OL | Organic Letters

Cite This: Org. Lett. XXXX, XXX, XXX−XXX

Letter

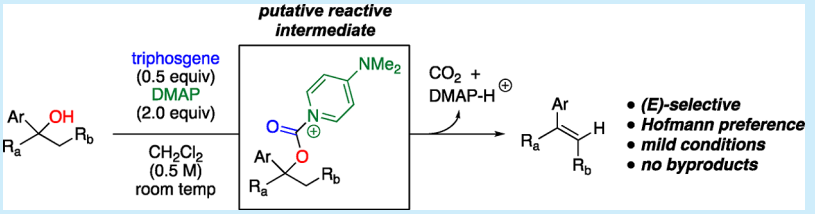
pubs.acs.org/OrgLett

Triphosgene and DMAP as Mild Reagents for Chemoselective Dehydration of Tertiary Alcohols

Moshood O. Ganiu, Alexander H. Cleveland, Jarrod L. Paul, and Rendy Kartika*

Department of Chemistry, Louisiana State University, 232 Choppin Hall, Baton Rouge, Louisiana 70803, United States

Supporting Information

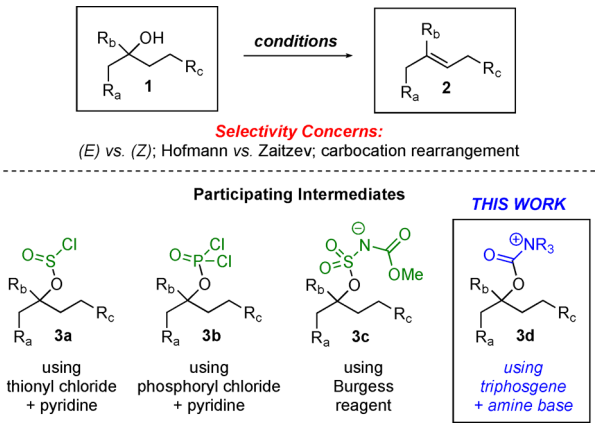


ABSTRACT: The utility of triphosgene and DMAP as mild reagents for chemoselective dehydration of tertiary alcohols is reported. Performed in dichloromethane at room temperature, this reaction is readily tolerated by a broad scope of substrates, yielding alkenes preferentially with the (*E*)-geometry. While formation of the Hofmann products is generally favored, a dramatic change in alkene selectivity toward the Zaitzev products is observed when the reaction is carried out in dichloroethane at reflux.

Dehydration of tertiary alcohols is a useful synthetic reaction to produce substituted alkenes, but it remains a formidable challenge particularly with respect to controlling the resulting double bond selectivity. The difficulty in this functional group interconversion can be also underscored by the fact that the required reagents are often incompatible with various sensitive functional groups. For instance, it is well precedented that dehydration of tertiary alcohols can be effectively promoted by strong Brønsted acids.[1] Nonetheless, such conditions are not generally amendable to complex molecules synthesis, and this reaction can potentially lead to a mixture of alkene isomers due to the propensity of the participating carbocation intermediates to undergo structural rearrangement.[2] Other broadly used reagents include thionyl chloride[3] and phosphoryl chloride,[4] but a mixture of dehydration products could be similarly produced due to the involvement of chlorosulfite **3a** or dichlorophosphate **3b** intermediates (Scheme 1) that are reportedly subject to facile self-ionization to carbocations. While there are several elegant accounts on this fundamental transformation that highlight heterogeneous,[5] homogeneous,[6] and enzymatic catalysis,[7] arguably the most applicable method to dehydrate tertiary alcohols in complex molecular systems can be found in the use of the Burgess reagent.[8] With respect to Burgess activation,[9] the origin of alkene selectivity arises from controlling the regioselective *syn* (Ei) elimination of the participating sulfamate ester **3c**.

In recent years, our group has developed methods to chlorinate primary and secondary alcohols using a mixture of triphosgene and amine bases, particularly triethylamine or pyridine.[10] Recognizing that $SOCl_2$ or $POCl_3$ also serve as reagents for the chlorination of alcohols, we hypothesized that our triphosgene-amine base chemistries could be perhaps applied to dehydrate tertiary alcohols. Drawing a parallel

Scheme 1. Elimination of Tertiary Alcohol



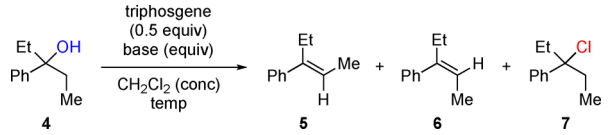
reaction mechanism from our chlorination reactions, we envisioned an intermediacy of ammonium carbamate ion **3d** that could, in theory, be subjected to elimination, therefore producing the double bond. From the operational perspective, the use of triphosgene as a dehydration reagent would be more advantageous than $SOCl_2$ or $POCl_3$, as triphosgene exists as stable, nonhygroscopic crystalline materials at room temperature that can be conveniently and safely handled in typical laboratory operations.[11]

Table 1 depicts our screening study. To test our hypothesis, we employed tertiary alcohol **4** as a model substrate. As shown in entry 1, this compound was initially subjected to conditions pertinent to our chlorination technology, i.e. 0.5 equiv of triphosgene and 2.0 equiv of pyridine, in dichloromethane at

Received: June 6, 2019

DOI: 10.1021/acs.orglett.9b01959
Org. Lett. XXXX, XXX, XXX−XXX

Table 1. Reaction Optimization[12]



entry	base[c]	equiv	temp (°C)	conc (M)	time (h)	4:5:6:7[a]
1	pyridine	2.0	reflux	0.5	0.2	0:57:17:26
2	pyridine	2.0	rt	0.5	2	0:58:12:30
3	pyridine	2.0	0	0.5	2	0:63:08:29
4	pyridine	2.0	−78	0.5	4	7:66:04:23
5	pyridine	2.0	rt	0.1	24	0:61:14:25
6	**DMAP**	**2.0**	**reflux**	**0.5**	**18**	**0:80:16:4**
7	**DMAP**	**2.0**	**rt**	**0.5**	**18**	**0:78:13:9**
8	DMAP	2.0	0	0.5	26	1:76:12:11
9	DMAP	2.0	−20	0.5	22	11:70:10:09
10	DMAP	2.0	−40	0.5	22	77:18:03:03
11	DMAP	2.0	−78	0.5	28	100:00:00:00
12	DMAP	5.0	rt	0.5	22	0:80:13:07
13	DMAP	1.5	rt	0.5	24	10:58:13:19
14	DMAP	1.0	rt	0.5	24	0:41:09:50
15	DMAP	0.0	rt	0.5	24	100:00:00:00
16[b,c]	DMAP	2.0	rt	0.5	24	100:00:00:00

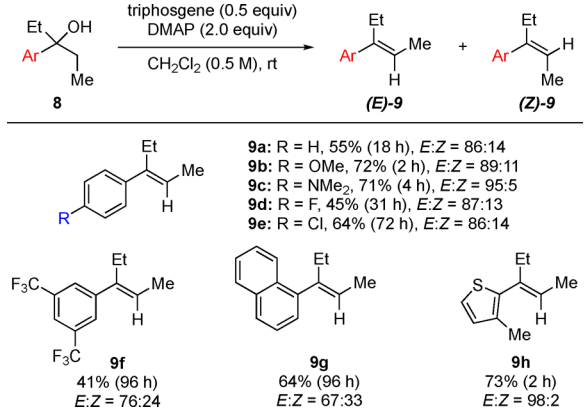
[a]Ratio of the compounds was determined by GC-MS analyses with an assumption that they elicited identical response. The alkene geometry was deduced by NOE. [b]Triphosgene was absent from the reaction mixture. [c]The use of other organic bases, such as 2,6-lutidine and DBU, led to the recovery of starting material **4**.

reflux.[10b,c] Interestingly, this reaction indeed produced elimination products **5** and **6**, favoring the (*E*)-isomer, but a substantial amount of chlorination product **7** was also observed. Attempts to minimize chlorination by systematically cooling the reaction temperature and diluting the reaction concentration were not successful (entries 2 to 5). Nonetheless at −78 °C, the reaction exhibited much higher selectivity toward (*E*)-alkene **5**.

Assuming that alkyl chloride **7** was produced via an S_N1 pathway that occurred competitively, we proposed that the utility of a slightly stronger base could perhaps further favor kinetics toward the desired elimination. As noted in entry 6, replacement of pyridine with DMAP indeed suppressed chlorination. The reaction temperature was then systematically modulated to improve alkene selectivity, but the (*E*) vs (*Z*) selectivity was relatively unchanged (entries 6−9). Interestingly, substrate **4** failed to react when the temperature was cooled below −40 °C. We also surveyed the molar amount of DMAP (entries 12−14). While excess DMAP did not affect the statistical distribution of products, lowering its equivalence to 1.5 and 1.0 surprisingly led to a significant increase of chlorination. Our control experiments are shown in entries 15 and 16, as starting material **4** was not affected when DMAP or triphosgene was absent from the reaction mixture. Given the reactions produced comparable results both at reflux and at room temperature (entries 6−7), the latter was chosen as optimized conditions due to its operational simplicity.

We proceeded to evaluate the scope of substrates in preparative scale reactions, commencing with tertiary alcohols **8** that were elaborated with various aromatic groups (Scheme 2).[12] These initial studies revealed that substrates bearing electron-rich anisole and dimethylamino substituents further favored the (*E*)-geometry in the resulting alkenes **9b** and **9c**,

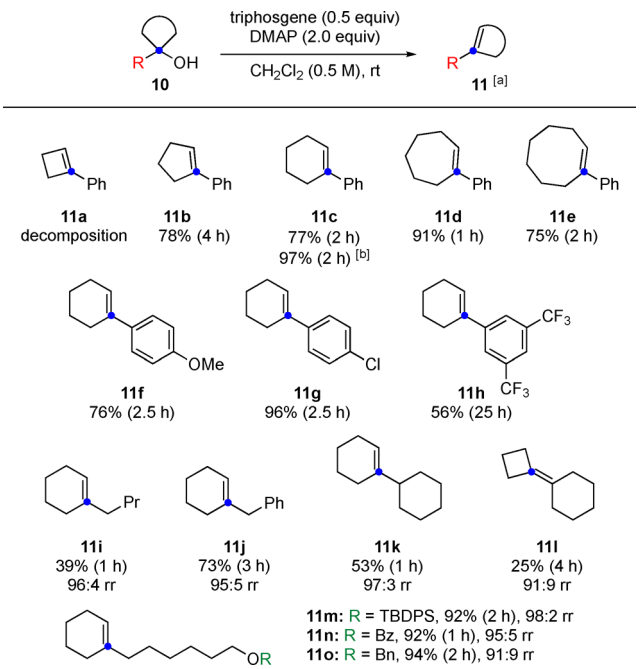
Scheme 2. Scope of Aromatic Groups[12]



whereas the alkene stereoselectivity in **9f** eroded with electron-deficient CF_3 groups. Halogenated substituents (**9d** and **9e**) did not alter the ratio of (*E*) vs (*Z*) from that of the parent phenyl group **9a**;[12e] but longer reaction times were noted. The utility of other aromatic rings was also investigated. While the naphthyl substrate led to product **9g** with reduced selectivity, the thiophene variant **9h** was obtained essentially only as an (*E*)-isomer.

The utility of our method to dehydrate cyclic tertiary alcohols, viz. **10**, was also examined. As shown in Scheme 3, we

Scheme 3. Scope of Substrates[12]



[a]rr = regiomeric ratio. [b]The reaction was performed in 2-g scale.

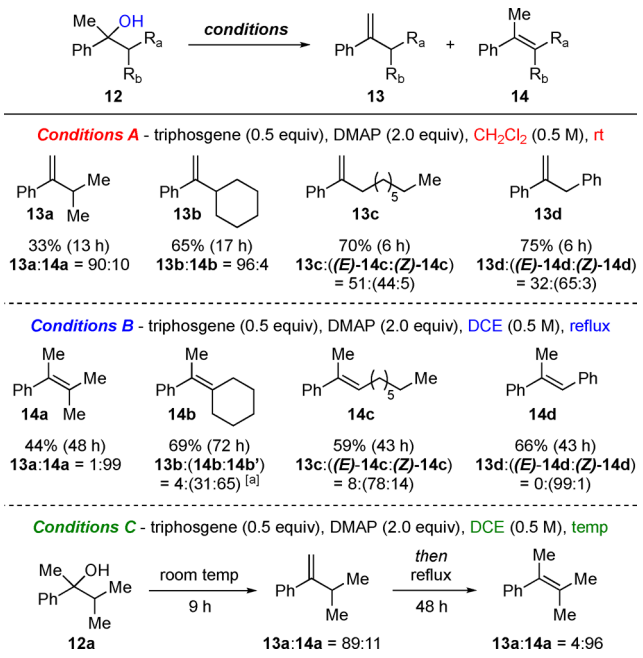
subjected various ring sizes to this study.[13] With the exception of a cyclobutanol-derived substrate that resulted in decomposition, 5−8-membered starting materials could be smoothly eliminated with triphosgene and DMAP to produce the corresponding 1-phenylcycloalkenes **11b**−**11e** in good yields. Our reaction is amendable for scale-up, as product **11c** was cleanly obtained in 97% yield from 2 g of the respective substrate. Tertiary alcohols bearing electronically diverse aryl substituents **11f**−**11h** and aliphatic groups **11i**−**11k** were

DOI: 10.1021/acs.orglett.9b01959
Org. Lett. XXXX, XXX, XXX−XXX

found to be tolerated. Remarkably, compounds **11i**−**11k** were furnished as the predominant regioisomers, rendering elimination to the methylenecyclohexane isomer relatively noncompetitive. An attempt to dehydrate 1-cyclohexyl-1-cyclobutanol did not yield cyclobutene. Instead, the reaction produced tetrasubstituted alkene **11l**. We also prepared and evaluated substrates containing common protecting groups. While TBDPS, Bz, and Bn were found to be compatible and furnish cyclohexenes **11m**−**11o** in high yields, TBS and MOM ethers were surprisingly cleaved under the reaction conditions.

As shown in Scheme 4,[12] our studies continued with substrate motif **12** to identify whether regioselectivity between

Scheme 4. Hofmann vs Zaitzev Selectivity[12]



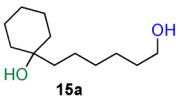
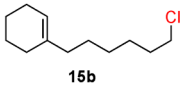
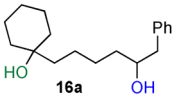
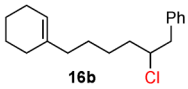
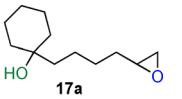
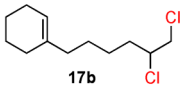
[a]Further alkene isomerization to trisubstituted endocyclic alkene 1-(cyclohexen-1-yl)ethyl)benzene, i.e. compound **14b′**, was observed.

Hofmann and Zaitsev products **13** and **14**, respectively, could be biased. Using our optimized conditions (Conditions A), we found that tertiary alcohols bearing a sterically congested isopropyl and cyclohexyl group predominantly generated exomethylene products **13a** and **13b**. Nonetheless, the Hofmann preference eroded with an *n*-octyl substituent in **13c** or a phenyl group in **13d**, most likely driven by π conjugation in the resulting stilbene. Remarkably, the Zaitzev products **14a**−**14d** could be primarily formed simply by changing the solvent to dichloroethane and performing the reactions at reflux (Conditions B). Both Conditions A and B, furthermore, yielded alkenes **14c** and **14d** with a strong preference toward the (*E*)-geometry. The equilibrium between the Hofmann vs Zaitzev products could be directly monitored by subjecting substrate **12a** to triphosgene-DMAP in dichloroethane at two successive temperature profiles (Conditions C). While at room temperature the reaction initially produced exomethylene **13a**, gradual isomerization to the fully substituted alkene **14a** was noted as the same crude mixture was heated to reflux.

Given that functional groups, such as primary and secondary alcohols as well as epoxides, could be effectively chlorinated with a mixture of triphosgene and pyridine,[10b−d] we then examined the applicability of our method toward dehydration of tertiary alcohols concomitantly with chlorination of these functional groups. As depicted in Table 2, we prepared a series

Table 2. Concomitant Dehydration and Chlorination[12]

Reaction Conditions
triphosgene (1.0 equiv), DMAP (4.0 equiv), CH_2Cl_2 (0.5 M), rt

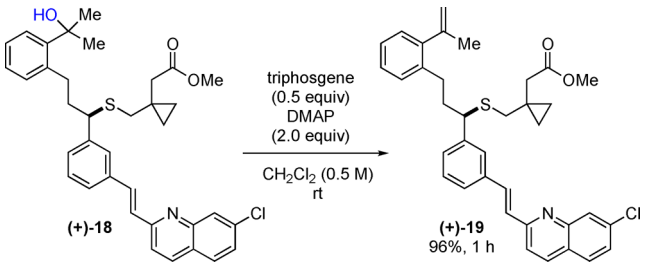
starting material	product	yield [a]	time
 **15a**	 **15b**	64% 92:8 rr	1 h
 **16a**	 **16b**	82% 90:10 rr	1 h
 **17a**	 **17b**	62% 91:9 rr	0.5 h

[a]rr = regiomeric ratio.

of substrates **15a**−**17a**. To affect transformation for each functional group, these compounds were subjected to reaction conditions in which the molar amount of the reagents was doubled, i.e. 1.0 equiv of triphosgene and 4.0 equiv of DMAP. These studies revealed that chemoselective dehydration and chlorination could be achieved in a single synthetic operation, as cyclohexene-bearing aliphatic chlorides **15b** and **16b**, as well as dichloride **17b**, were generated in good yields.

Scheme 5 signifies the advantage of our method, as it tolerates a complex molecule that bears various functional

Scheme 5. Application to a Complex Molecule[12]

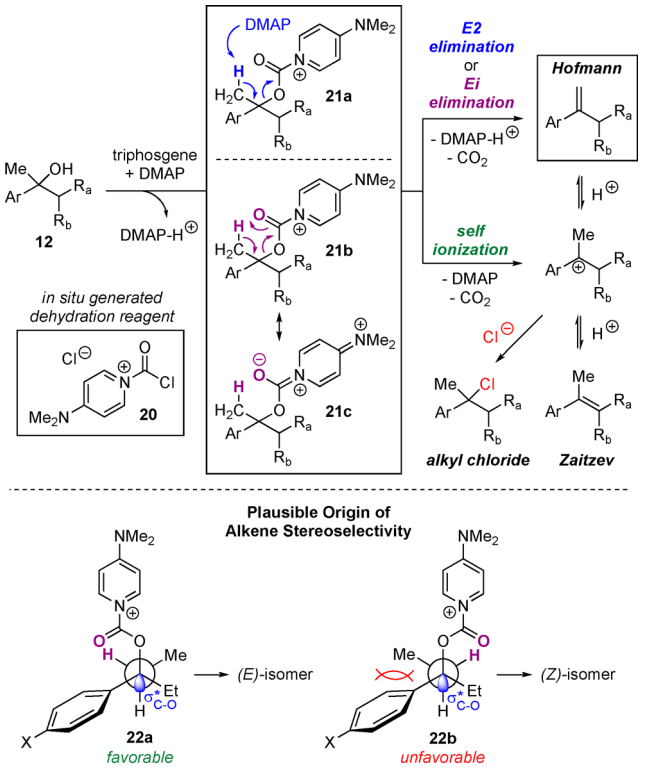


groups. Using montelukast methyl ester (+)-**18** as an example, exposure of this compound to triphosgene and DMAP in dichloromethane at room temperature cleanly furnished the corresponding dehydration product (+)-**19** in 96% yield. In this instance, the thioether, cyclopropyl, methyl ester, and quinoline moieties were found to be inconsequential to the reaction conditions for the elimination of the tertiary alcohol.

As proposed in Scheme 6, the mechanism for our dehydration reaction commences with the decomposition of triphosgene by DMAP to yield *in situ* generated, putative dehydration reagent **20**.[14] This species subsequently activates the tertiary alcohol moiety to pyridinium carbamate ion **21a**, leading to E2 elimination of one of the least sterically congested β-hydrogens by excess DMAP to afford the Hofmann products. Nonetheless, the effectiveness of DMAP in this chemistry as opposed to pyridine or other amine bases (Table 1) can also imply an alternative mechanism, in particular the Ei elimination.[15] The possibility for this pathway

DOI: 10.1021/acs.orglett.9b01959
Org. Lett. XXXX, XXX, XXX−XXX

Scheme 6. Proposed Reaction Mechanism



can be reasoned by a notion that activation of the carbamate moiety by electron-rich DMAP enables resonance structures **21b** ↔ **21c**, thus substantially raising the HOMO en route to the proposed internal elimination mechanism.

Whether proceeding via E2 or Ei elimination,[16] either mechanism will overall recycle 2 molar equiv of DMAP in its protonated state and simultaneously extrude CO_2 gas as the sole byproduct. Furthermore, the strong preference toward (*E*) vs (*Z*) alkene geometry as described in Scheme 2 can be explained from the minimization of destabilizing gauche interactions in the respective reactive intermediate **22a** vs **22b**, preceding the elimination of the pyridinium carbamate moiety in a *syn* fashion for the Ei pathway or *antiperiplanar* for E2. Supported by the trend in electronic effects (i.e., electron-rich arene groups improve (*E*) selectivity), the underlying factor toward this preorganized conformational bias most likely originates from stabilization of the σ^*_{C-O} antibonding orbital by the π electrons, which requires orientation of the aryl substituents that consequently render **22b** unfavorable due to steric repulsion.

Formation of the alkyl chloride and Zaitsev byproducts can be accounted by the following scenarios. While less likely,[17] it is conceivable that pyridinium carbamate ion **21a** (or its chloroformate analog) can similarly undergo self-ionization to produce a tertiary carbocation, which can be captured by chloride ions that are liberated in abundance from triphosgene. As observed in Table 1, this E1 pathway becomes competitive with the use of pyridine or with the decreasing amount of DMAP in the reaction mixture based on the increasing amount of alkyl chloride. Naturally, the involvement of carbocationic intermediates will also lead to the Zaitzev product. Based on the facile conversion of **13a** to **14a** under equilibration conditions (Scheme 4), we cannot rule out the possibility that the Zaitzev product is actually produced via isomerization of the Hofmann product upon its protonation to the carbocationic intermediate by the conjugate acid of DMAP.

In conclusion, we have developed a new synthetic reaction for the chemoselective dehydration of tertiary alcohols using a mixture of triphosgene and DMAP. Our chemistry exhibited interesting reactivity behaviors, which include its preference toward formation of (*E*)-alkene as well as its ability to affect the Hofmann versus Zaitzev selectivity through the change of solvent and reaction temperature. Further studies on the reaction mechanism are currently ongoing in our laboratory. Our results will be reported in due course.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.9b01959.

Experimental procedures and spectral data of new compounds (PDF)

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: rkartika@lsu.edu.

ORCID

Rendy Kartika: 0000-0002-2042-2812

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

This material is based upon work supported by the National Science Foundation under CHE-1464788. Generous financial supports from Louisiana State University are gratefully acknowledged. A.H.C. thanks the Louisiana Board of Regents for the Graduate Fellowship (LEQSF(2015-20)-GF-02).

■ REFERENCES

(1) Henne, A. L.; Matuszak, A. H. *J. Am. Chem. Soc.* **1944**, *66*, 1649.

(2) (a) Dubois, J. E.; Lomas, J. S.; Sagatys, D. S. *Tetrahedron Lett.* **1971**, *12*, 1349. (b) Grob, C. A.; Schiess, P. W. *Angew. Chem., Int. Ed. Engl.* **1967**, *6*, 1.

(3) Lomas, J. S.; Sagatys, D. S.; Dubois, J. E. *Tetrahedron Lett* **1971**, *12*, 599.

(4) Sauers, R. R. *J. Am. Chem. Soc.* **1959**, *81*, 4873.

(5) (a) Frija, L. M. T.; Afonso, C. A. M. *Tetrahedron* **2012**, *68*, 7414. (b) D'Onofrio, F.; Scettri, A. *Synthesis-Stuttgart* **1985**, *1985*, 1159. (c) Firouzabadi, H.; Iranpoor, N.; Hazarkhani, H.; Karimi, B. *Synth. Commun.* **2003**, *33*, 3653. (d) Hoffman, R. V.; Bishop, R. D.; Fitch, P. M.; Hardenstein, R. *J. Org. Chem.* **1980**, *45*, 917. (e) Nishiguchi, T.; Kamio, C. *J. Chem. Soc., Perkin Trans. 1* **1989**, *1*, 707.

(6) (a) Alvarez-Manzaneda, E. J.; Chahboun, R.; Torres, E. C.; Alvarez, E.; Alvarez-Manzaneda, R.; Haidour, A.; Ramos, J. *Tetrahedron Lett.* **2004**, *45*, 4453. (b) Martin, J. C.; Arhart, R. J. *J. Am. Chem. Soc.* **1971**, *93*, 4327.

(7) (a) Demming, R. M.; Fischer, M. P.; Schmid, J.; Hauer, B. *Curr. Opin. Chem. Biol.* **2018**, *43*, 43. (b) Nestl, B. M.; Geinitz, C.; Popa, S.; Rizek, S.; Haselbeck, R. J.; Stephen, R.; Noble, M. A.; Fischer, M. P.; Ralph, E. C.; Hau, H. T.; Man, H.; Omar, M.; Turkenburg, J. P.; van Dien, S.; Culler, S. J.; Grogan, G.; Hauer, B. *Nat. Chem. Biol.* **2017**, *13*, 275.

(8) Recent examples: (a) Liu, Y.; Wang, H. *Chem. Commun.* **2019**, *55*, 3544. (b) Yu, X.; Xiao, L.; Wang, Z.; Luo, T. *J. Am. Chem. Soc.* **2019**, *141*, 3440. (c) Peter, D.; Brückner, R. *Eur. J. Org. Chem.* **2018**, *2018*, 6256. (d) Feng, J.; Yu, T.; Zhang, Z.; Li, J.; Fu, S.; Chen, J.; Liu,

DOI: 10.1021/acs.orglett.9b01959
Org. Lett. XXXX, XXX, XXX−XXX

B. *Chem. Commun.* **2018**, *54*, 7665. (e) Xuan, J.; Zhu, A.; Ma, B.; Ding, H. *Org. Lett.* **2018**, *20*, 4153. (f) Peter, D.; Brückner, R. *Chem. - Eur. J.* **2017**, *23*, 12104. (g) Cheng, H.; Zhang, Z.; Yao, H.; Zhang, W.; Yu, J.; Tong, R. *Angew. Chem., Int. Ed.* **2017**, *56*, 9096.

(9) (a) Atkins, G. M.; Burgess, E. M. *J. Am. Chem. Soc.* **1968**, *90*, 4744. (b) Burgess, E. M.; Penton, H. R.; Taylor, E. A. *J. Am. Chem. Soc.* **1970**, *92*, 5224. (c) Burgess, E. M.; Penton, H. R.; Taylor, E. A. *J. Org. Chem.* **1973**, *38*, 26.

(10) (a) Ayala, C. E.; Villalpando, A.; Nguyen, A. L.; McCandless, G. T.; Kartika, R. *Org. Lett.* **2012**, *14*, 3676. (b) Villalpando, A.; Ayala, C. E.; Watson, C. B.; Kartika, R. *J. Org. Chem.* **2013**, *78*, 3989. (c) Villalpando, A.; Saputra, M. A.; Tugwell, T. H.; Kartika, R. *Chem. Commun.* **2015**, *51*, 15075. (d) Cleveland, A. H.; Fronczek, F. R.; Kartika, R. *J. Org. Chem.* **2018**, *83*, 3367.

(11) (a) Eckert, H.; Forster, B. *Angew. Chem., Int. Ed. Engl.* **1987**, *26*, 894. (b) Damle, S. B. *Chem. Eng. News* **1993**, *71*, 4. (c) Cotarca, L. *Org. Process Res. Dev.* **1999**, *3*, 377.

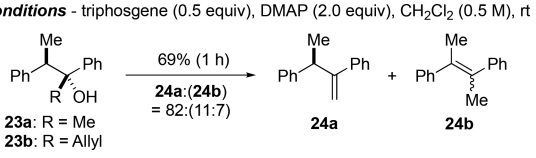
(12) (a) Isolated yields after column chromatography. (b) The ratio of alkene isomers was determined by GC-MS analyses of the crude reaction mixtures with an assumption that they elicited an identical response. (c) The alkene geometry of the major isomer was deduced by NOE. (d) The calculated ratio of alkene isomers may not be reflective of the actual ratio in the crude reaction mixtures due the possibility for some alkenes to isomerize under our GC conditions, e.g. compounds **13c** and **14c**. (e) The lower isolated product yields in some examples were due to the high volatility of the alkenes. (f) The content of an alkyl chloride in the crude reaction mixture, as determined by GC-MS with an assumption that they elicited an identical response, typically ranges between 0% to 9%. The only exception is substrate **8d**, which produced 18% of the chlorination product. See Table S-1 and GC chromatograms in the Supporting Information for details on each substrate.

(13) During the course of our study, a single example on the dehydration of tertiary cyclohexanol using excess triphosgene and pyridine was reported: Liu, Y.; Yeung, Y.-Y. *Org. Biomol. Chem.* **2017**, *15*, 6478.

(14) Putative dehydration reagent **20** was proposed given the molar equivalances of triphosgene and DMAP in our reaction. A second addition of DMAP to this active species is also hypothetically possible. For an analogous reaction between phosgene and pyridine: King, J. A.; Donahue, P. E.; Smith, J. E. *J. Org. Chem.* **1988**, *53*, 6145.

(15) Ei elimination generally favors the formation of Hofmann products: (a) Froemsdorf, D. H.; Collins, C. H.; Hammond, G. S.; DePuy, C. H. *J. Am. Chem. Soc.* **1959**, *81*, 643. (b) Haag, W.; Pines, H. *J. Org. Chem.* **1959**, *24*, 877. (c) DePuy, C. H.; King, R. W. *Chem. Rev.* **1960**, *60*, 431.

(16) Preliminary attempts to discern the E2 vs Ei mechanism using diastereomerically pure tertiary alcohols **23a** and **23b** were not productive. Dehydration of **23a** afforded primarily exomethylene **24a** along with a lesser amount of stilbenes **24b** as as mixture of alkene isomers, which most likely have been generated via carbocationic intermediates. The major isomer of **24b** was not determined. Substrate **23b** was unreactive under the reaction conditions.



(17) (a) Dehydration of substrate **4** with catalytic TsOH (0.1 equiv) in dichloromethane (0.5 M) at reflux furnished alkenes **5** and **6** as a 62:38 mixture. Had our reaction proceeded primarily via the E1 mechanism, we believed that poorer (*E*) vs (*Z*) alkene selectivity as well as the Zaitzev preference would have been observed. (b) For comparison, dehydration of substrate **4** was performed with $SOCl_2$ or $POCl_3$ in the presence of pyridine, see refs 3 and 4, respectively. Treatment with $SOCl_2$ (1.5 equiv) and pyridine (5.0 equiv) produced a 41:8:51 mixture of products **5**:**6**:**7**, whereas $POCl_3$ (2.5 equiv) and pyridine (15 equiv) furnished alkene mixtures **5**:**6** in a 81:19 ratio without the presence of alkyl chloride **7**.

DOI: 10.1021/acs.orglett.9b01959
Org. Lett. XXXX, XXX, XXX−XXX