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1,3-Diol Synthesis via Controlled, Radical-Mediated C−H Functionalization

Ke Chen, Jeremy M. Richter, and Phil S. Baran*

Department of Chemistry, The Scripps Research Institute, 10550 North Torrey Pines Road, La Jolla, California 92037

Received April 9, 2008; E-mail: pbaran@scripps.edu

Nature's ability to functionalize C−H bonds has inspired and motivated organic chemists for decades.[1] From the vantage point of complex molecule synthesis, such methods hold the potential to dramatically transform the practice of retrosynthetic analysis.[2] Yet, a consistent and profound challenge for C−H oxidation remains in achieving complete control of chemo-, regio-, and stereospecificity. This communication presents a classical, yet powerful, approach to C−H functionalization inspired by the venerable Hofmann−Löffler−Freytag (HLF) reaction.[3] The described process accomplishes the conversion of an alcohol into a 1,3-diol and has been demonstrated in multiple contexts and utilized in rapid syntheses of four natural products.

Several conventional methods are available to access 1,3-diols, such as aldol/reduction, conjugate addition/reduction, or various manipulations of allyl alcohols (Figure 1A). To the best of our knowledge, no methods for the conversion of alcohols to 1,3-diols exist, despite the intrinsic value of this hypothetical transform. Such a conversion has the potential to expedite or at least provide a valuable alternative route to numerous natural products and medicinally important compounds.

The HLF reaction, well-known for its ability to intramolecularly form C−N bonds, has been a powerful method for the direct halogenation of C−H bonds since its inception in the 1880s.[3] Indeed, the HLF reaction might be considered one of the first directed C−H activation reactions ever reported.[1] Figure 1B illustrates how the principles of the HLF reaction were incorporated into our reaction design. The proposed conversion of a carbamate (**A**) into a 1,3-diol (**F**) via alkyl bromide **C** is accompanied by two primary challenges. First, the formation of **C** from **B** requires a 1,6-hydrogen atom transfer (seven-membered transition state), while the HLF reaction has been predominately used for the synthesis of five-membered rings via 1,5-hydrogen atom transfer (H_a vs H_b abstraction). Second, even if **C** were successfully formed, cyclization at the oxygen rather than the nitrogen of the carbamate would be required (to form iminocarbonate **D** instead of cyclic carbamate **E**).[4,5]

The first challenge was addressed by studying the effect of carbamate structure in the conversion of **B** to **C** (the C−H activation step). Of the *N*-bromocarbamates evaluated (Figure 2), most gave very low (<30%) conversion to the corresponding alkyl bromide (**C**) and returned only debrominated starting material (**A**) after photolysis with a 100 W flood lamp.[6] In order to generate a more reactive *N*-centered radical,[7,8] the trifluoroethyl carbamate was investigated. In the end, the use of this moiety (never before employed in an HLF reaction) was found to be essential in rendering this process synthetically useful. Furthermore, a simple procedure was developed for the near quantitative conversion of alcohols to the corresponding carbamate using 1 equiv of CF_3CH_2NCO (see Supporting Information for details).

The second challenge (conversion of **C** to **D** rather than **E**) was addressed using Ag_2CO_3 to promote cyclization to iminocarbonate

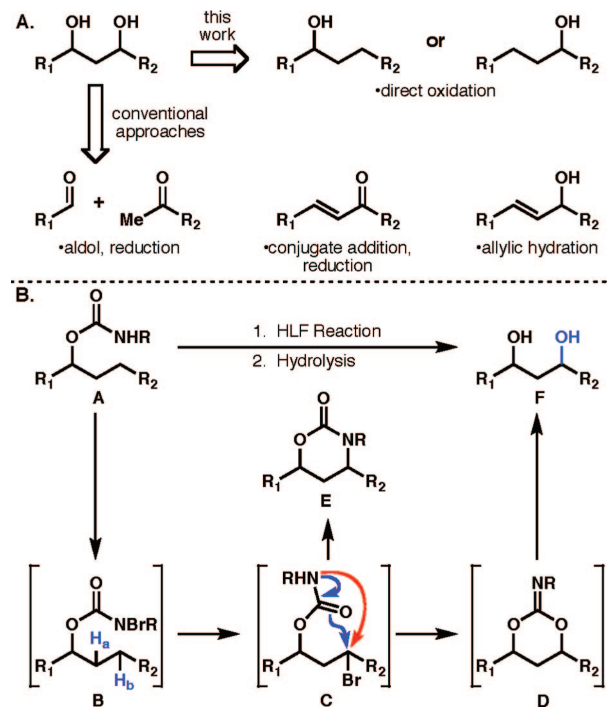


Figure 1. 1,3-Diol synthesis using a modified HLF reaction.

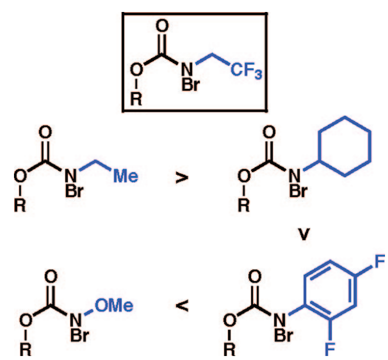
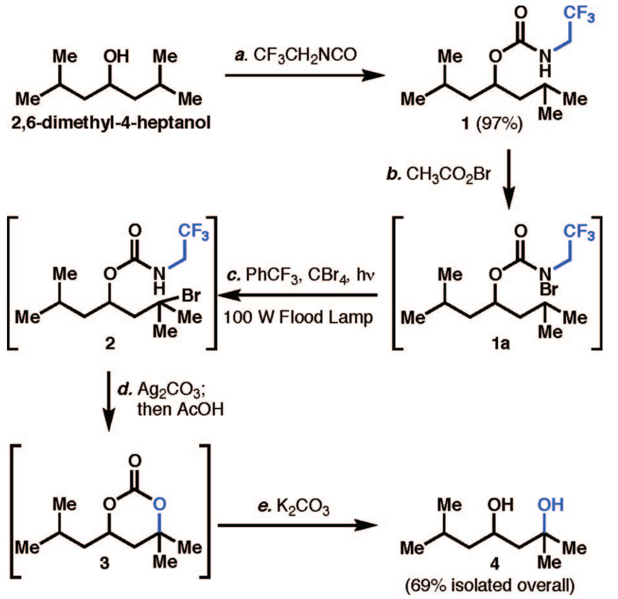


Figure 2. Relative efficiency of selected *N*-bromocarbamates.

D. Hydrolysis with acetic acid and K_2CO_3 provided **F** in short order.[9] All intermediates in this process were isolated and fully characterized (see Supporting Information for a detailed optimization table). The overall transformation is shown in Scheme 1 for substrate **1**.

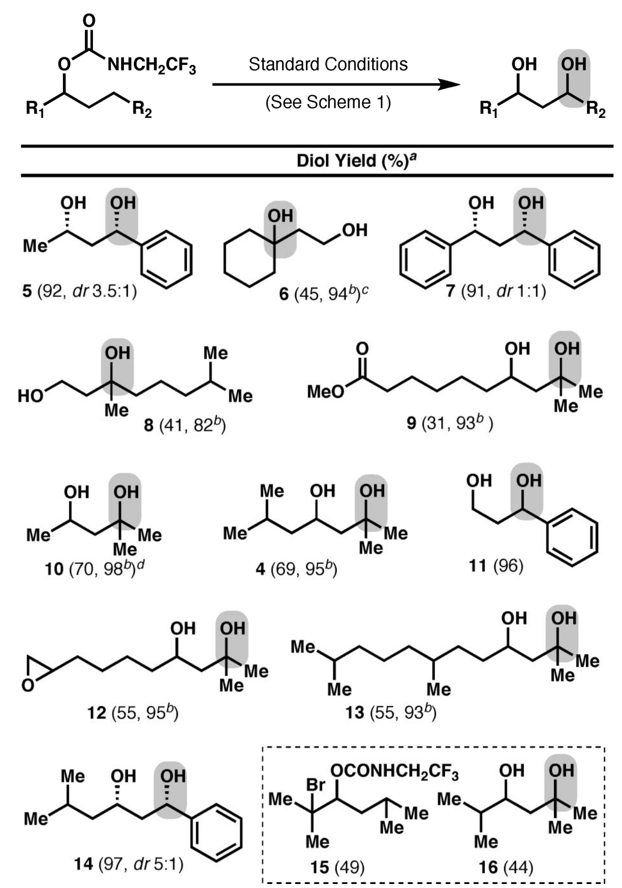
With optimized conditions in hand for the efficient and practical preparation of 1,3-diols, the scope of this reaction was investigated (Table 1). This methodology proved amenable for the directed oxidation of a variety of simple tertiary centers (**4**, **6**, and **10**) to provide the diols in good yields. Esters (**9**) and epoxides (**12**) are

Scheme 1. Synthesis of 1,3-Diol **4** from Carbamate **1**[a]



[a] Reagents and conditions: (a) CF_3CH_2NCO (1.0 equiv), DCM, Pyr (1.0 equiv), 23 °C, 2 h, 97%; (b) CH_3CO_2Br (1.0 equiv), DCM, 0 °C, 5 min; (c) $PhCF_3$ (0.05 M), CBr_4 (1.0 equiv), 23 °C, $h\nu$, 7 min; (d) Ag_2CO_3 (1.25 equiv), DCM, 23 °C, 1 h; then AcOH, 15 min; (e) K_2CO_3 (5.0 equiv), MeOH, 23 °C, 2 h, 69% overall. DCM = dichloromethane, Pyr = pyridine.

Table 1. Scope of Directed C−H Oxidation



[a] Isolated yield. [b] Yield brsm. [c] CBr_4 is not necessary. [d] A 56% isolated yield on gram scale; 88% yield brsm.

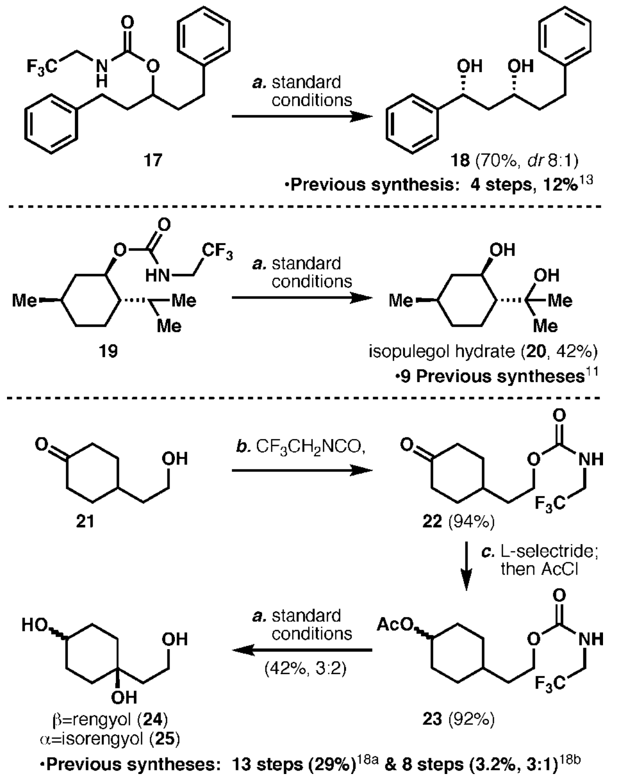
tolerated in this sequence, even though alternate side reactions can be envisioned under these conditions. It is noteworthy that the 1,3-diols **8**, **13**, and **20** (isopulegol hydrate)[10,11] are obtained selectively, despite the presence of additional tertiary centers that can participate in the HLF reaction, a point which will be returned to shortly (vide infra). The reaction also proved effective for the generation of 1,3-benzylic diols (**5**, **7**, **11**, and **18**[12,13]) in excellent yields and moderate to good diastereoselectivities. Due to the ability of sp^3 carbon radicals to trigonalize, no diastereoselection is observed during C-bromination; any diastereomeric ratios observed in the 1,3-diol products arise during the silver-promoted cyclization. As a demonstration of this effect, racemic compound **8** is obtained when either racemic or enantiopure tetrahydrogeraniol is utilized in this oxidation protocol. When a competition experiment is performed between tertiary and benzylic centers, the benzylic 1,3-diol (**14**) is the sole product obtained. Finally, in simple acyclic cases, where both 1,5- and 1,6-hydrogen transfer can occur, no selectivity is observed and the products of both 1,5- (**15**) and 1,6- (**16**) hydrogen transfer are obtained, although the former cannot cyclize under these conditions.

Certain limitations have been identified for this method: (1) only benzylic and tertiary C−H bonds are oxidized in synthetically useful yields, and (2) olefins,[14] free carboxylic acids, amines, amides, unprotected alcohols, and azides are not tolerated (as with most C−H oxidations). Aside from the use of stoichiometric Ag_2CO_3, a reagent used in many C−H functionalization protocols,[15] this method uses readily available reagents and a simple, scalable protocol. The typical reaction sequence, from alcohol to 1,3-diol, only requires 6−8 h. It should also be noted that this reaction can easily be performed on a gram scale (**10**, 56% yield).

To further demonstrate the utility of this method, the simple natural products **18**, **20**, **24**, and **25** were synthesized (Scheme 2). Upon exposure to the conditions developed herein, carbamate **17** cleanly provided the natural product (**18**) in high yield and good diastereoselectivity. Furthermore, carbamate **19** provided isopulegol hydrate (**20**) efficiently in one step. It is noteworthy that **20** has been prepared by non-selective microbial oxidation (*Cephalosporium aphidicola*) of menthol in only 4.8% isolated yield.[16] Finally, triols rengyol and isorengyol (**24** and **25**)[17,18] were synthesized utilizing this procedure, beginning with installation of the carbamate on the commercially available alcohol **21**. Reduction of the ketone (**22**) and in situ acetylation generated **23**, which could be used directly in the oxygenation reaction to give **24** and **25** in 42% yield as a 3:2 mixture of diastereomers. This synthesis proceeds in only three steps and 36% overall yield from **21**.

One of the most useful features of the transformation discussed herein is the unique chemo- and regioselectivity[19] observed during the course of the reaction, specifically in cases when multiple tertiary C−H bonds can be activated. Figure 3 presents a comparison between this method and those of Curci[20] and White.[2a] For example, carbamate **26** leads to diol **13** as a single regioisomer in 55% isolated yield under our conditions (via activation of C−H_c). In comparison, the catalyst system developed by White[2a] selectively activates C−H_a in a 3:1 ratio with C−H_b (42% combined yield) and no C−H_d activation observed. Curci conditions[20] (1 equiv of TFDO, −15 °C) indiscriminately provides a complex mixture of oxidized products in 91% combined yield. As a further example of the orthogonal nature of this transformation, menthol carbamate **19** was investigated under the three sets of conditions. Our conditions selectively activated C−H_c (**20**, 42% isolated yield), the White conditions selectively activated C−H_a (51% isolated yield), and TFDO (1 equiv, −15 °C) provided a complex mixture of oxidized products in 86% combined yield. It is notable that the current system undergoes regioselective 1,6-activation (H_c), even

Scheme 2. Total Synthesis of **15**, **17**, **21**, and **22**[a]



[a] Reagents and conditions: (a) CH_3CO_2Br (1 equiv), DCM, 0 °C, 5 min; then $PhCF_3$, 23 °C, $h\nu$, 25 min; then Ag_2CO_3 (1.25 equiv), DCM, 23 °C, 4 h; then AcOH, 23 °C, 15 min; then K_2CO_3 (5.0 equiv), MeOH, 18 h, 42%; (b) Pyr (1.0 equiv), CF_3CH_2NCO (1.0 equiv), DCM, 0 to 23 °C, 2 h, 94%; (c) L-Selectride (1.0 equiv), THF, −78 °C, 1 h; then Pyr (10 equiv), AcCl (5.0 equiv), DMAP (cat.), DCM, 0 °C, 30 min, 92%. DCM = dichloromethane, THF = tetrahydrofuran, Pyr = pyridine.

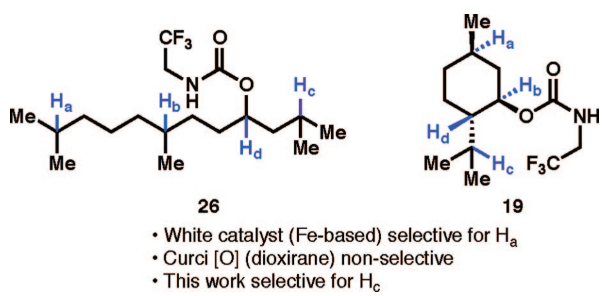


Figure 3. Comparison of selectivity of tertiary C−H bond activation.

though H_d (1,5-activation) is readily accessible. The observed selectivity in this case is likely due to the conformational bias of this system rather than a preference of the carbamoyl radical for 1,6-hydrogen transfer (c.f., **16**, Table 1).

Inspired by the age-old HLF reaction and enabled by the use of a unique trifluoroethyl-substituted carbamate, a practical method using simple reagents has been developed for the net conversion of an alcohol to a 1,3-diol. Mechanistic studies and efforts to expand the scope of this transformation are underway.

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Supporting Information Available: Detailed experimental procedures, copies of all spectral data, and full characterization. This material is available free of charge via the Internet at http://pubs.acs.org.

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