Organic Letters
Letter
Cite This: Org. Lett. 2018, 20, 5541−5545
pubs.acs.org/OrgLett

Pummerer Cyclization Revisited: Unraveling of Acyl Oxonium Ion and Vinyl Sulfide Pathways

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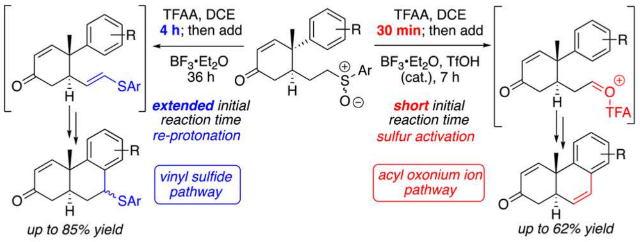
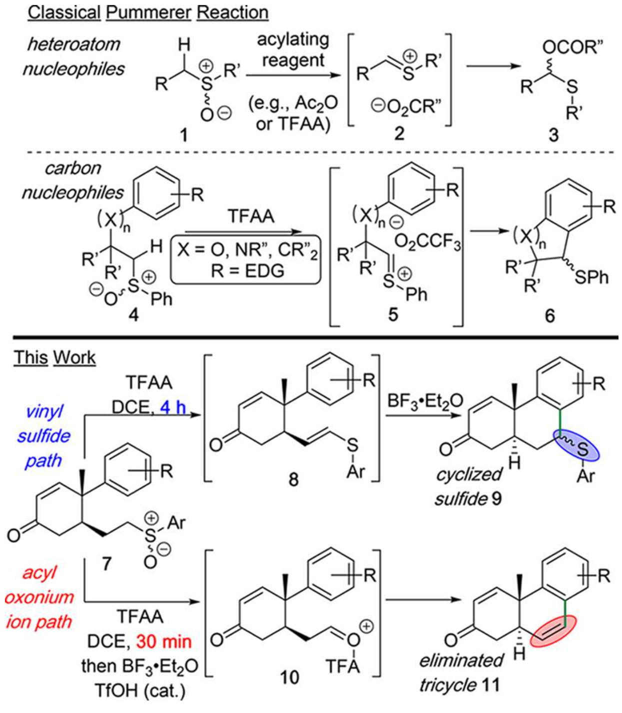
Supporting Information

ABSTRACT: Two viable pathways (vinyl sulfide and acyl oxonium ion) for the Pummerer cyclization have been unraveled that expand the reaction scope and capabilities. Use of Brønsted-*enhanced* Lewis acidity was key to realization of the vinyl sulfide pathway, whereas selective complexation of the sulfur lone pair facilitated the unprecedented acyl oxonium ion pathway. Preliminary mechanistic investigations support these hypotheses. A range of substrates have been explored to understand the reaction parameters.



Scheme 1. Previous Pummerer Chemistry and This Work



For over 100 years, sulfoxides have held an important role in organic chemistry due to their orthogonal reactivity, including as ligands for transition metal catalysis[1] as well as for *syn*-eliminations, Pummerer reactions[2] and numerous other manifolds.[3] It is noteworthy that revisiting early uses of sulfoxides has proven instrumental in expanding their utility. For example, DMSO's extensive use in Pd(II)-mediated oxidations[4] likely enabled White and co-workers to harness the sulfoxide's potential as a ligand in C−H activation chemistry.[5,6]

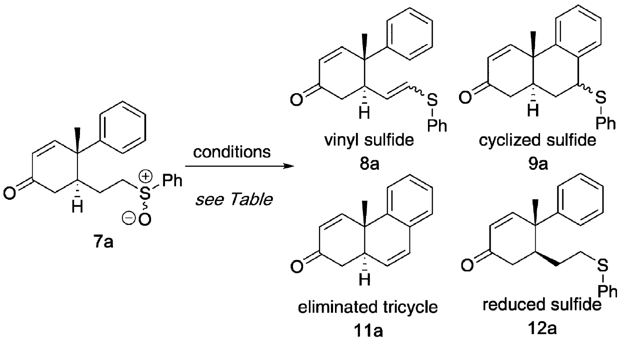
Named after the individual who first discovered the sulfoxide's umpolong reactivity (Scheme 1),[7] the Pummerer reaction mechanistically generates a thionium ion which is trapped by its counterion to form an α-acetoxy- (or α-trifluoroacetoxy-) sulfide. Proctor and co-workers described four different Pummerer pathways: classical, additive, vinylogous, and interrupted.[8] A subset of the "classical" pathway involves harnessing the thionium ion intermediate to react with internal nucleophiles to produce carbon−heteroatom[9] or carbon−carbon bonds[10] in this intramolecular transformation. Unfortunately, the lack of tolerance for β-hydrogens in compound **4** (R′ = H, particularly when X = carbon) and the need for electron-rich nucleophiles have prevented further expansion of this technology. Our laboratory has had a long-standing interest in the reactivity of sulfur-based compounds.[11] Herein, we report the unraveling of the vinyl sulfide pathway and the discovery of the acyl oxonium ion pathway as well as the preliminary evaluation of both pathways' reaction scope and mechanism.

We synthesized a series of enantiomerically enriched polycyclic scaffolds utilizing an asymmetric Yamada−Otani cyclization developed in our laboratory[12−14] to explore their potential utility in the Pummerer cyclization (see Supporting Information). With the necessary sulfoxides in hand, we selected sulfoxide **7a** as the prototypical example to explore its reactivity (Table 1). We were mindful of the previously reported challenges of cyclization on systems containing β-hydrogens. Not surprisingly, treatment of **7a** with TFAA smoothly produced the corresponding vinyl sulfide **8a** in excellent yield (92%) after 4 h.[10f,g,15] Interestingly, use of other electrophiles (e.g., Tf_2O or Ac_2O) proved completely ineffective. This product is likely derived from slow ionization of the trifluoroacetoxy moiety followed by elimination of the β-hydrogen to produce the vinyl sulfide **8a**. We hypothesized that this vinyl sulfide could be protonated to regenerate the required

Received: July 1, 2018
Published: September 10, 2018

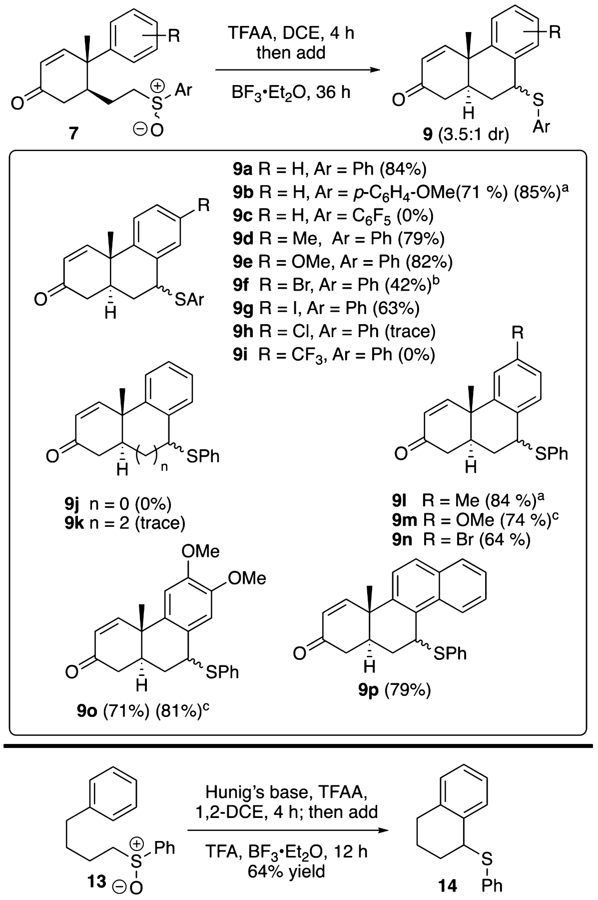
DOI: 10.1021/acs.orglett.8b02059
Org. Lett. 2018, 20, 5541−5545

Table 1. Optimization of Interrupted Pummerer Cyclization



entry	conditions	yields (%)
1	TFAA, 1,2-DCE, 4 h	92 (**8a**), <5 (**12a**)
2	TFAA, 1,2-DCE, 40 h	85 (**8a**), <5 (**9a**), <5 (**12a**)
3	TFAA, 1,2-DCE, 4 h; then add TFA, 36 h	43 (**9a**), 35 (**8a**), <5 (**11a**)
4	TFAA, 1,2-DCE, 4 h; then add $Zn(OTf)_2$, 36 h	87 (**8a**), <5 (**12a**), <5 (**11a**)
5	TFAA, 1,2-DCE, 4 h; then add BF_3·Et_2O, 36 h	84 (**9a**), 3 (**12a**), 8 (**11a**)
6	TFAA, CH_2Cl_2, 4 h; then add BF_3·Et_2O, 36 h	81 (**9a**), <5 (**12a**), 8−10 (**11a**)
7	TFAA, 1,2-DCB, 4 h; then add BF_3·Et_2O, 36 h	78 (**9a**), <5 (**12a**), 13 (**11a**)
8	TFAA, $PhCF_3$, 4 h; then add BF_3·Et_2O, 36 h	73 (**9a**), 15 (**12a**), 5−8 (**11a**)
9	TFAA, $CHCl_3$, 4 h; then add BF_3·Et_2O, 36 h	77 (**9a**), <5 (**12a**), 10 (**11a**)

Scheme 2. Scope of Pummerer Cyclization[a]



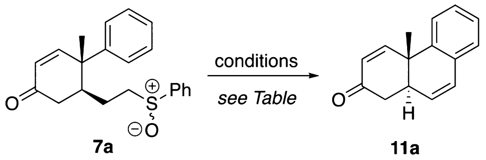
[a]Hunig's base was added; see Supporting Information, General Procedure B. [b]Contaminated with the reduced sulfide **12f**. [c]Hunig's base was added (no BF_3·Et_2O added); see Supporting Information, General Procedure C.

thionium ion for Pummerer cyclization. Prior examples have utilized superstoichiometric addition/presence of Brønsted acid(s)—often at elevated temperatures to enable this reprotonation.[10f,16] In addition, we were particularly inspired by Sano and co-workers' pioneering work with β-phenylthioenamines and BF_3·Et_2O.[17] To our delight, we found that treatment with a Lewis acid (BF_3·Et_2O) indeed regenerated the thionium ion, likely by increasing the Brønsted acidity of trifluoroacetic acid (entry 5). A small amount of the reduced sulfide **12a** and the eliminated tricycle **11a** were also produced under the reaction conditions. Screening of other Lewis acids and solvents confirmed that BF_3·Et_2O in 1,2-DCE was the optimum reaction conditions. Limited previous examples of the Pummerer cyclization in systems with β-hydrogens (relative to the sulfoxide) have been reported, usually with an electron-withdrawing group (e.g., N or O atom) located at the β-position.[10f−i,16,17] Our work shows that the vinyl sulfide can effectively access the key Pummerer cyclization thionium ion intermediate under mild conditions. Previously, vinyl sulfides were often viewed as incapable of re-entering a productive pathway in Pummerer reactions.[10f,g] Key to this advancement was the knowledge gained that the vinyl sulfide must be generated as an initial intermediate prior to facilitating the Pummerer cyclization through utilization of a *Lewis-enhanced* Brønsted acid.

With these optimized conditions in hand, we explored the substrate scope of the Pummerer cyclization (Scheme 2). Electron-rich sulfoxide **7b** proved similarly effective as the parent sulfoxide **7a**. In contrast, the electron-deficient sulfoxide **7c** did not provide any of the desired product, likely due to the reduced nucleophilicity of the sulfoxide oxygen in the key acylation step. The mild reaction conditions developed through our studies (TFAA, 1,2-DCE, 4 h; then add BF_3·Et_2O, 36 h) enabled the expansion of the reaction scope to include sulfides with β-hydrogens as well as a wider range of aromatic substituents. The Pummerer cyclization performed well on both electron-neutral and electron-rich aromatic system. The effectiveness on electronically neutral systems is particularly encouraging as other related cyclizations often require strongly electron-donating substituents to be effective.[10b−h,j,k] Systems in which the aromatic ring is electron-deficient and/or mismatched with the substitution pattern (e.g., **9f** vs **9n**) gave low yield or no observed cyclization. Variation of ring size (five- and seven-membered ring systems) also proved problematic, likely due to the rigid conformation of the tricyclic system. We were pleased to see that meta-substituted substrates **7l**−**7p** were highly effective in this transformation with excellent regioselectivity. Halides **9f**−**9g** and **9n** also contain handles for further functionalization. Finally, it is critical to note that these conditions are not limited to this particular tricyclic scaffold **9**; the simplified sulfoxide **13** smoothly provided the desired bicyclic scaffold **14** in 64% yield.[18]

During the optimization of the Pummerer cyclization, we noticed a pronounced impact of the reaction time for the initial formation of the vinyl sulfide intermediate on the efficiency of this process (Table 2). Although we settled on 4 h as the ideal time window between the addition of the two reagents, we became intrigued by the behavior of this reaction. To our surprise, treatment with BF_3·Et_2O after just 30 min after the

Table 2. Optimization of Eliminated Tricycle Product

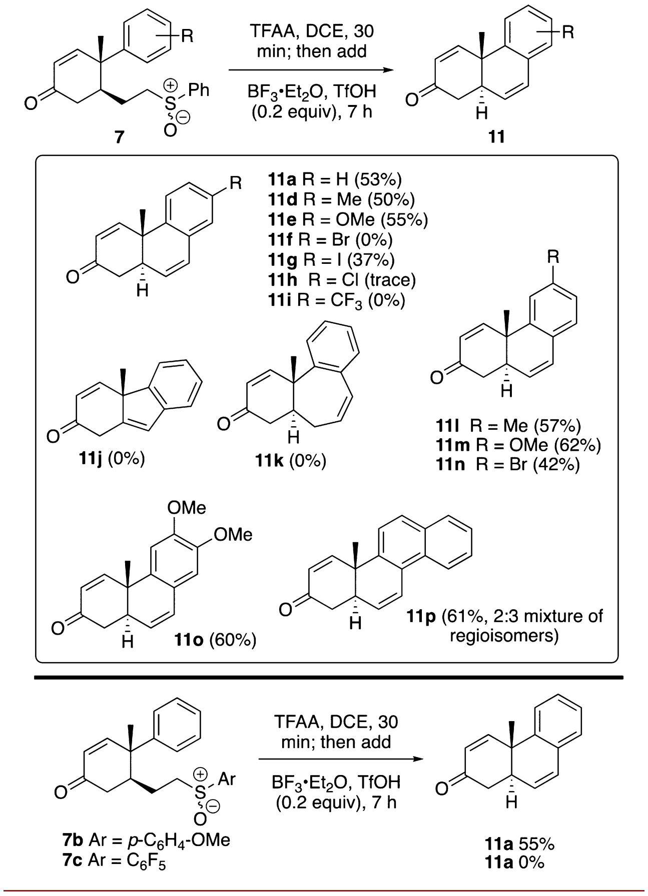


entry	conditions	yields (%)
1	TFAA, 1,2-DCE, 4 h; then add $BF_3·Et_2O$, 36 h	84 (**9a**), 8 (**11a**)
2	TFAA, 1,2- DCE, 30 min; then add $BF_3·Et_2O$, 7 h	37 (**11a**), 26 (**12a**)
3	TFAA, DCE, 30 min; then add $BF_3·Et_2O$, TfOH (0.2 equiv), 7 h	53 (**11a**), 18 (**12a**)

addition of TFAA to the reaction mixture led to a different reaction pathway, instead generating the eliminated tricycle **11a**. This compound was previously only observed in minor (<10%) amounts. Optimization of this reaction pathway revealed that addition of a small amount of TfOH improved the reaction performance.[19]

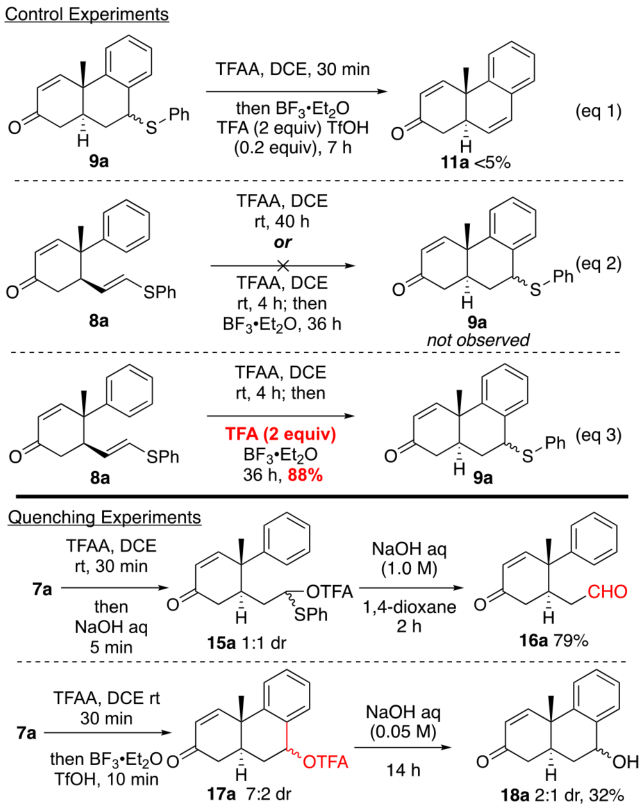
Given the rareness of this transformation, we systematically studied its substrate scope (Scheme 3). The electron-rich and electron-neutral substrates proved effective in the transformation. As before, electron-poor systems produced none of the eliminated tricyclic products. This reactivity pattern is analogous to the tricyclic sulfide series (Scheme 2). In contrast to the previous conditions, we noticed an erosion of the regioselectivity of cyclization with the naphthalene **7p** to yield **11p** in a poor 2:3 ratio. As previously observed, the five- and seven-membered ring systems proved problematic in the cyclization, likely due to the rigid, polycyclic ring system. The electron-deficient sulfoxide **7c** was again problematic due to the reduced nucleophilicity of the sulfoxide oxygen.

Scheme 3. Scope of Eliminated Tricycle Process



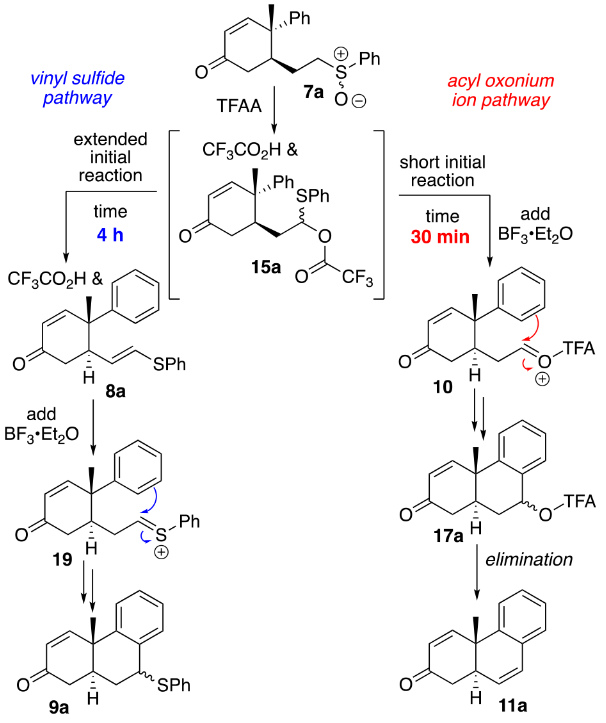
The mechanistic underpinnings that led to both the tricyclic sulfide **9** and the eliminated tricycle **11** warranted further study (Scheme 4). Regarding the eliminated tricycle, we had initially hypothesized that **11a** was simply derived from the same Pummerer cyclization pathway through ionization of the carbon−sulfur bond in tricyclic sulfide **9a** and *β*-elimination of the resultant benzylic carbocation. We were surprised to discover that resubmission of the tricyclic sulfide **9a** to the reaction conditions produced trace (<5%) amounts of the eliminated tricycle **11a** (eq 1). Confirmation of the intermediate present 30 min after addition of the TFAA through quenching of the reaction at that moment with aqueous base revealed formation of the expected aldehyde **16a** in excellent yield. On the other hand, we were able to characterize the unstable TFA ester intermediate **17a** by stopping the reaction after addition of $BF_3·Et_2O$ prior to complete consumption of the starting sulfoxide **7a** (20% recovered), which was converted onto the alcohol **18a** (32%) by treatment with 0.05 M NaOH [along with **11a** (24%) and **12a** (11%)]. Confirmation of the TFA ester **17a** provides critical evidence for the existence of an unprecedented reaction pathway in the formation of the eliminated tricycle. We also conducted experiments to probe the formation of the tricyclic sulfide **9** through treatment of the isolated vinyl sulfide **8a** with TFAA, which produced neither of the cyclized products **9a** nor **11a** (no change was observed after 36 h, eq 2).[10f,g] In contrast, treatment of the vinyl sulfide **8a** with TFAA in the presence of trifluoroacetic acid (2 equiv) and $BF_3·Et_2O$ did smoothly deliver the expected tricycle **9a** (eq 3).

Scheme 4. Select Control and Quenching Experiments



Based on these results, we hypothesized an unexpected set of mechanistic pathways (Scheme 5). For the Pummerer cyclization that yields the tricyclic sulfide **9a**, the acylated sulfoxide fragmentation to a sulfonium ion is initially trapped as the traditional Pummerer product **15a**. This acetate **15a** is unstable due to the presence of β-hydrogens and undergoes elimination to form the vinyl sulfide **8a**. Upon addition of the $BF_3{\cdot}Et_2O$, the *Lewis-enhanced* Brønsted acidity regenerates the thionium ion while sequestering the TFA counterion. This combination of reagents enables formation of the key carbon−carbon bond via electrophilic aromatic substitution. In contrast, treatment of the traditional Pummerer product **15a** with $BF_3{\cdot}Et_2O$ prior to elimination to the vinyl sulfide **8a** induces the unexpected ionization of the sulfide moiety to generate the highly reactive acylated oxonium ion **10**. The preferential ionization of the carbon−sulfur bond may be driven by initial complexation of the Lewis acid with the more Lewis basic sulfur lone pair, which sufficiently weakens the carbon−sulfur bond to facilitate its cleavage. This acylated oxonium ion rapidly undergoes electrophilic aromatic substitution to generate the tricyclic trifluoroacetate **17a**. Not surprisingly, the benzylic trifluoroacetate **17a** has a limited lifetime under the reaction conditions and undergoes subsequent elimination to produce the observed tricycle **11a**. Overall, we have demonstrated that careful control of reaction conditions can alter the fate of the initial α-trifluoroacetoxy phenylsulfide **15a**, enabling ultimate cleavage of either (a) the C−OTFA bond to generate a thionium ion (using Brønsted-acid-catalyzed elimination followed by Lewis-enhanced Bronsted acid protonation of the vinyl sulfide moiety) or (b) the C−SPh bond to generate to an acylated oxonium ion (using Lewis acid complexation of the sulfur lone pair).

Scheme 5. Plausible Explanation for Observed Products via the Vinyl Sulfide and Acyl Oxonium Ion Pathways



In summary, we have unearthed novel reaction parameters which have both expanded the scope of the Pummerer cyclization and unearthed two new and/or underutilized reaction pathways for acylated sulfoxides. These pathways expand the tolerated functionalities on the aromatic ring system as well as the substitution pattern near the sulfoxide moiety. The discovery of the acyl oxonium ion pathway should provide the synthetic community with access to a highly reactive electrophilic moiety which will enable its further exploration. In the following paper, we detail our application of these discoveries to the efficient, enantioselective total synthesis of multiple members of the abietane diterpenoids.[20]

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.8b02059.

Complete experimental details (PDF)
^{1}H and ^{13}C NMR spectra (PDF)

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

Prof. Claudia Maier (OSU) and Jeff Morré (OSU) are acknowledged for mass spectra data. The authors are grateful to Prof. Paul Ha-Yeon Cheong (OSU), Subir Goswami (OSU), Maxson Richards (OSU), Michael Standen (Valliscor), and Dr. Roger Hanselmann (Akebia Therapeutics) for their assistance and helpful discussions. Financial support has been provided by the National Science Foundation (CHE-1665246) and Oregon State University.

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(18) Hunig's base was added to this experiment as it appears to largely suppress unwanted formation of the reduced sulfide ($PhCH_2CH_2CH_2CH_2SPh$). Without the addition of Hunig's base, we observe approximately 30% of this byproduct. We are unsure at this juncture of the rationale for this behavior.

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