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Cyclopropenium-Activated Cyclodehydration of Diols

Brendan D. Kelly and Tristan H. Lambert*

Department of Chemistry, Columbia University, New York, New York 10027, United States

tl2240@columbia.edu

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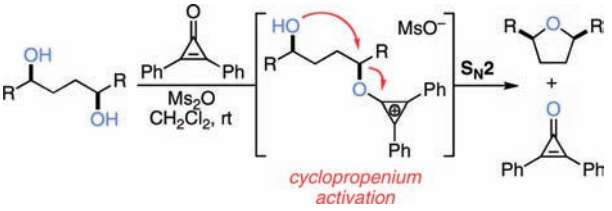
ABSTRACT



The dehydrative cyclization of diols to cyclic ethers via cyclopropenium activation is described. Using 2,3-diphenylcyclopropene and methanesulfonic anhydride, a series of 1,4- and 1,5-diols are rapidly cyclized to furnish tetrahydrofurans and tetrahydropyrans in high yield. Eleven total substrates are shown, including a gram scale cyclization of a diterpene derivative.

Chemical processes that involve the direct or formal loss of water, collectively termed dehydration reactions, represent perhaps the most widely utilized and important class of reactions in organic synthesis. Included in this category are such ubiquitous transformations as amidation (e.g., peptide coupling), esterification, glycosylation, ether formation, and Mitsunobu inversion, to name a few. Despite this importance, the traditional reagents used to effect substitution reactions often suffer from numerous limitations, which may include reagent harshness, lack of substrate scope, poor reactivity, offensive byproduct formation, and, most notably, a profound lack of amenability to enantioselective catalysis.

In an effort to address these limitations, we recently disclosed a novel strategy for the promotion of dehydration reactions using cyclopropenium ions, a process we termed "cyclopropenium activation" (Figure 1a).[1] With this approach, hydroxyl-bearing substrates such as alcohols,[1a] carboxylic acids,[1b] or oximes[1c] are treated with a cyclopropene of the type **1** bearing geminal leaving groups, typically generated in situ from the corresponding cyclopropenone **2**. The propensity of cyclopropenes **1** to ionize due to aromatic stabilization of the resulting 2π-electron cyclopropenium ions[2,3] leads to a rapid combination with hydroxylic substrates to produce intermediates **3**. As electron-deficient carbocations, these "cyclopropenium-activated" intermediates are highly susceptible to nucleophilic displacement of the neutral cyclopropenone to produce substitution or rearrangement products. Our initial reports[1] of this concept described the potency and synthetic utility of cyclopropenium activation in the context of alcohol chlorodehydration, carboxylic acid chlorodehydration, and Beckmann rearrangement (Figure 1b). Each of these processes ultimately relies on the chloride ion to serve as both the cyclopropenyl leaving group and the nucleophilic species.

In this Letter, we report the advancement of our cyclopropenium activation strategy with the invention of a powerful and convenient new strategy to achieve the cyclodehydration of diols **4** to produce cyclic ethers **5**. This

(1) (a) Kelly, B. D.; Lambert, T. H. *J. Am. Chem. Soc.* **2009**, *131*, 13930. (b) Hardee, D. J.; Kovalchuke, L.; Lambert, T. H. *J. Am. Chem. Soc.* **2010**, *132*, 5002. (c) Vanos, C. M.; Lambert, T. H. *Chem. Sci.* **2010**, *1*, 705.

(2) (a) Breslow, R. *J. Am. Chem. Soc.* **1957**, *79*, 5318. (b) Breslow, R.; Yuan, C. *J. Am. Chem. Soc.* **1958**, *80*, 5991.

(3) For a review on cyclopropenium ions, see: Komatsu, K.; Kitagawa, T. *Chem. Rev.* **2003**, *103*, 1371.

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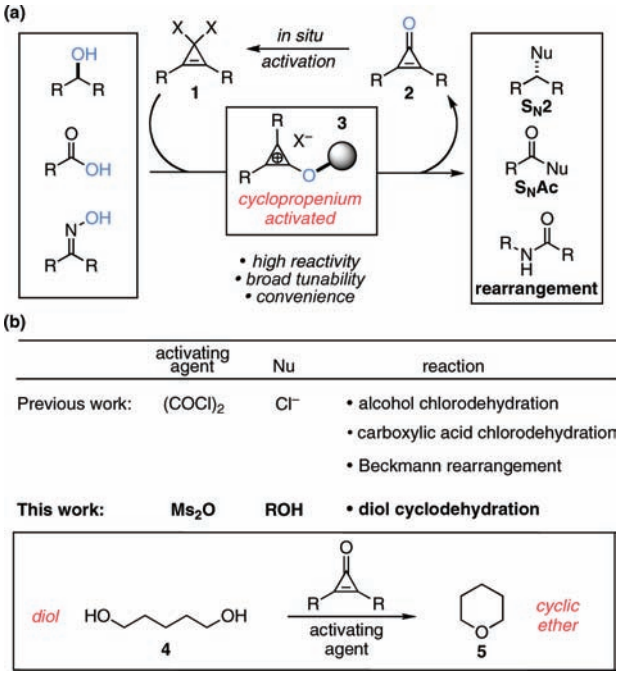


Figure 1. Cyclopropenium activation.

work encompasses two key developments in our cyclopropenium program, namely, (1) demonstration of the effectiveness of alternative cyclopropenyl leaving groups in the form of methanesulfonate ions and (2) extension of the nucleophilic species to include alcohols.

Cyclic ethers are a prevalent motif in biologically active compounds. Accordingly, numerous synthetic methods have been developed to access this important class of heterocycles.[4] Although the dehydrative cyclization of diols is one of the most conceptually straightforward strategies by which to construct cyclic ethers, from a practical standpoint methods to achieve these transformations often suffer from lack of selectivity, the need for forcing conditions, or the use of reagents that are inconvenient to prepare, leave undesirable byproducts, and lack broad tunability.[5] In contrast, we reasoned that cyclopropenium activation could offer a powerful alternative strategy for diol cyclodehydration by combining high reactivity

(4) Heitmann, W.; Strehlke, G.; Mayer, D. Ethers, Aliphatic. In *Ullmann's Encyclopedia of Industrial Chemistry*; Wiley-VCH: Weinheim, Germany, 2002.

(5) See the following selected papers for diol cyclodehydrations using: Platinium: (a) Shibata, T.; Fujiwara, R.; Ueno, Y. *Synlett*, 2005, *152*. Triphenylphosphine: (b) Barry, C. N.; Evans, S. A., Jr. *J. Org. Chem.* **1981**, *46*, 3361. (c) Robinson, P. L.; Barry, C. N.; Kelly, J. W.; Evans, S. A., Jr. *J. Am. Chem. Soc.* **1985**, *107*, 5210. DMSO:(d) Gillis, B. T.; Beck, P. E. *J. Org. Chem.* **1963**, *28*, 1388. Silver(I) oxide: (e) Bouzide, A.; Sauvé, G. *Org. Lett.* **2002**, *4*, 2329. Sulfuranes:(f) Martin, J. C.; Franz, J. A.; Arhart, R. J. *J. Am. Chem. Soc.* **1974**, *96*, 4604. Triphosphonitrilic chloride:(g) Matuszko, A. J.; Chang, M. S. *J. Org. Chem.* 1966, *31*, 2004. (h) Török, B.; Bucsi, I.; Beregszászi, T.; Kapocsi, I.; Molnár, A. *J. Mol. Catal. A: Chem.* **1996**, *107*, 305. Heteropoly acids:(i) Duffy, M. G.; Grayson, D. H. *J. Chem. Soc., Perkin Trans. I* **2002**, 1555. Methanesulfonyl chloride:(j) Mihailovic, M. L.; Gojkovic, S.; Cekovic, Z. *J. Chem. Soc., Perkin Trans. I* **1972**, 2460.

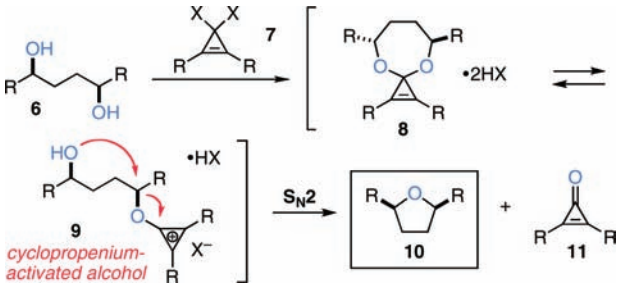
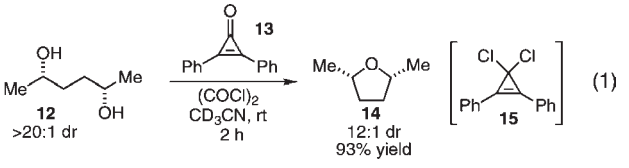


Figure 2. Mechanistic design for cyclopropenium ion mediated cyclization of diols to form cyclic ethers.

with extreme convenience through the use of reagents readily amenable to steric and electronic modulation.

In the design of a cyclopropenium activated cyclodehydration reaction, we expected that a diol substrate **6** would react with an activated cyclopropene reagent **7** to form an equilibrium mixture of cyclopropene acetal[6] **8** and the corresponding cyclopropenium ether **9** (Figure 2). Intramolecular nucleophilic closure of this intermediate would then furnish cyclic ether **10** with concomitant production of cyclopropenone **11**. Key to the success of this design would of course be the ability to readily access monoactivated intermediate **9** and the ability of the cyclopropenium ion to sufficiently activate a hydroxyl group for displacement by the relatively poor nucleophilic alcohol moiety.

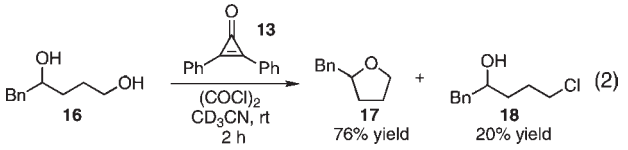
To test the feasibility of this proposed design, we first examined the reaction of commercially available (*S*,*S*)-2,5-hexanediol (**12**) with 1,1-dichloro-2,3-diphenylcyclopropene (**15**), prepared in situ from commercially available 2,3-diphenylcyclopropenone **13** by treatment with oxalyl chloride. In fact, when **12** and was added to a mixture of **13** and oxalyl chloride in acetonitrile at room temperature, (*R*,*S*)-2,5-dimethyltetrahydrofuran (**14**) was produced in 93% yield (^{1}H NMR) as a 12:1 diastereomeric mixture after 2 h (eq 1). This experiment thus demonstrates the power of cyclopropenium activation to effect dehydration in the context of ether linkages and is notable for its relatively high rate of reaction, the complete absence of elimination or chlorination side products, and the lack of need for base to effect ring closure.



On the other hand, the incomplete stereospecificity observed in this transformation suggested that simple S_N2 closure is not the exclusive reaction pathway. In addition, we found that certain other substrates, especially those possessing primary alcohols, were prone to

(6) For a review on cyclopropenone acetals, see: Nakamura, M.; Isobe, H.; Nakamura, E. *Chem. Rev.* **2003**, *103*, 1295.

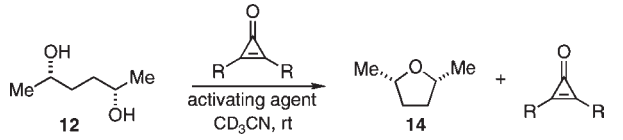
competitive chlorination. Thus for example diol **16** was found to react to produce a mixture of 2-benzyltetrahydrofuran **17** and chloride **18** in 76% and 20% yields, respectively (eq 2). This finding was not surprising, given our previous description of **15** as a potent chlorodehydrating reagent. To solve this problem, we thus decided to investigate the use of alternative cyclopropenes with the intention of identifying a superior reagent.



(2)

In this regard, we took note of the fact that the reaction of cyclopropenones with trifluoroacetic anhydride (TFAA) had previously been shown[7] to produce the corresponding 1,1-bistrifluoroacetoxycyclopropenes, a rather unusual transformation for ketone functionality. We thus decided to investigate whether various acid anhydrides could take the place of oxalyl chloride in our activation strategy, and thereby minimize or eliminate the problems plaguing the chloride-based reagents.

Table 1. Optimization Studies for Dehydrative Cyclization of Diols[a,b]

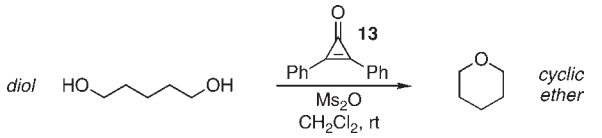


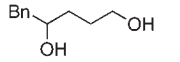
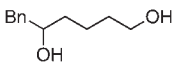
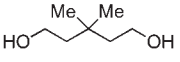
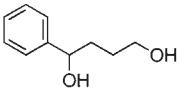
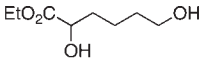
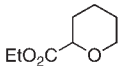
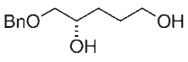
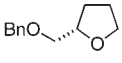
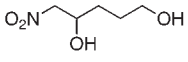
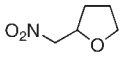
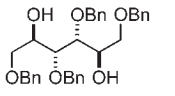
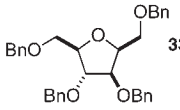
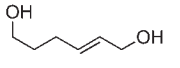
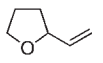
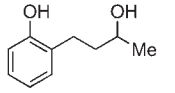
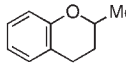
entry	R		activating agent	time (h)	yield (%)	*syn*:*anti*[c]
1	Ph	**13**	$(COCl)_2$	2	93	12:1
2	Ph	**13**	TFAA	24	7	>20:1
3	i-Pr	**19**	TFAA	24	38	>20:1
4	Ph	**13**	Ms_2O	2.5	95	>20:1
5	*i*-Pr	**19**	Ms_2O	2.5	91	>20:1
6	none		$(COCl)_2$	24	0	
7	none		TFAA	24	0	
8	none		Ms_2O	24	0	

[a] Reactions were performed by the addition of "activating agent" (1.5 equiv) to a solution of cyclopropenone (1.6 equiv) in CD_3CN. After 30 min, diol **12** was added to the solution. [b] Yields determined by ^1H NMR analysis using internal standard (Bn_2O). [c] Diastereomeric ratio determined by ^1H NMR.

As before, the following series of experiments were conducted by in situ activation of cyclopropenone by treatment with a given anhydride, followed by addition of the diol **12** to the resulting cyclopropene solution. Thus the use of TFAA and diphenylcyclopropenone **13**[7] resulted in low yet appreciable conversion of diol **12** to ether **14** (7%) after 24 h (Table 1, entry 2). Notably, changing the cyclopropene substituents from phenyl to isopropyl, which leads to more stable (higher pK_{R^+}) cyclopropenium ions, significantly improved the rate of cyclic ether formation (cf. **19**, entry 3). Not surprisingly, we found that cyclopropenes bearing methanesulfonate (mesylate) groups were significantly more effective than those bearing trifluoroacetoxy substituents. For example, methanesulfonic anhydride (Ms_2O) and 2,3-diphenylcyclopropenone effected the cyclization of diol **12** in 95% yield after 2.5 h (entry 4), a reaction time only slightly longer than that observed with the dichlorocyclopropene **15**. Interestingly, changing from phenyl to isopropyl substituents did not offer any benefit in this case (entry 5). It is important to note that, in contrast to the dichlorocyclopropene example noted

Table 2. Substrate Scope Studies for Dehydrative Cyclization of Diols[a,b]



entry	substrate		product		time (h)	% yield
1		**16**		**17**	4	91
2		**20**		**21**	10	89
3		**22**		**23**	1	91[c]
4		**24**		**25**	1	94
5		**26**		**27**	3.5	87
6		**28**		**29**	7	92
7		**30**		**31**	6	81
8		**32**		**33**	11	82
9		**34**		**35**	3	95[c]
10		**36**		**37**	22	83[d]

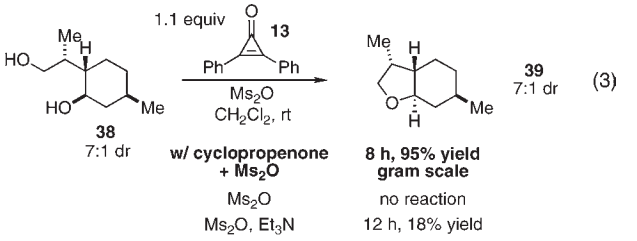
[a] General reaction conditions: Reactions were performed by the addition of methanesulfonic anhydride (1.1 equiv) to a solution of cyclopropenone **13** (1.2 equiv) in CH_2Cl_2. After 30 min, the diol substrate was added to the solution. [b] Yields determined on isolated and purified products unless otherwise noted. [c] Yield determined by ^1H NMR analysis using internal standard (Bn_2O). [d] 1.4 equiv of **13** and 1.3 equiv of Ms_2O were used.

(7) Oda, M.; Breslow, R.; Pecoraro, J. *Tetrahedron Lett.* **1972**, *13*, 4415.

above, diastereomeric integrity was retained in all cases with the use of anhydride activating agents. It should also be stressed that no cyclization products were observed with the use of oxalyl chloride, trifluoroacetic anhydride, or mesyl anhydride in the absence of cyclopropenone (entries 6−8), or with the use of HCl, TFA, or methanesulfonic acid (see the Supporting Information).

Substrate scope studies have shown 2,3-diphenylcyclopropenone (**13**) and Ms_2O to be an effective reagent combination for the dehydrative cyclization of 1,4- and 1,5-diols (Table 2).[8] For example, the conversion of diol **16** to 2-benzyltetrahydrofuran (**17**) was readily achieved in 91% yield after 4 h at room temperature (entry 1). Similar efficiency was found for the one-carbon homologated substrate **20** for the production of the corresponding tetrahydropyran **21**, albeit with an expectedly longer reaction time (entry 2). We note that, although dichlorocyclopropene **13** was only poorly effective for these substrates due to competitive chlorination (see eq 2), the use of mesylate counterions resulted in no observable sulfonate substitution products. Indeed, even the bis-primary alcohol substrate **22** could be converted to tetrahydropyran **23** in high yield without complication (entry 3). In addition, benzylic alcohol **24** (entry 4), α-hydroxyester **26** (entry 5), and protected 1,2-diol **28** (entry 6) were all found to be productive for dehydrative cyclization. Importantly, diol **28** was optically enriched, and stereochemical analysis of the product **29** revealed that cyclization occurred exclusively via nucleophilic substitution of the primary alcohol by the secondary hydroxyl. Furthermore, despite its potential sensitivity nitroalcohol **30** underwent cyclodehydration without any observable β-elimination (entry 7). As further proof of the S_N2 nature of this reaction, we found that the stereochemically complex tetra-*O*-benzylmannitol (**32**) cleanly converted to tetrahydrofuran **33** in good yield as a single diastereomer (entry 8). Cyclization in an S_N2' sense was also facile, producing 2-vinyltetrahydrofuran (**35**) in 95% yield (entry 9). Interestingly, a phenolic hydroxyl was found to be a capable nucleophile for the preparation of 2-methylchroman (**31**) with good efficiency (entry 10), suggesting that this strategy can also be effective for the preparation of benzocyclic ethers.

Finally, in order to demonstrate the potential preparative utility of this strategy, we examined the cyclization of diol **38**, which is the hydroboration/oxidation adduct of (−)-isopulegol (eq 3). In the presence of 2,3-diphenylcyclopropenone (**13**) and methanesulfonic anhydride in CH_2Cl_2 at room temperature, this substrate underwent dehydrative cyclization to produce the bicyclic ether **39** in 95% yield over 8 h with complete stereospecificity on a gram scale. For comparison, treatment of **38** under the same conditions with methanesulfonic anhydride itself resulted in no product, and in the presence of triethylamine led to only 18% product over 12 h. Clearly the cyclopropenone provides a powerful enhancement of the dehydrating ability of methanesulfonic anhydride.



(3)

In conclusion, we have extended the concept of cyclopropenium activation with the demonstration of new activating agents and an alternative nucleophile in the context of a novel dehydrative cyclization of 1,4- and 1,5-diols. This method offers a potent and convenient means to construct stereodefined tetrahydrofurans and pyrans from their corresponding acyclic diol precursors. Further development of this strategy and application of cyclopropenium activation to other reaction manifolds is currently underway.

Acknowledgment. T.H.L. is grateful for an Alfred P. Sloan Research Fellowship and Young Investigator Awards from Abbott and Amgen.

Supporting Information Available. Full experimental details and characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.

(8) Efforts to extend the current protocol to the formation of ring sizes smaller than 5 or greater than 6 have not yet been successful.