Published in final edited form as:

Tetrahedron Lett. 2013 December 18; 54(51): . doi:10.1016/j.tetlet.2013.10.097.

Base mediated deprotection strategies for trifluoroethyl (TFE) ethers, a new alcohol protecting group

Qingliang Yang and Jon T. Njardarson*

Department of Chemistry and Biochemistry, University of Arizona, 1306 E. University Blvd., Tucson, AZ 85721, USA

Abstract

A trifluoroethyl (TFE) ether is specifically introduced as a protecting group in organic chemistry. Its first strategic application and removal in the total synthesis of vinigrol is discussed. Two lithium base mediated deprotection strategies for its removal are presented in this Letter. In one deprotection approach, the trifluoroethyl ether is converted to a difluorovinyl ether and then catalytically cleaved using osmium tetroxide, while in the second approach a difluorovinyl anion is formed and trapped with an electrophilic oxygen reagent (MoOPH) to form a labile difluoroacetate. To further aid the reader, a summary of approaches for forming trifluoroethyl ethers is included as well as a discussion of alternate deprotection strategies.

Keywords

Trifluoroethyl ether; Difluorovinyl; Deprotection; Dihydroxylation; Electrophilic oxygen

In our recent total synthesis of vinigrol¹ we required a unique alcohol protecting group that needed to serve several critical roles (Scheme 1). We needed a small group that would not interfere with and survive a challenging Dakin oxidation. This same group was then expected to be electron withdrawing enough to guide an oxidative dearomatization reaction to the more hindered ether. In this same key step, the protecting group also needed to deactivate the resulting enol ether to allow a key intramolecular Diels Alder reaction to proceed while hindering unproductive *ortho*-quinone formation.² This protecting group was then expected to survive a plethora of metal-catalyzed, oxidative, reductive, nucleophilic, acidic and basic reactions all the way to the final step of the synthesis. Finally, a successful deprotection of the protected tertiary alcohol was expected to deliver vinigrol. Remarkably, we did find a protecting group that delivered the specific size and electronic functions we required. It also survived an amazing array of reactions and could be selectively deprotected in the final step. The group we identified as being optimal for all these tasks was a trifluoroethyl (TFE) ether.

From what we gather from the literature, this is the first example that a trifluoroethyl ether is used strategically as protecting group in target oriented synthesis.³ The aim of this Letter is to educate the reader about this unique new protecting group. Current state of the art approaches for protecting alcohols with a TFE ether will first be summarized followed by a discussion of current and proposed deprotection approaches inspired by our vinigrol

synthetic pursuit. Finally, the results from two successful base mediated deprotection strategies we have developed are presented.

How are trifluoroethyl ethers synthesized? Current state of the art approaches are summarized in Scheme 2. In addition to what one would consider classic nucleophilic displacement approaches (S_N2 or S_N1),⁴ several intriguing trifluoroethyl ether forming reactions have been developed. Because of the strong inductive effects of the trifluoroethyl groups more strategies are available than otherwise would be for normal alkyl ethers. For example, Mitsunobu reactions are feasible with trifluoroethanol⁵ as a nucleophile as are copper catalyzed cross-couplings.⁶ A particularly interesting approach is the conversion of alcohols to TFE protected alcohols employing bis(fluoroalkoxy)triphenyl phosphoranes.⁷ Finally, it has been shown that trifluorodiazethane can be treated with a mild acid in the presence of an alcohol as a way to access TFE protected alcohol products.⁸

Not surprisingly, since TFE ether has not been used purposefully as a protecting group, there is not much literature dedicated to cleaving it. In 1980, inspired by the uniquely attractive solvolysis properties of trifluoroethanol Sargent decided to evaluate conditions for deprotecting these solvolysis products (TFE protected alcohols). He found that sodium naphthalene was suited for this deprotection task.⁹ In his studies of diamondoid fluorides, Schreiner has shown that adamantane type trifluoroethyl ethers can be subjected to refluxing trifluoroacetic thus affording trifluoroacetate products.¹⁰ Neither one of these deprotection approaches were suitable for the last step in our vinigrol synthesis, which meant we needed to develop new solutions to cleave the TFE ether. We were drawn to two key clues from the literature (Scheme 3). It has been known for some time, from the work of Nakai, that lithium bases could be used to transform trifluoroethyl ethers into difluorovinyl ethers.^{11,12} The same authors soon thereafter revealed that treatment with excess alkyllithium forms acetylenic ethers from trifluoroethyl ethers.¹³ We proposed that the intermediate difluorovinyl ether provided two different deprotection options for accessing the free alcohol. It could be oxidatively cleaved with reagents such as osmium tetroxide (Method A), or alternatively, it could be deprotonated and the resulting vinyl anion trapped with an electrophilic oxygen (Method B) reagent to afford a base labile difluoroacetate product. A more aggressive approach would be to use Nakai's conditions to convert the trifluoroethyl ether to an acetylenic ether, which could be transformed to an ester upon treatment with an appropriate acid and hydrolyzed or reductively cleaved to afford the alcohol. For our vinigrol total synthesis, method A was shown to be successful albeit with the use of stoichiometric amounts of osmium tetroxide.¹⁴

We were eager to learn if the deprotection conditions (Method A) we had developed for vinigrol could be further improved (employing catalytic instead of stoichiometric osmium) and to explore the feasibility of Method B as an alternative TFE ether deprotection strategy. We were delighted to learn that the intermediate difluorovinyl ether could indeed be cleaved using catalytic amounts of osmium (Table 1).^{15,16} The eight substrates shown in Table 1 can all be deprotected using this approach (Method A) with the exception of entry 4, which cleanly affords the intermediate difluorovinyl ether but in our hands does not undergo the oxidative cleavage reaction. TFE ether protected adamantane alcohol **7** required a slight procedural modification in the form of a stronger base (*t*-BuLi). Yields range from moderate to very good for this deprotection approach. For our second base mediated deprotection approach, we wanted to explore the feasibility of trapping the vinyl anion of the intermediate difluorovinyl ether in situ with an electrophilic oxygen reagent (Method B). We were inspired by recent success from the Wood laboratory, wherein such a strategy (*t*-BuLi, O₂) had been applied to an extremely challenging deprotection of a benzyl protected amine.¹⁷ These conditions failed in our hands to deprotect TFE ether. Using LDA as a base we screened what we considered based on the literature to be the most promising sources of

electrophilic oxygen (O_2 ,¹⁸ Davis oxaziridine,¹⁹ MoOPH,²⁰ and peroxides²¹). Our studies revealed that MoOPH was far superior to all other electrophilic oxygen trapping agents²² in affording the desired intermediate difluoroacetate, which was hydrolyzed during workup. This new deprotection approach affords the alcohol product in modest to very good yields (Table 1, Method B).

Trifluoroethyl (TFE) ether is a new small and robust alcohol protecting group capable of surviving an incredible array of organic reactions. In this Letter we have demonstrated two new base mediated deprotection strategies. Both take advantage of the low pK_a of the trifluoroethylether protons and remarkably rapid β -elimination of HF to afford a difluorovinyl ether we then show can be either oxidatively cleaved or converted into a labile difluoroester. These new deprotection strategies are complementary to the reductive approach developed by Sargent. The strong electron withdrawing properties of the TFE ether provide opportunities for achieving additional synthetic goals beyond protection as highlighted in our total synthesis of vinigrol wherein the TFE ether also played a critical enabling role in a Dakin oxidation and oxidative dearomatization steps. It is our hope that the chemistry and strategies detailed in this Letter will inspire and catalyze new investigations into target oriented applications of the TFE ether.

Representative experimental conditions for Methods A and B

Method A

n-BuLi (2.5 M in hexanes, 0.59 mL, 1.47 mmol) was added dropwise to a solution of diisopropylamine (0.23 mL, 1.60 mmol) in THF (2.8 mL) at -78°C . The reaction was further stirred at -78°C for 15 min, and then warmed to 0°C and stirred for 15 min. The resultant LDA solution was cooled back to -78°C and **1** (100.0 mg, 0.458 mmol) in THF (1.0 mL) was added over 30 min. After the addition was completed, the stirring was continued for 45 min at -78°C . The reaction solution turned from colorless to dark yellow. The reaction was then quenched with saturated NH_4Cl solution at -78°C and warmed to rt, diluted with ethyl acetate, washed with brine, dried over anhydrous Na_2SO_4 , and concentrated. Purification by a silica gel plug (5% ethyl acetate/hexanes) and careful evaporation of solvent afforded the difluorovinyl ether with trace residual hexanes. The ether was then dissolved in *t*-butanol (2.5 mL) and water (2.5 mL). Potassium ferricyanide (452.4 mg, 1.37 mmol), potassium carbonate (189.9 mg, 1.37 mmol), potassium osmium (VI) oxide dihydrate (3.0 mg, 0.00824 mmol), and pyridine (0.10 mL) were then added. The mixture was stirred at rt for 16 h at which point solid Na_2SO_3 (0.5 g) was added and stirred for 30 min. The mixture was diluted with water, extracted with ethyl acetate three times. The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4 , filtered, and concentrated. The resulting residue was purified by column chromatography (30% ethyl acetate/hexanes) to afford the alcohol as a white solid (45.4 mg, 73%).

Method B

n-BuLi (1.6 M in hexanes, 0.22 mL, 0.354 mmol) was added dropwise to a solution of diisopropylamine (0.06 mL, 0.400 mmol) in THF (1.0 mL) at -78°C . The reaction was further stirred at -78°C for 15 min then warmed to 0°C and stirred for 15 min. The resultant LDA solution was cooled back to -78°C and **4** (25.0 mg, 0.0886 mmol) in THF (0.5 mL) was added over 30 min. Stirring was then continued for 2 h at -78°C at which point MoOPH (192.4 mg, 0.443 mmol) was added. Following two additional hours of stirring at -78°C , the reaction was quenched with saturated NaHSO_3 , warmed to rt and then extracted three times with ethyl acetate. The combined organic layers were washed with saturated NaHCO_3 and brine, dried over Na_2SO_4 before being concentrated in vacuo. Purification by silica gel plug (30% ethyl acetate/hexanes) afforded the alcohol as a white

solid (12.0 mg, 68% yield). *Note:* Depending on substrates, if the basic hydrolysis of difluoroacetate was not completed after work-up, the crude product was then taken up in methanol and stirred with saturated NaHCO₃ solution overnight to complete ester hydrolysis.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

We would like to thank the NIH-NIGMS (RO1 GM 086584) for supporting our complex molecule synthesis program, which opened led to the science presented in this Letter.

References and notes

1. Yang Q, Njardarson JT, Draghici C, Li F. *Angew Chem, Int Ed.* 2013; 52:8648–8651. For our earlier attempts towards vinigrol, see: Morton JGM, Draghici C, Kwon LD, Njardarson JT. *Org Lett.* 2009; 11:4492–4495. [PubMed: 19728692] Morton JGM, Kwon LD, Freeman J, Njardarson JT. *Tetrahedron Lett.* 2009; 50:1684–1686. Morton JGM, Kwon LD, Freeman J, Njardarson JT. *Synlett.* 2009:23–27.
2. In our earlier studies we had demonstrated that tosylates (Ts) and benzoates (Bz) were effective in accomplishing the electronic tasks associated with the oxidative dearomatization/Diels-Alder step. These groups did however not survive or hinder the Dakin oxidation reaction, which led us on a quest for a more robust protecting group with strong electron withdrawing characteristics.
3. Baldwin and Tomesch used trifluoroethanol as a solvent for cationic cyclization reactions used for their synthesis of cyclosativene, which resulted in the formation of a trifluoroethyl ether. Baldwin SW, Tomesch JC. *J Org Chem.* 1980; 45:5052–5057. This trifluoroethyl ether was found to be resistant to reductive and oxidative cleavage conditions. Only by using a large excess of sodium naphthalene developed as described by Sargent could the group be cleaved (Ref. 8).
4. (a) Magid RM. *Tetrahedron.* 1980; 36:1901–1930. (b) Garayt MR, Percy JM. *Tetrahedron Lett.* 2001; 42:6377–6380. (c) Audouard C, Garayt MR, Kerouredan E, Percy JM, Yang H. *J Fluorine Chem.* 2005; 126:611–632. (d) Schwertfeger H, Wurtele C, Serafin M, Hausmann H, Carlson RMK, Dahl JEP, Schreiner PR. *J Org Chem.* 2008; 73:7789–7792. [PubMed: 18761438]
5. Falck JR, Yu J, Cho HS. *Tetrahedron Lett.* 1994; 35:5997–6000.
6. Vuluga D, Legros J, Crousse B, Bonnet-Delphon D. *Eur J Org Chem.* 2009:3513–3518.
7. a Kubota T, Kitazume T, Ishikawa N. *Chem Lett.* 1978:889–892. b Kubota T, Miyashita S, Kitazume T, Ishikawa N. *J Org Chem.* 1980; 45:5052–5057.
8. Koller KL, Dorn HC. *Anal Chem.* 1982; 54:529–533. Recently Carreira has shown that this reagent can be formed and used in situ: Kunzi SA, Morandi B, Carreira EM. *Org Lett.* 2012; 14 1900–1901.
9. Sargent GD. *J Am Chem Soc.* 1971; 93:5268–5269.
10. Schwertfeger H, Wurtele C, Hausmann H, Dahl JEP, Carlson RMK, Fokin AA, Schreiner PR. *Adv Synth Catal.* 2009; 351:1041–1054.
11. Nakai T, Tanaka K, Ishikawa N. *Chem Lett.* 1976:1263–1266.
12. Nakai's approach (Ref. 10) has been used by others to access more complex difluorovinyl ethers or exploit their reactivity in clever ways: Metcalf BW, Jarvi ET, Burkhart JP. *Tetrahedron Lett.* 1985; 26:2861–2864. Lee J, Tsukazaki M, Snieckus V. *Tetrahedron Lett.* 1993; 34:415–418. Patel ST, Percy JM, Wilkes RD. *Tetrahedron.* 1995; 51:9201–9216. Howarth JA, Otwon WM, Percy JM, Rock MH. *Tetrahedron.* 1995; 51:10289–10302. Ichikawa J, Wada Y, Fujiwara M, Sakoda K. *Synthesis.* 2002:1917–1936. Ramachandran PV, Chatterjee A. *Org Lett.* 2008; 10:1195–1198. [PubMed: 18288854] Ramachandran PV, Chatterjee A. *J Fluor Chem.* 2009; 130:144–150. Riss PJ, Aigbirio FI. *Chem Commun.* 2011:11873–11875.
13. Tanaka K, Shiraishi S, Nakai T, Ishikawa N. *Tetrahedron Lett.* 1978; 19:3103–3106.

14. We attempted to use catalytic conditions, but these few attempts failed (no reaction). This might be due to the small scale we were working with at the time and how precious the material was, which is why we cannot say conclusively that catalytic conditions could not work.
15. Dihydroxylations of similar fluorinated olefins have been reported: Herrmann WA, Eder SJ, Scherer W. *Angew Chem, Int Ed.* 1992; 31:1345–1347.
16. We attempted to use acidic conditions to cleave the difluorovinyl ether, but those were not successful.
17. Kong K, Enquist JA Jr, McCallum ME, Smith GM, Matsumaru M, Menhaji-Klotz E, Wood JL. *J Am Chem Soc.* 2013; 135:10890–10893. [PubMed: 23837485] These conditions were originally reported by: Williams RM, Kwast E. *Tetrahedron Lett.* 1989; 30:451–454.
18. (a) Wasserman HH, Lipshutz BH. *Tetrahedron Lett.* 1975; 16:1731–1734. (b) Paquette LA, DeRussy DT, Pegg NA, Taylor RT, Zydowsky TM. *J Org Chem.* 1989; 54:4576–4581. (c) Moller M, Husemann M, Boche G. *J Organomet Chem.* 2001; 624:47–52. (d) Lubin H, Tessier A, Chaume G, Pytkowicz J, Brigaud T. *Org Lett.* 2010; 12:1496–1499. [PubMed: 20218638]
19. (a) Davis FA, Wei J, Sheppard AC, Gubernick S. *Tetrahedron Lett.* 1987; 28:5115–5118. (b) Davis FA, Sheppard AC. *Tetrahedron.* 1989; 45:5703–5742.
20. (a) Vedejs E. *J Am Chem Soc.* 1974; 98:5944–5945. (b) Milgram BC, Liao BB, Shair MD. *Org Lett.* 2011; 13:6436–6439. [PubMed: 22084899]
21. (a) Taddei M, Ricci A. *Synthesis.* 1986:633–635. (b) Pohmakotr M, Winotai C. *Synth Commun.* 1988; 18:2141–2146. (c) Ishikawa H, Elliott GI, Velcicky J, Choi Y, Boger DL. *J Am Chem Soc.* 2006; 128:10596–10612. [PubMed: 16895428]
22. Davis oxaziridine was shown to be the second best of the trapping agents although far less successful than MoOPH.

Scheme 1.
Trifluoroethyl ether protecting group in total synthesis.

Scheme 2.
How to synthesize trifluoroethyl ethers.

Scheme 3.
Base mediated TFE ether deprotection approaches.

Table 1

Two new TFE ether base-mediated deprotection approaches

Entry		Method A (%)	Method B (%)
1		73	41 (66)
	1		
2		42 (49) ^a	29 ^a
	2		
3		50	34 (53)
	3		
4		80 ^b	68
	4		
5		49 (60)	54 (75)
	5		
6		34 (44)	71 (83)
	6		
7		63 (67) (<i>t</i> -BuLi used)	75 ^b
	7		
8		44 (79)	28 (88)
	8		

Method A: LDA then catalytic OsO₄. **Method B:** LDA followed by in situ MoOPH trapping. Isolated yields, with numbers in parentheses representing yields based on recovered starting material.

^aVolatile product.

^bYield of difluorovinyl ether.