. *J. Am. Chem. Soc.* **1980**, *102*, 6268. (d) Cordes, E. H.; Bull, H. G. *Chem. Rev.* **1974**, *74*, 581. (e) Fife, T. H. *Acc. Chem. Res.* **1972**, *5*, 264.

(20) (a) Claisen, L. *Ber.* **1898**, *31*, 1010. (b) Clark, F. E.; Cox, S. F.; Mack, E. *J. Am. Chem. Soc.* **1917**, *39*, 712. (c) Hughes, W. B.; Kleene, R. D. *J. Am. Chem. Soc.* **1954**, *76*, 5161. (d) Keith, D. D.; Tortora, J. A.; Yang, R. *J. Org. Chem.* **1978**, *43*, 3711.

(21) Gallucci, R. R.; Going, R. C. *J. Org. Chem.* **1982**, *47*, 3517. Also see ref 38a.

(22) Vinyl ether with TFA: (a) Nedolya, N. A.; Papsheva, N. P.; Afonin, A. V.; Trofimov, B. A.; Kukhareva, V. A.; Kashik, T. V. *Sulfur Lett.* **1992**, *14*, 103. (b) Moriguchi, T.; Endo, T.; Takata, T. *J. Org. Chem.* **1995**, *60*, 3523. (c) Bihovsky, R.; Kumar, M. U.; Ding, S.; Goyalt, A. *J. Org. Chem.* **1989**, *54*, 4291. (d) Razumov, A. I.; Gurevich, P. A.; Baigil'dina, S. Yu. *Zh. Obshch. Khim.* **1974**, *44*, 458. (e) Another method of preparing hemiacetal TFA esters was reported by oxidation of ethers with iodine tris(trifluoroacetate) in moderate yields, see: von Buddrus, J.; Plettenberg, H. *Angew. Chem.* **1976**, *88*, 478.

(23) Observed as a Criegee rearrangement product: Goodman, R. M.; Kishi, Y. *J. Org. Chem.* **1994**, *59*, 5125.

(24) Living polymers: (a) Shohi, H.; Sawamoto, M.; Higashimura, T. *Macromolecules* **1992**, *25*, 58. (b) Kamigaito, M.; Sawamoto, M.; Higashimura, T. *Macromolecules* **1991**, *24*, 3988. (c) Moriguchi, T.; Endo, T. *Macromolecules* **1995**, *28*, 4334.

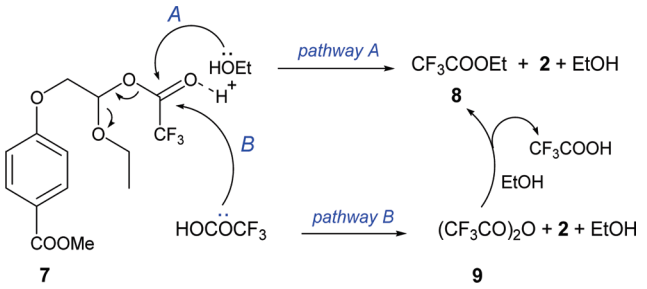
(25) In sugar chemistry: (a) Ding, P. Y.; Zhu, X. X.; Cai, M. S. *Chin. Chem. Lett.* **1986**, *7*, 545. (b) Kobayashi, M.; Shimadate, T. *Chem. Pharm. Bull.* **1986**, *34*, 4069. (c) Summerfelt, S. T.; Selosse, E. J.-M.; Reily, P. J.; Trahanovsky, W. S. *Carbohydr. Res.* **1990**, *203*, 163. (d) Zajac, W. W., Jr.; Ditrow, P. D. D. *J. Org. Chem.* **1986**, *51*, 2617. (e) von Paulsen, H.; Kolar, C.; Stenzel, W. *Angew. Chem.* **1976**, *88*, 478. (f) Li, Z.-J.; Li, Z.-Z.; Li, W.-K. *Synth. Commun.* **1995**, *25*, 2545. (g) Nomura, H.; Yoshioka, Y.; Minami, I. *Chem. Pharm. Bull.* **1979**, *27*, 899.

(26) (a) Nordlander, J. E.; Catalane, D. B.; Kotian, K. D.; Stevens, R. M.; Haky, J. E. *J. Org. Chem.* **1981**, *46*, 778. (b) Ferrières, V.; Roussel, M.; Gelin, M.; Plusquellec, D. *J. Carbohydr. Chem* **2001**, *20*, 855.

(27) Lactols with TFAA: (a) Brands, K. M. J.; Payack, J. F.; Rosen, J. D.; Nelson, T. D.; Candelario, A.; Huffman, M. A.; Zhao, M. M.; Li, J.; Craig, B.; Song, Z. J.; Tschaen, D. M.; Hansen, K.; Devine, P. N.; Pye, P. J.; Rossen, K.; Dormer, P. G.; Reamer, R. A.; Welch, C. J.; Mathre, D. J.; Tsou, N. N.; McNamara, J. M.; Reider, P. J. *J. Am. Chem. Soc.* **2003**, *125*, 2129. (b) Chen, Y.; Zhou, G. X.; Brwon, N.; Wang, T.; Ge, Z. *Anal. Chim. Acta* **2003**, *497*, 155.

(28) Hemiacetal TFA ester by TFAA/base: Caravano, A.; Dohi, H.; Sina, P.; Vincent, S. P. *Chem. Eur. J.* **2006**, *12*, 3114.

SCHEME 3. Plausible Pathways for the Formation of the TFA Ethyl Ester 8



As discussed previously, the structure and formation of the intermediate **7** had been established, but the pathway for transformation of **7** to the aldehyde **2** remained unsolved (Scheme 2). Two pathways could be envisioned with this regard and both of them involve a nucleophilic attack of **7** (Scheme 3). In pathway A, the nucleophile is the ethanol formed from the preceding step (Scheme 2). This attack leads to the direct formation of the TFA ethyl ester **8**, aldehyde **2**, and another ethanol molecule. As discussed before, TFA has already served as a nucleophile in the formation of the intermediate **7** (Scheme 2). If TFA again acts as a nucleophile to attack **7**, the products are aldehyde **2**, ethanol, and the TFAA **9**, which reacts subsequently with the ethanol to generate the TFA ester **8** indirectly (pathway B). Although the likelihood of the competitive nucleophilic attack by TFA here appears to be low, it remains a possibility for consideration.

If proven, the hypothesis of pathway A not only explains the origin of the TFA ester, but also answers the question how the intermediate **7** transforms to the aldehyde **2**. On the basis of this hypothesis, formation of one molecule of the TFA ester **8** should also simultaneously generate one molecule of the aldehyde **2**, and such an event should be reflected in the ^{1}H NMR spectra. In other words, we should observe a 1:1 ratio of the TFA ester **8** to the aldehyde **2** along the course of the reaction. The ratio of 1:1 is a threshold for pathway A, since less than 1:1 implicates the formation of TFA ester lagged behind the formation of the aldehyde, which would disprove the hypothesis and implicate the existence of other pathways, such as pathway B, the stepwise mechanism. Interestingly, examination of the ^{1}H NMR spectra (Figure 2) at any time point (t = 5, 10, and 30 min.) revealed that the ratio of TFA ester **8** to the aldehyde **2** was always greater than 1:1 (1.24:1.00, 1.45:1.00, and 1.58:1.00, at 5, 10, and 30 min, respectively) with continuous increments in favor of the ester.

On the basis of the chemical equation, formation of the aldehyde **2** from the acetal **1** should release a total of two ethanol molecules, and these two ethanol molecules are generated at different stages along the reaction course. For the clarity of discussion at this juncture, we designate the ethanol generated from the formation of the oxonium **2a** (Scheme 2) as *the first ethanol* molecule, and the one generated from the degradation of **7** to **2** (Scheme 3) as *the second ethanol*. What pathway A has addressed is the pathway converting the intermediate **7** to aldehyde **2**, transforming *the first ethanol* to the first TFA ester, and releasing *the second ethanol* (Scheme 3). It is clear that pathway A only answered the question regarding the formation of the first

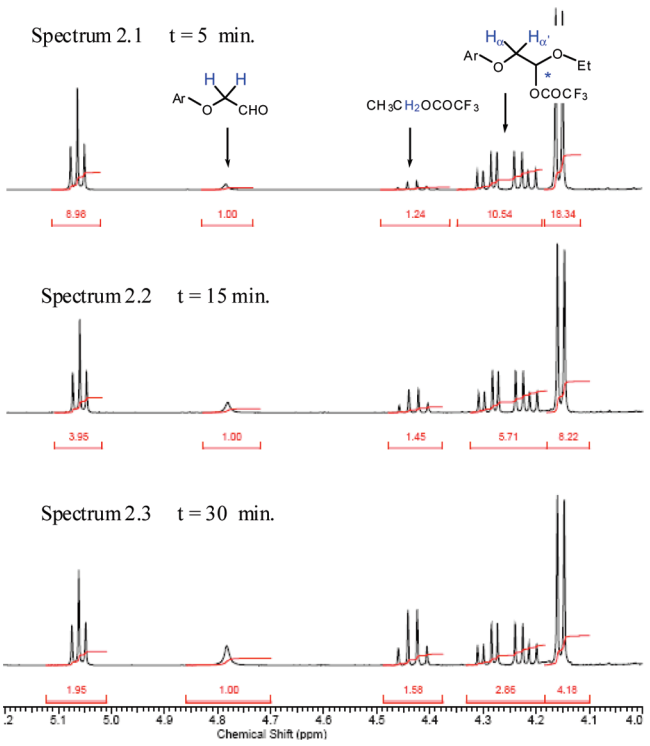


FIGURE 2. Supporting evidence for the simultaneous formation of TFA ester **8** and the aldehyde **2**.

TFA ester from *the first ethanol*. The detection of 2 equiv of TFA ester at the end of the reaction implies there must be another unknown pathway X to convert *the second ethanol* to the second TFA ester **8**. The observed ratio of **8** to **2** always being greater than 1:1 along the reaction course suggests that this pathway X happens concurrently with pathway A. The two concurrent pathways complicated the elucidation of the entire reaction mechanism. For example, if the reaction rate of pathway X is fast enough, it could potentially give a ^{1}H NMR where the ratio of **8** to **2** is greater than 1:1. In other words, an observed ratio of greater than 1:1 is a necessity for pathway A, but not sufficient for providing an unambiguous conclusion.

For pathway A (Scheme 3), the key action is the nucleophilic attack on the intermediate **7** by *the first ethanol* that triggers the formation of the aldehyde and the TFA ester. If *the first ethanol* is removed in situ from the system, the reaction should be stopped at the stage of intermediate **7**. This argument in turn suggested a viable measure to confirm the existence of pathway A chemically. Since the ethanol here is a transient and active intermediate, once formed, it should be removed instantaneously from the reaction system to prevent it from reacting with **7** to confirm the hypothesis. Therefore, the key question is how to design new reaction conditions to remove *the first ethanol*. We reasoned that the introduction of TFAA, which is more reactive toward ethanol than the hemiacetal ester **7**, would remove ethanol via ester formation.

This hypothesis was tested by conducting a modified experiment based on the same conditions as described in entry 4 (Table 1), but with the exception of introducing TFAA (10 equiv) to the reaction. The interim ^{1}H NMR (t = 10 min) showed no presence of ethanol, nor was

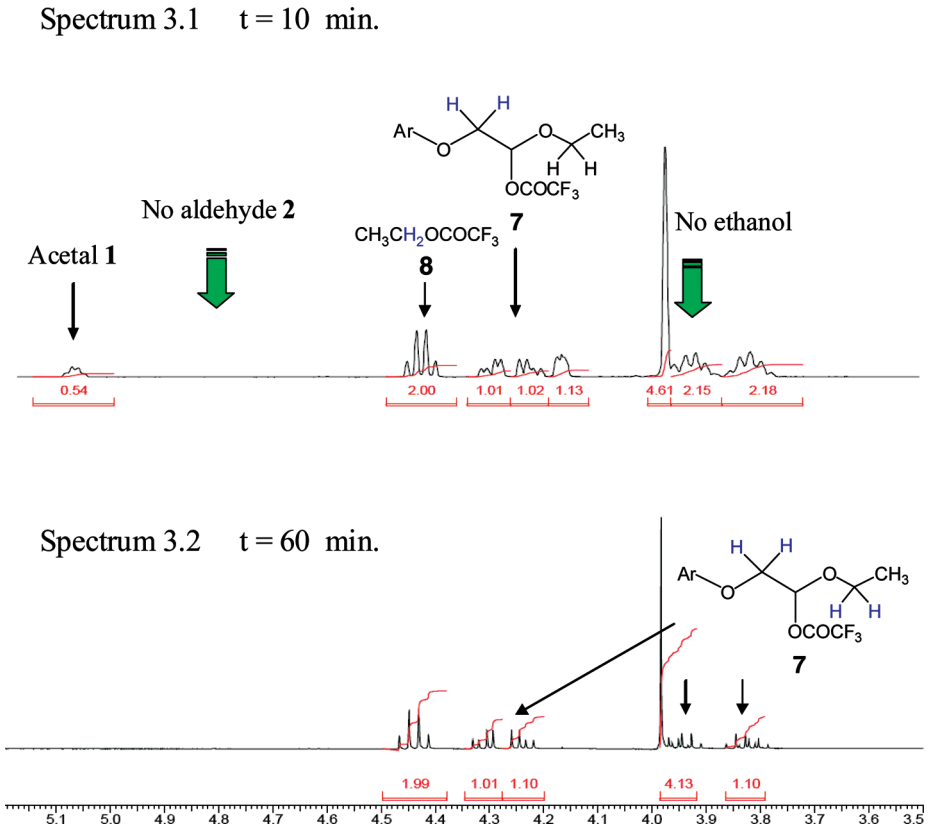


FIGURE 3. Acetal **1** treated with TFA/TFAA only generated **7** and **8**, no ethanol and aldehyde **2**.

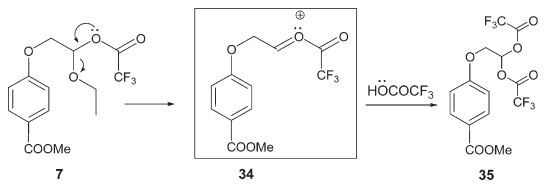
aldehyde **2** detected (green arrows in spectrum 3.1, Figure 3). Only the starting material **1**, hemiacetal **7**, and the TFA ethyl ester **8** were observed (spectrum 3.1, Figure 3). Further evidence for the efficient removal is the ratio of the TFA ethyl ester **8** to the intermediate **7**, which maintained a 1:1 ratio during the entire course of the reaction, indicating a clean conversion of molecule to molecule. All the above data confirmed that *the first ethanol* was immediately trapped by TFAA before reacting with **7**. The complete removal of *the first ethanol* and the fact of the clear absence of aldehyde **2** in the NMR suggested that *the first ethanol* is responsible for the degradation of **7** to form the aldehyde **2**, since detection of any trace amounts of **2** would compromise the proposed reaction mechanism (pathway A). The fact that no aldehyde was formed also implied that under the reaction conditions, the TFA could not act as a nucleophile to attack the intermediate **7**, which was the hypothesis of pathway B for the degradation of **7** to **2** (Scheme 3).[29]

At the end of the reaction (t = 60 min), the only products recorded were the two TFA esters: TFA ethyl ester **8** and the hemiacetal TFA ester **7** with a ratio of 1:1 (spectrum 3.2, Figure 3). The neat appearance of spectrum 3.2 indicates the reaction is exceptionally clean, and introduction of TFAA to the reaction system completely stopped the cascade process at the middle stage of the original reaction. It is interesting to point out that the hemiacetal TFA ester **7** had been the active intermediate in the cascade reaction process (Table 1 and Scheme 2), but now became the final product under the new reaction conditions. Evaporation of the volatile components from the TFA/TFAA reaction mixture afforded the pure compound **7**, purification and characterization of which had been problematic when trying to isolate **7** as an intermediate from the original reaction mixture containing **1**, **2**, ethanol, and **7**.

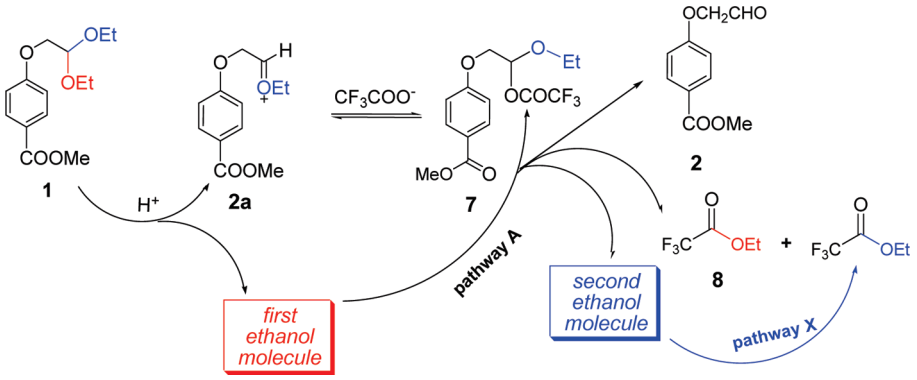
Up to this point, the NMR data and evidence support the reaction mechanism summarized below (Scheme 4) for the TFA-mediated deacetalization. Clearly, this is a cascade process, in which the first step is the formation of the oxonium ion **2a** with the release of *the first ethanol*. The active intermediate **2a** was not detected by the ^{1}H NMR, and the subsequent nucleophilic attack by TFA results in the formation of the fairly stable, detectable, and yet reactive intermediate hemiacetal TFA ester **7**, which was degraded by reacting with *the first ethanol* to generate the desired aldehyde **2**, along with the release of the first ethyl TFA ester **8** and *the second ethanol*. If the reaction had stopped here, the reaction mixture would have contained only three species (**2**, **8**, and *the second ethanol*) in a 1:1:1 ratio.

Since no ethanol was detected and 2 mol of TFA ethyl ester **8** was observed at the end of the reaction, what remains to be accomplished is the identification of pathway X that transformed *the second ethanol* to the second TFA ester **8** (Scheme 4).

(29) The results of this TFA/TFAA experiment also ruled out the following pathway for the formation of the TFA ester from **7**, in which the acyl oxonium **34** serves as the potential intermediate. Since **34** should be more reactive toward nucleophiles than the ethyl oxonium **2a** (Scheme 1), it would trap the TFA to form the acylal **35**, which was not detected from this reaction.



SCHEME 4. A Cascade Reaction Mechanism for TFA-Mediated Deacetalization



Pathway X: Formation of the Second TFA Ester from the Second Ethanol. On the basis of the reactants and reagents in the reaction system, the most likely mechanism for the formation of the second TFA ester from *the second ethanol* is the self-catalyzed esterification. However, there were no strong literature precedents to support this assumption, as TFA esters are commonly prepared by reaction of TFAA with alcohols[30] in the presence of base.[31] In some cases, even more active trifluoroacetylating reagents, such as trifluoroacetyl triflate (TFAT)[32] were employed for the formation of trifluoroacetates from certain alcohols. TFA was reported to form esters with alcohols, but under harsh reaction conditions (neat TFA with alcohol,[33] or refluxing in the presence of a strong acid, such as concd H_2SO_4[34]). Nonetheless, we conducted the reaction by mixing TFA with ethanol (10:1) in chloroform-*d* and monitoring the progress by ^{1}H NMR. Formation of **8** was observed at ambient temperature. Thus, pathway X, proposed to be the self-catalyzed esterification of TFA with ethanol, is confirmed.

TFA esters have found unique synthetic applications. For example, TFA esters are used as a donor to transfer the trifluoromethylketone (CF_3CO-) functional group via either palladium-catalyzed cross-coupling reaction[35] or reaction with organolithium species.[36] We were therefore encouraged to further explore the synthetic potential of this transformation, and the results from these investigations will be published elsewhere.

With the identification of pathway X, we have completely established the mechanism of the TFA-mediated deacetalization. The most interesting aspects of this cascade process are the transient intermediate hemiacetal ester **7**, which bridges the transformation of the acetal to aldehyde, and the formation of the ethyl TFA ester, which makes the reaction irreversible.

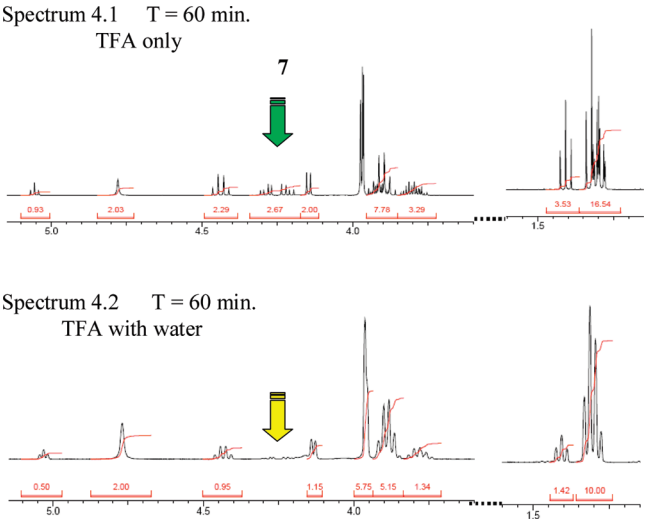


FIGURE 4. The in process ^{1}H NMR data showed the reaction courses of the TFA-mediated deacetalization (spectrum 4.1) and the classical TFA/water hydrolysis (spectrum 4.2).

Comparison to the Classical Acid-Catalyzed Hydrolysis. To explore the differences between the TFA-mediated deacetalization and the classical acid hydrolysis of acetals, **1** was subjected to the classical conditions at ambient temperature. The ^{1}H NMR spectra for both reactions are shown above (Figure 4).

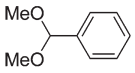
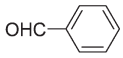
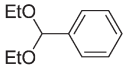
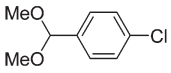
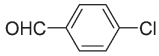
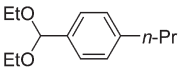
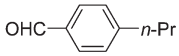
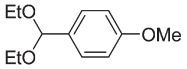
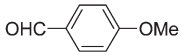
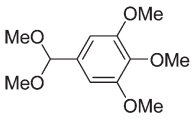
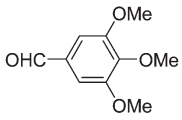
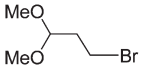
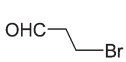
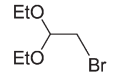
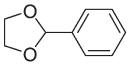
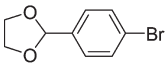
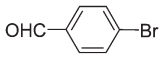
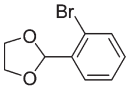
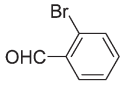
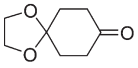
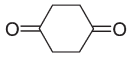
As shown in Figure 4, spectrum 4.1 is the ^{1}H NMR of the TFA-mediated reaction, which contains all the components identified and discussed previously. Spectrum 4.2 is the ^{1}H NMR of the classical acid hydrolysis (10 equiv of TFA, 4 equiv of water) of acetal **1**. Both spectra were taken at the time point of 60 min, which allowed us to cover the crucial information for analysis and discussion.

The remarkable difference between spectrum 4.1 and 4.2 is the apparent absence of the hemiacetal TFA ester **7** in spectrum 4.2 as indicated by the yellow arrow.[37] This is a clear indication that the classical acid hydrolysis of acetal to aldehyde occurred through a different intermediate, rather than **7**. The putative, but well-accepted, intermediate is the hemiacetal **6** (Scheme 2), which is

(30) Kuethe, J. T.; Wong, A.; Davies, I. W. *Org. Lett.* **2003**, *5*, 3975.
(31) Recent literature: (a) Parcerisa, J.; Romero, M.; Pujol, M. D. *Tetrahedron* **2008**, *64*, 500. (b) Diaba, F.; Ricou, E.; Bonjoch, J. *Org. Lett.* **2007**, *9*, 2633.
(32) Forbus, T. R., Jr.; Taylor, S. L.; Martin, J. C. *J. Org. Chem.* **1987**, *52*, 4156.
(33) (a) Hagen, A. P.; Miller, T. S.; Bynum, R. L.; Kapila, V. P. *J. Org. Chem.* **1982**, *47*, 1345. (b) Gallaher, T. N.; Gaul, D. A. *J. Chem. Educ.* **1996**, *73*, 465.
(34) Yuan, C.; Li, J.; Zhang, W. *J. Fluorine Chem.* **2006**, *127*, 44.
(35) Kakino, R.; Shimizu, I.; Yamamoto, A. *Bull. Chem. Soc. Jpn.* **2001**, *74*, 371.
(36) Selected references: (a) Reeves, J. T.; Song, J. J.; Tan, Z.; Lee, H.; Yee, N. K.; Senanayake, C. H. *J. Org. Chem.* **2008**, *73*, 9476. (b) Palacios, F.; Ochoa de Retana, A. M.; Oyarzabal, J.; Pascual, S.; Fernandez de Troconiz, G. *J. Org. Chem.* **2008**, *73*, 4568. (c) Grau, B. T.; Devine, P. N.; DiMichele, L. N.; Kosjek, B. *Org. Lett.* **2007**, *9*, 4951.

(37) A trace amount of **7** could be seen in an excessive enlargement of the area indicated by the yellow arrow, demonstrating the competitive nature of the different pathways.

TABLE 2. General Scope of the Deacetalization and Deketalization with TFA

entry		S.M.	TFA (equiv.)	temp (° C)	time (h)		product	yield
1	**10**		20	25	7	**22**		95%
2	**11**		20	25	7	**22**		95%
3	**12**		20	25	10	**23**		84%
4	**13**		20	25	7	**24**		83%
5	**14**		20	25	6	**25**		86%
6	**15**		20	25	4	**26**		92%
7	**16**		20	25	4	**27**		95%
8	**17**		20	25	6	**28**		100%
9	**18**		20	25	10	**22**		95%
10	**19**		20	25	10	**29**		95%
11	**20**		20 20	25 75	40 4	**30**		93% 90%
12	**21**		20	25	12	**31**		90%

deemed as an unstable species and rapidly degrades to the aldehyde.[38]

At this point with the evidence provided by spectrum 4.1, it can be confidently concluded that the influence of the in situ water on the reaction course is limited. The previous discussions also indicate that the formation of the *first* TFA ethyl ester does not generate any water (Scheme 4). The water generated from the self-catalyzed esterification does not appear to alter the course to the pathway of classical acid hydrolysis (spectrum 4.2).

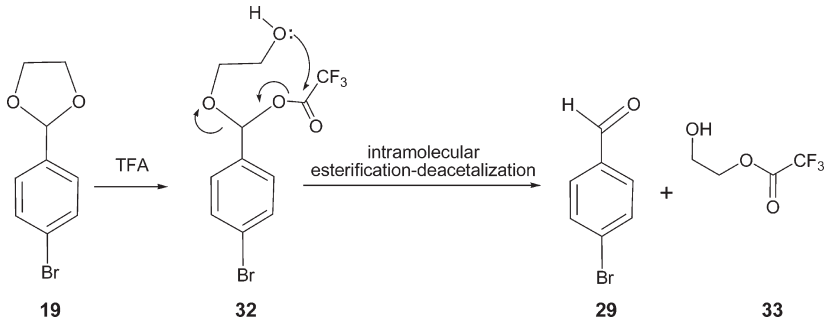
It is also noted that the TFA ethyl ester was also formed in the acid hydrolysis (spectrum 4.2, Figure 4), but lagged behind the formation aldehyde (0.95:2.00).[39] We further followed the reaction to the end and observed a continuous conversion of ethanol to the TFA ester after 24 h. This fact demonstrates the robustness of the self-catalyzed TFA esterification that could tolerate the presence of pre-existing water. As mentioned before, scope and limitation of this mild TFA esterification will be published separately.

Therefore, it could be concluded that the TFA-mediated deacetalization reaction is mechanistically different from the classical acid-catalyzed hydrolysis. This is a new process comprised of a sequence of new reactions that have not been

(38) (a) Hurd, C. D. *J. Chem. Educ.* **1966**, *43*, 527. (b) Smith, B. M.; March, J. *Advanced Organic Chemistry*, 5th ed.; John Wiley & Sons, Inc.: New York, 2001; p 1181.

(39) Although the presence of **6** is not detected, the ratio of less than one reflects this classical hydrolysis pathway. At this juncture, we may also address the concern from the reviewer that possible moisture from the $CDCl_3$ and TFA might have made the TFA-mediated deacetalization a hydrolysis. As we observed here in the classical acid-mediated hydrolysis, the ratio of the TFA ester **8** to the aldehyde **2** is less than one (0.98:2.0). The ratio we have observed previously is always more than one at any time point (Figure 1). Therefore, although the moisture, if any, might compete, the predominant pathway is via the intermediate **7**, not **6**.

SCHEME 5. The Intramolecular Attack Leads to the Direct Formation of the Aldehyde 29 with No Detection of the Intermediate 32 by ^{1}H NMR



19 **32** **29** **33**

previously reported. A name should be credited to this process, and the term *acidolysis* appears to be the most appropriate.

The Scope of the TFA-Mediated Deacetalization and Deketalization. With the understanding of the reaction mechanism, we examined a broad range of acetal and ketal examples to explore the generality of the reaction. The reaction is very general to all the examples tested. Table 2 shows the results from selected acetals and ketals.

All the acetals and ketals, either acyclic or cyclic, were affected by TFA under the reaction conditions described and offered high yields. Different reactivity toward TFA is observed among the substrates and is closely related to their chemical structures. Several trends were observed. The commonly used ethyl and methyl acetals have similar activity (entries 1 and 2). It was also notable that aromatic acetals with electron-withdrawing groups on the phenyl ring are less reactive (entry 3 vs. entry 1), whereas electron-donating substituents accelerate the rate of the reaction (entries 5 and 6 vs. entry 1). Most of the aliphatic acetals were converted to the corresponding aldehydes within 6 h (entries 7 and 8). Cyclic acetals appear to be more stable than their acyclic counterparts toward TFA. For example, under similar reaction conditions, complete conversion to benzaldehyde required 10 h from the cyclic acetal (entry 9 vs. entry 1). Steric effect also affects the reaction rate as demonstrated by the rate difference of 2-(2-bromophenyl)-1,3-dioxolane (entry 11) and 2-(4-bromophenyl)-1,3-dioxolane (entry 10). The *o*-bromo group in **20** has significantly decreased the activity of the acetal toward deacetalization. This deactivation is apparently associated with the increased energy required to form the coplanar configuration for the transient carbocation intermediate. The ketals seem to be less reactive than the acetals in general as the lone example required longer reaction time to complete (entry 12).

We monitored the TFA-mediated deacetalization of 2-(4-bromophenyl)-1,3-dioxolane **19** (entry 10) to see the intramolecular version of the deacetalization. No intermediate **32** (Scheme 5), which is equivalent to the hemiacetal TFA ester **7** (Scheme 3), was detected by the ^{1}H NMR, only the starting material **19** and the product aldehyde **29** were observed. The absence of the hemiacetal TFA ester **32** provides additional evidence to support the proposed mechanism. The released "*first ethanol*" is still a part of the intermediate **32**, which attaches the TFA ester **32** intramolecularly to form the aldehyde **29**. The intramolecular reaction occurred so rapidly that intermediate **32** was not captured in the NMR spectrum.

Conclusions

We have investigated the mechanism of the unique TFA-mediated deacetalization based on NMR spectroscopic evidence. Different from the classical acid-mediated hydrolysis, the TFA-mediated deacetalization does not require the addition of water. We have further demonstrated that the deacetalization is a cascade process with sequential reactions as shown in Scheme 4. The first step is the formation of the oxonium ion **2a** with the release of *the first alcohol*. The intermediate **2a** undergoes subsequent nucleophilic attack by TFA, resulting in the formation of another reactive intermediate, the hemiacetal TFA ester **7**. Further chemical reaction evidence suggested that **7** was degraded by reacting with *the first ethanol* to generate the desired aldehyde **2**, along with the release of the first TFA ethyl ester **8** and *the second ethanol* (pathway A). Further downstream reaction was also investigated to identify the pathway X for the formation of the second TFA ethyl ester from *the second ethanol*. With the identification of the pathway X, we have established the mechanistic pathway of the TFA-mediated deacetalization. The most interesting aspects of this cascade process are the formation of the hemiacetal ester **7** and the formation of the two TFA ethyl esters. It is anticipated that our experimental observations and mechanistic investigations from this study, including the mild deacetalization and the formation of TFA ester from the TFA/alcohol mixture at room temperature, will find synthetic applications in organic chemistry.

Experimental Section

Methyl 4-(2-Oxoethoxy)benzoate (2). To a round-bottomed flask containing methyl 4-(2,2-diethoxyethoxy)benzoate (**1**) (2.68 g, 10 mmol) in 20 mL of chloroform was slowly added trifluoroacetic acid (6.84 g, 60 mmol) at ambient temperature. The resulting solution was allowed to stir for 20 h, and then the mixture was quenched with water (20 mL) and extracted with EtOAc (3 × 30 mL). The organic layer was washed with brine (2 × 40 mL) and dried over Mg_2SO_4. The solvents were removed under reduced pressure to afford the known product[40] **2** as a colorless oil (1.86 g, 95%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.97 (s, 3 H) 4.77 (s, 2 H), 6.95 (d, J = 9.1 Hz, 2 H), 8.03 (d, J = 9.1 Hz, 2 H), 9.87 (s, 1 H).

(40) Lee, K. L.; Foley, M. A.; Chen, L.; Behnke, M. L.; Lovering, F. E.; Kirincich, S. J.; Wang, W.; Shim, J.; Tam, S.; Shen, M. W. H.; Khor, S.; Xu, X.; Goodwin, D. G.; Ramarao, M. K.; Nickerson-Nutter, C.; Donahue, F.; Ku, M. S.; Clark, J. D.; McKew, J. C. *J. Med. Chem.* **2007**, *50*, 1380.

Methyl 4-(2-Ethoxy-2-(2,2,2-trifluoroacetoxy)ethoxy)benzoate (7). To a round-bottomed flask containing methyl 4-(2,2-diethoxyethoxy)benzoate (**1**) (0.268 g, 1.0 mmol) in 2.0 mL of chloroform was slowly added TFAA (2.10 g, 10.0 mmol) at ambient temperature followed by the addition of trifluoroacetic acid (1.14 g, 10.0 mmol). The resulting solution was stirred for 1 h, and then the solvents were removed under reduced pressure to afford the product **7** as a colorless oil (3.09 g, 92%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.29 (t, J = 7.1 Hz, 3 H), 3.73−3.82 (m, 1 H), 3.85−3.90 (m, 1 H), 3.90 (s, 3 H), 4.16−4.22 (m, 1 H), 4.23−4.29 (m, 1 H), 6.32 (dd, J = 5.9, 4.4 Hz, 1 H), 6.90−6.94 (m, 2 H), 7.98−8.02 (m, 2 H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.9, 52.2, 67.0, 67.6, 99.5, 114.3, 114.4, 123.4, 131.8, 157.3, 161.6, 167.2.

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Supporting Information Available: Analytical data (^{1}H, and ^{13}C NMR spectra) for all products. This material is available free of charge via the Internet at http://pubs.acs.org.