Published in final edited form as:

Chem Commun (Camb). ; 58(36): 5490–5493. doi:10.1039/d2cc01518h.

Generation of Formaldehyde and Formaldehyde-d_2 for Hydroxymethylations and Hydroxydeuteromethylations of Difluoroenolates and Difluorobenzyl Carbanions

Hari R. Khatri[a],

Changho Han[b],

Reem A. Alkhodier[a],

Amna T. Adam[a],

Baharul Islam[a],

David A. Colby[*,a]

[a]Department of BioMolecular Sciences, University of Mississippi, University Mississippi, United States.

[b]Department of Medicinal Chemistry and Molecular Pharmacology, Purdue University, West Lafayette, Indiana, United States.

Abstract

A method for the *in situ* production of formaldehyde from dimethylsulfoxide, bromine, and cesium carbonate is reported for reactions with difluoroenolates and difluorobenzyl carbanions. This process also generates formaldehyde-d_2 for the production of 2,2-difluoro-1,1-deuteroethanols. Mechanistic and computational studies further characterize the production of hydroxymethylated and hydroxydeuteromethylated difluorinated organic molecules.

Hydroxymethylation is a well-established synthetic process to generate valuable organic compounds.[1,2] Notable examples have appeared recently in the total synthesis of natural products,[3,4] drug discovery,[5] and biosynthesis.[6] The typical methods for hydroxymethylation require the use of formaldehyde or a reagent that serves as a formaldehyde equivalent.[3–5,7,8] Formaldehyde is present in formalin or produced from trioxane or paraformaldehyde; other typical sources are 1-benzotriazole-1-methanol, *N*-(hydroxymethyl)phthalimide, and 1,3-oxathiolane-3,3-dioxide (Figure 1). Alternatively, methods for the *in situ* generation of formaldehyde from dimethylsulfoxide (DMSO) or DMSO-like structures have been

* dacolby@olemiss.edu .

Author Contributions

The manuscript was written through the contributions of all authors. H.R.K. optimized the reactions and conducted the synthetic experiments. C.H. discovered the method and performed the mechanistic studies. R.A.A. conducted the computational analysis and additional reactions, and A.T.A. and B.I. performed additional reactions.

Conflicts of interest

D.A.C. serves as a scientific advisor for GnuPharma, and some of the studies in this manuscript were conducted with unrestricted support from GnuPharma. The authors declare no other competing financial interests.

†Electronic Supplementary Information (ESI) available: [details of any supplementary information available should be included here]. See DOI: 10.1039/x0xx00000x

reported; however, they are not as convenient because excess heat is required and many side products are generated.[9–12] Two examples are the production of a formaldehyde equivalent from DMSO and P_2O_5[9] and formaldehyde from DMSO and CuBr (10 mol %) at 100 °C.[10]

The incorporation of fluorine atoms on organic molecules is a common objective during drug development.[13] Synthetic methods for the fluorination and trifluoromethylation of compounds are significantly more advanced than strategies that create a difluoromethyl group. In 2011, we designed a mild process for the generation of α,α-difluoroenolates from the fragmentation of pentafluoro-*gem*-diols (Figure 2).[14] Although these difluorinated intermediates react with aldehydes[14,15] and imines,[16,17] the compatibility of the transformation with formaldehyde has not been established. Moreover, there is only one reaction of an α,α-difluoroenolate with formaldehyde in the existing literature.[18] Indeed, a broader expansion of the reactivity of formaldehyde to difluorocarbanions would allow access to valuable 2,2-difluoroethanols and open new avenues for the synthesis of difluorinated targets. To address this need, we report a protocol for the *in situ* generation of formaldehyde for the hydroxymethylation of difluoroenolates to create 2,2-difluoroethanols. The method also allows the production of formaldehyde-d_2 for hydroxydeuteromethylations, which constitutes a synthetic method for 2,2-difluoro-1,1-deuteroethanols. Also, this reaction is compatible with α,α-difluorobenzyl carbanions generated from the release of trifluoroacetate from electron-deficient aromatic and heteroaromatic rings.[19]

In 2019, we reported the production of difluorocarbanions from pentafluoro-*gem*-diols following the addition of K_2CO_3 in the solvent, DMSO.[19] The use of DMSO is an ideal starting point for the development of a method for hydroxymethylation of difluorocarbanions, because this solvent is a known precursor of formaldehyde.[9,10] Accordingly, we determined that the addition of bromine and 4Å molecular sieves along with K_2CO_3 in DMSO generates formaldehyde. We optimized these conditions for the simultaneous production of difluoroenolates from pentafluoro-*gem*-diols by adding LiBr[14] and proton sponge (see Table S1 for optimization experiments). Lastly, K_2CO_3 was replaced with Cs_2CO_3 after screening other carbonate bases (e.g, Na_2CO_3 and Li_2CO_3). Using these conditions, the pentafluoro-*gem*-diols were hydroxymethylated and formed the products **1**–**6** in 32–68% isolated yields (Scheme 1). The higher conversions were observed with substrates bearing a naphthyl ring **1**, a benzodioxoyl ring **2**, an adamantyl group **3**, or a benzothiophene **4**, whereas the lower yields were obtained from the *p*-CF_3 benzene **5** and the styrene derivative **6**. The incorporation of deuterium into the structure of organic molecules is a growing field, especially for metabolic probes, leads in drug discovery,[20,21] and internal standards in analytical techniques.[22,23] Moreover, the presence of both deuterium and fluorine atoms on organic structures is an under-explored area, and few synthetic strategies are available to create these types of molecules.[24–26] In order to address this shortcoming, we have adapted this method for hydroxydeuteromethylation by exchanging DMSO with DMSO-d_6. The pentafluoro-*gem*-diols were subjected to these modified conditions (see Scheme 1). The difluorodideuteroethanols **7**–**9** were synthesized with high levels of incorporation of deuterium (88–94%) in similar conversions as the hydroxymethylations.

This process for hydroxymethylation could be simplified in the case of difluorobenzyl carbanions; however, higher temperatures were required. Specifically, only Cs_2CO_3, bromine, and 4Å molecular sieves were added in the presence of the pentafluoro-*gem*-diols shown in Scheme 2 and warmed to 60–65 °C. The transformation produces the aryl substituted difluoroethanols displaying 4-nitrobenzenes **10**–**11** or 5-nitro-2-pyridines **12**–**13** in isolated yields of 55–58%. The 5-trifluoromethyl-2-pyridine adduct **14** was produced in a lower 25% yield, but this observation was anticipated from our previous findings.[19] The quinoxaline **15** represents another application of this reaction for the creation of heterocycles. Also, the difluorodideuteroethanols **16**–**18** were synthesized, by replacing DMSO with DMSO-d_6, with high levels of incorporation of deuterium (93–100%) in similar yields as the respective hydroxymethylations.

A Pummerer-like process is expected in this hydroxymethylation reaction.[27] A plausible mechanism is proposed that initiates with the generation of methyl(methylene)sulfonium cation (Figure 3). Next, a carbonate base (e.g., K_2CO_3) serves as a nucleophile and adds to the electrophilic thionium cation. Then, the methylsulfide group is oxidized by bromine, and the resulting intermediate displaying the bromosulfonium ion fragments by the release of methanesulfenyl bromide and decarboxylation. The final result is the production of formaldehyde. Accordingly, after stirring K_2CO_3, Br_2, and 4Å molecular sieves in DMSO at 60 °C for two hours, formaldehyde is observed in the ^{1}H NMR spectrum with the characteristic peak at 9.68 ppm (in acetone-d_6). Computational studies were performed using density functional theory[28] in DMSO. The M06-2X[29] level of theory and 6-311++G(3df,3pd) basis set were utilized. The free energies and enthalpy (i.e., $\Delta G = -36.12$ and $\Delta H = -13.97$ kcal/mol) are lower for the concerted fragmentation of the key bromosulfonium intermediate compared to both the reverse process, the regeneration of the (methylthio)methyl carbonate intermediate, and the stepwise fragmentation (see Figure S1 and Table S2). These results support a tandem fragmentation/decarboxylation process. The production of formaldehyde from this reaction allows the hydroxymethylation of the difluorobenzyl carbanion.

Additional mechanistic insight for this process was gathered from the reaction of 1,1,1,3,3-pentafluoro-3-(4-nitrophenyl)propane-2,2-diol with K_2CO_3 and H_2O in DMSO. First, if this reaction is conducted at 65 °C without the presence of an electrophile, such as formaldehyde, the 1-(difluoromethyl)-4-nitrobenzene **19** is produced (Figure 4). Product **19** arises from the slow protonation of the difluorobenzyl carbanion. Second, if this same reaction is conducted with D_2O instead of H_2O, the 1-(deuterodifluoromethyl)-4-nitrobenzene **20** is isolated. Methods for the production of deuterodifluoromethylbenzenes are rare in the literature.[30] Overall, the data obtained from the protonation and deuteration studies with the difluoromethylbenzenes compare favorably to our similar studies with difluoromethyl ketones.[26]

In summary, we have reported an approach for the hydroxymethylation and hydroxydeuteromethylation of difluoroenolates and difluorobenzyl carbanions generated from pentafluoro *gem*-diols. This process produces formaldehyde or formaldehyde-d_2 in the presence of a weak base, and in the latter case, high levels of deuterium incorporation are observed. The synthesis of a 2,2-difluoro-1,1-dideuteroethanol (i.e., RCF_2CD_2OH) has been

previously reported via reduction of a difluorinated ester or amide using the deuterated reducing agents, $NaBD_4$ or $LiAlHD_4$;[31–33] however, these reagents can concomitantly reduce other carbonyl or susceptible groups.[33] No other preparations of 2,2-difluoro-1,1-dideuteroethanols exist in the literature, to our knowledge; therefore, our methodology provides a viable option for these targets. A plausible mechanism for hydroxymethylation is proposed and supported with experimental and computational studies; formaldehyde was observed by NMR. This strategy not only demonstrates new reactions for difluoroenolates and difluorobenzyl carbanions but also presents another method for the *in situ* formation of formaldehyde.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Notes and references

1. Alexanian EJ and Shenouda H, Org. Lett 2019, 21, 9268–9271. [PubMed: 31689117]
2. Tokala R, Bora D, Sana S, Nachtigall FM, Santos LS and Shankaraiah N, J. Org. Chem, 2019, 84, 5504–5513. [PubMed: 30945857]
3. Min L, Lin X and Li C-C, J. Am. Chem. Soc, 2019, 141, 15773–15778. [PubMed: 31545036]
4. Boeckman RK Jr., Niziol JM and Biegasiewicz KF, Org. Lett, 2018, 20, 5062–5065. [PubMed: 30074398]
5. Barcan GA, Conde JJ, Mokhallati MK, Nilson MG, Xie S, Alle CL, Andemichael YW, Calandra NA, Leitch DC, Li L and Morris MJ, Org. Process. Res. Dev, 2019, 23, 1396–1406.
6. Marin-Valls R, Hernandez K, Bolte M, Joglar J, Bujons J and Clapes P, ACS Catal, 2019, 9, 7568–7577.
7. Kutwal MS, Dev S and Appayee C, Org. Lett, 2019, 21, 2509–2513. [PubMed: 30938529]
8. Rauch M, Strater Z and Parkin G, J. Am. Chem. Soc, 2019, 141, 17754–17762. [PubMed: 31638772]
9. Wang J, Rochon FD, Ying Y, Hua L and Kayser MM, Tetrahedron: Asymmetry, 2007, 18, 1115–1123.
10. Ni Y, Zuo H, Yu H, Wu Y and Zhong F, Org. Lett, 2018, 20, 5899–5904. [PubMed: 30199259]
11. Jones-Mensah E, Karki M and Magolan J, Synthesis, 2016, 48, 1421–1436.
12. Forrester J, Jones RVH, Preston PN, Simpson ESC, J. Chem. Soc. Perkin Trans. 1, 1995, 18, 2289–2291.
13. Gillis EP, Eastman KJ, Hill MD, Donnelly DJ and Meanwell NA, J. Med. Chem, 2015, 58, 8315–8359. [PubMed: 26200936]
14. Han C, Kim EH and Colby DA, J. Am. Chem. Soc 2011, 130, 5802–5805.
15. Zhang P and Wolf C, Angew. Chem. Int. Ed 2013, 52, 7869–7873.
16. Xie C, Wu L, Mei H, Soloshonok VA, Han J and Pan Y, Org. Biomol. Chem, 2014, 12, 7836–7843. [PubMed: 25167342]
17. Nguyen AL, Khatri HR, Woods JR, Baldwin CS, Fronczek FR and Colby DA, J. Org. Chem, 2018, 83, 3109–3118. [PubMed: 29446944]
18. Balnaves AS, Gelbrich T, Hursthouse MB, Light ME, Palmer MJ and Percy JM, J. Chem. Soc., Perkins Trans 1, 1999, 2525–2535.
19. Khatri HR, Han C, Luong E, Pan X, Adam AT, Alshammari MD, Shao Y and Colby DA, J. Org. Chem, 2019, 84, 11665–11675. [PubMed: 31449418]
20. Meng Y, Yu B, Huang H, Peng Y, Li E, Yao Y, Song C, Yu W, Zhu K, Wang K, Yi D and Du J, J. Med. Chem, 2021, 64, 925–937. [PubMed: 33459024]
21. Schmidt C, Nat. Biotechnol, 2017, 35, 493–494. [PubMed: 28591114]

22. Atzrodt J, Derdau V, Kerr WJ and Reid M, Angew. Chem. Intl. Ed, 2018, 57, 1758–1784.
23. Gant TG, J. Med. Chem, 2014, 57, 3595–3611. [PubMed: 24294889]
24. Huang L, Liu W, Zhao L-L and Yan X, J. Org. Chem, 2021, 86, 3981–3988. [PubMed: 33591190]
25. Fu WC and Jamison TF, Angew. Chem. Int. Ed 2020, 59, 13885–13890.
26. Sowaileh MF, Han C, Hazlitt RA, Kim EH, John JP and Colby DA, Tetrahedron Lett., 2017, 58, 396–400. [PubMed: 28943667]
27. Bur SK and Padwa A, Chem. Rev, 2004, 104, 2401–2432. [PubMed: 15137795]
28. Becke AD, J. Chem. Phys, 2014, 140, 18A301.
29. Zhao Y and Truhlar DG, Theor. Chem. Acc, 2008, 120, 215–241.
30. Miao W, Zhao Y, Ni C, Gao B, Zhang W and Hu J, J. Am. Chem. Soc, 2018, 140, 880–883. [PubMed: 29278333]
31. Yang Y, Mikeš F, Koike Y and Okamoto Y, Macromolecules, 2004, 37, 7918–7923.
32. King JF and Gill MS, J. Org. Chem, 1998, 63, 808–811. [PubMed: 11672077]
33. Andersen TL, Frederiksen MW, Domino K and Skrydstrup T, Angew. Chem. Int. Ed, 2016, 55, 10396–10400.

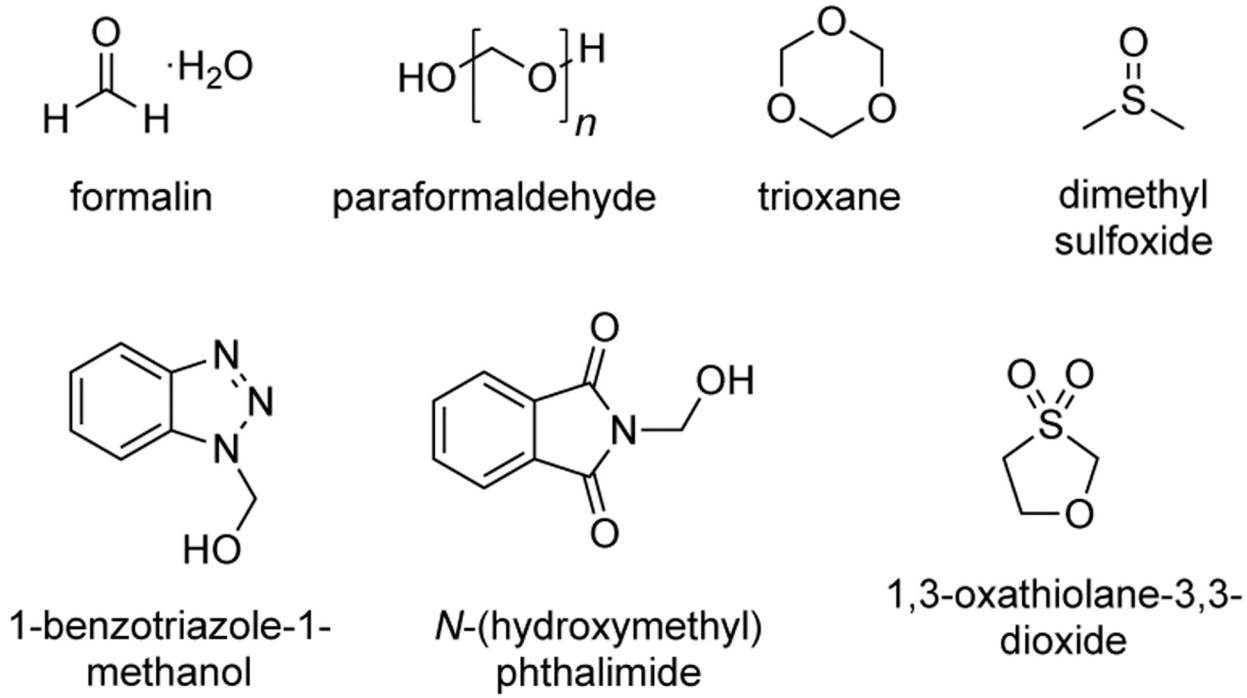


Figure 1.
Typical sources of formaldehyde.

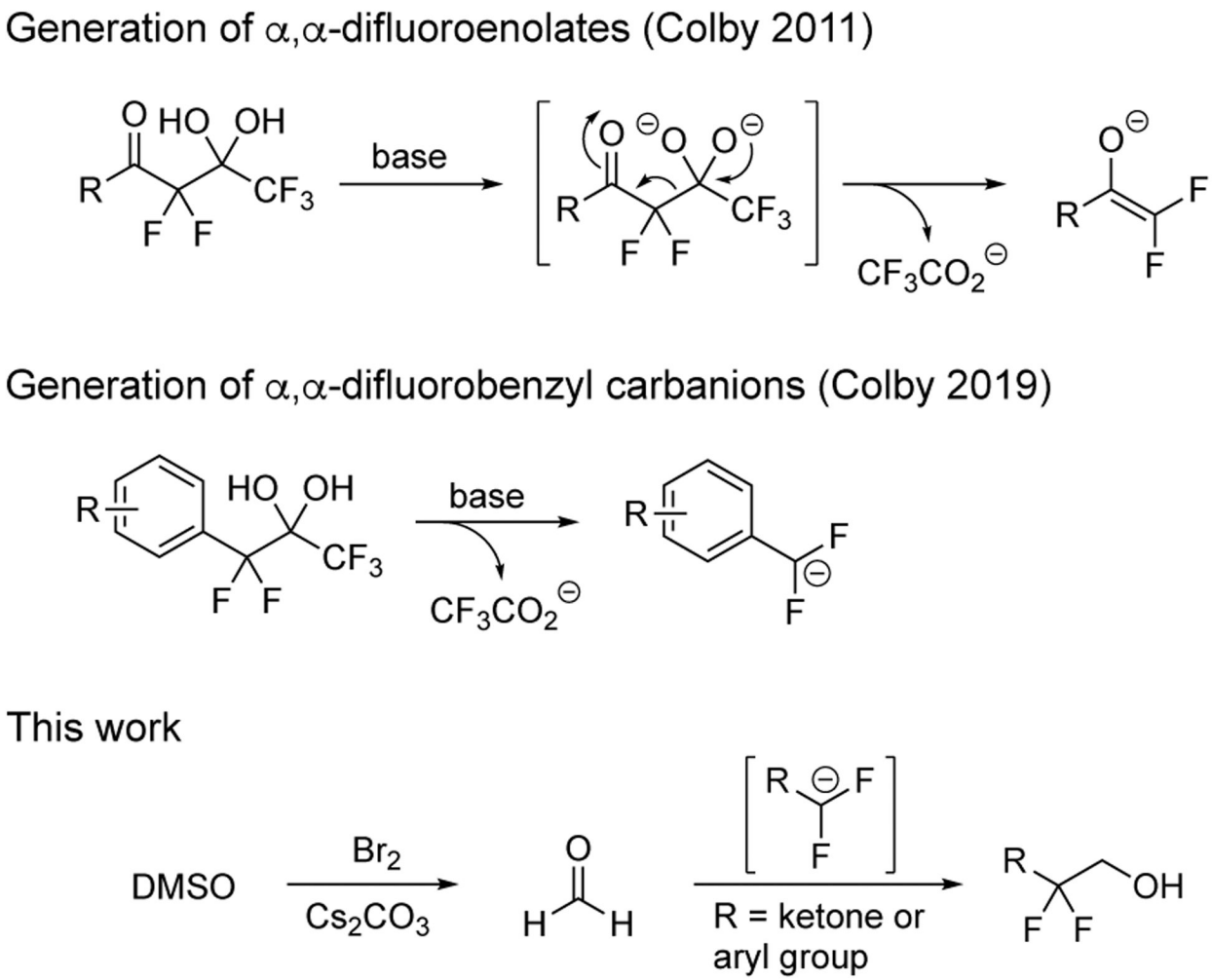


Figure 2.

The generation of difluorocarbanions from the release of trifluoroacetate and the preparation of 2,2-difluoroethanols from the generation of formaldehyde in the presence of these reactive intermediates.

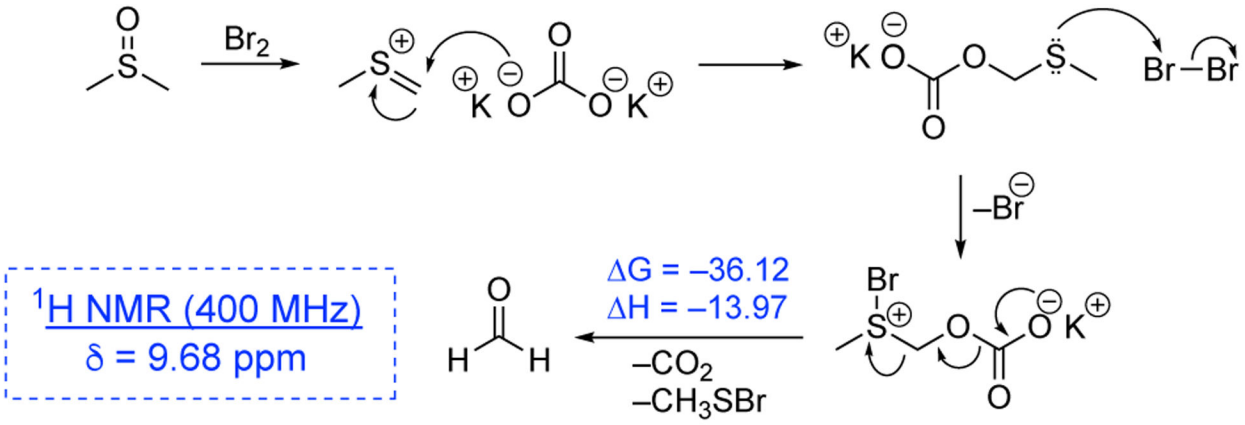


Figure 3.

Proposed mechanism for the generation of formaldehyde from K_2CO_3, Br_2, and DMSO starting from the methyl(methylene)sulfonium cation. The changes in free energy and enthalpy for the fragmentation step are shown (in kcal/mol at 298.15 K). ^{1}H NMR data was obtained in acetone-d_6 at 400 MHz at rt.

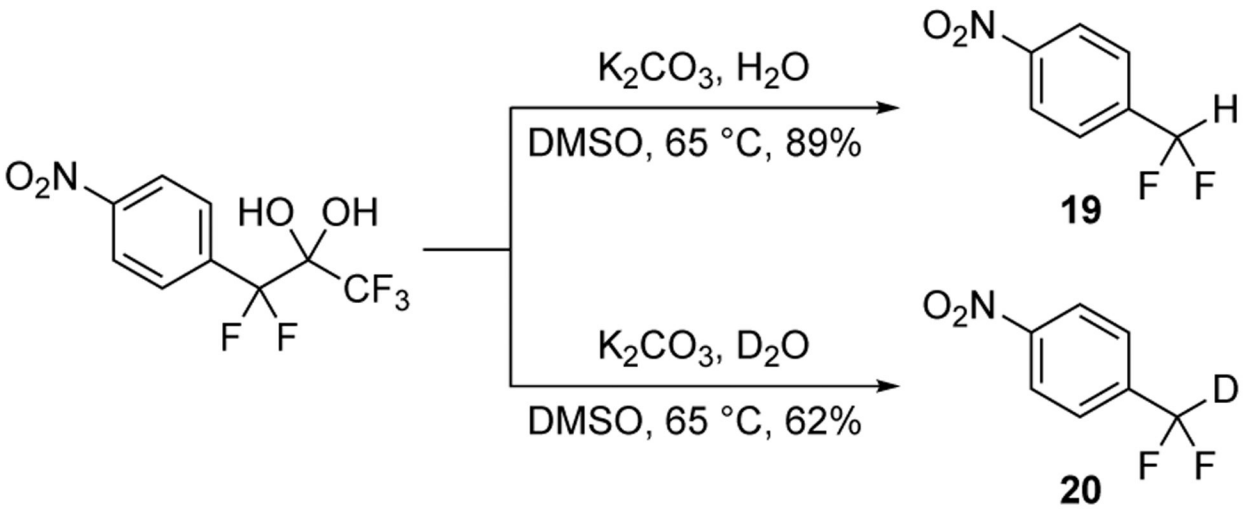
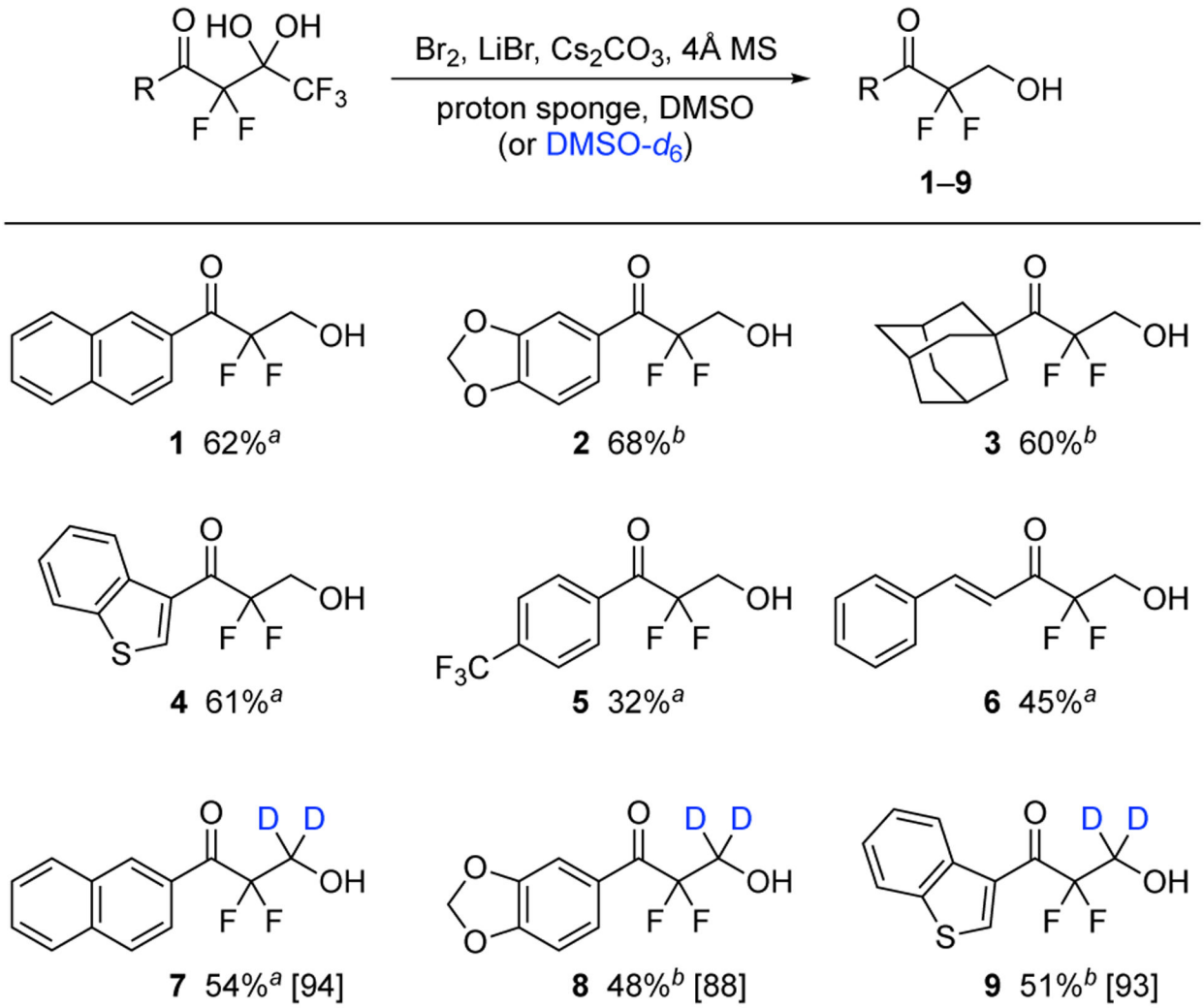


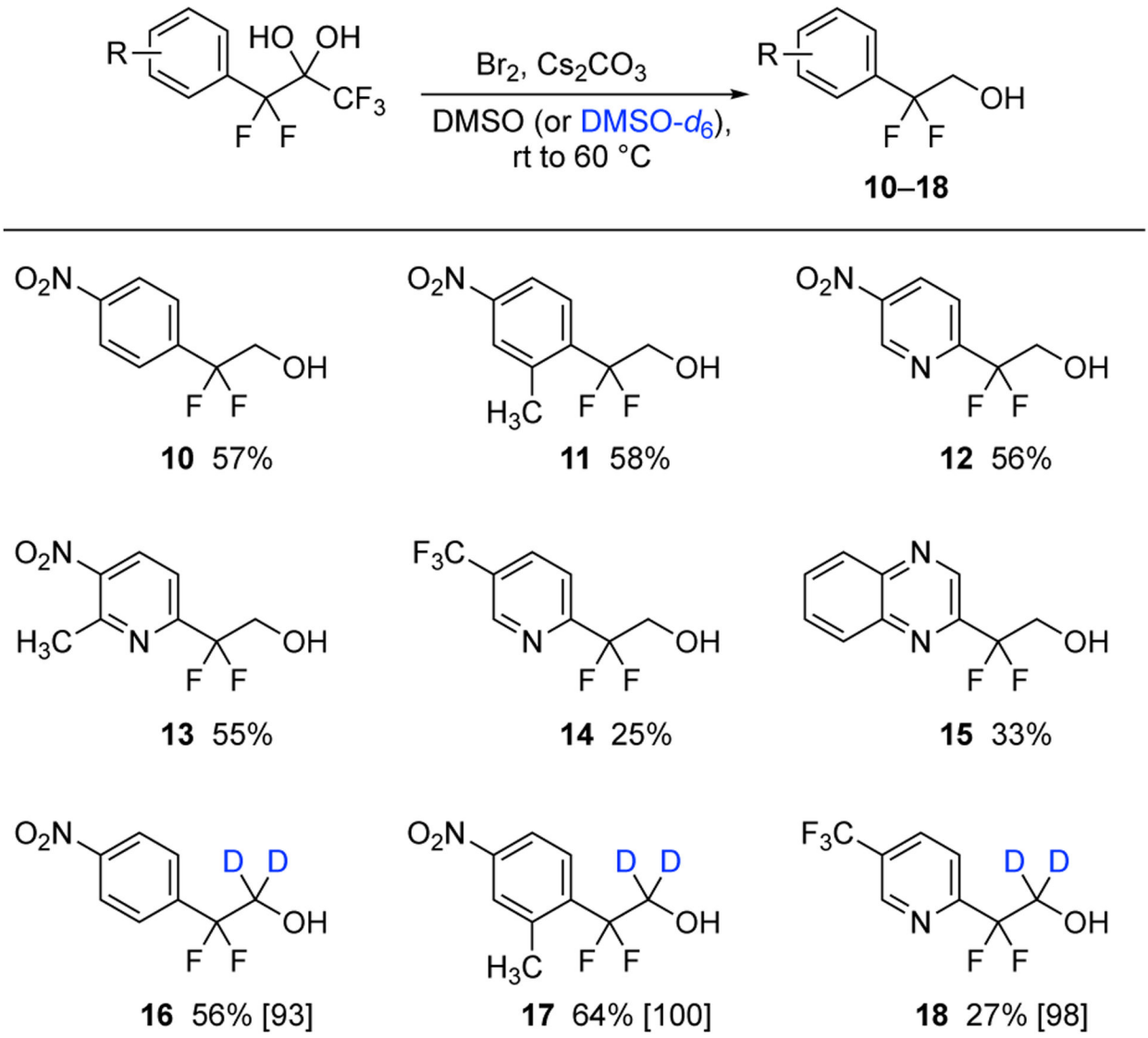
Figure 4.

Conversion of 1,1,1,3,3-pentafluoro-3-(4-nitrophenyl)propane-2,2-diol into 1-(difluoromethyl)-4-nitrobenzene **19** and 1-(deuterodifluoromethyl)-4-nitrobenzene **20** with K_2CO_3 in DMSO at 65 °C.



Scheme 1.

Synthesis of difluoroethanols **1**–**6** by hydroxymethylation from the *in situ* generation of formaldehyde and difluoroenolates, and synthesis of difluorodideuteroethanols **7**–**9** by hydroxydeuteromethylation (percent deuterium incorporation is listed in brackets). [a]Stirred at rt. [b]Stirred at 40 °C.



Scheme 2.

Synthesis of difluoroethanols **10**–**15** by hydroxymethylation from the *in situ* generation of formaldehyde and difluorobenzyl carbanions, and synthesis of difluorodideuteroethanols **16**–**18** by hydroxydeuteromethylation (percent deuterium incorporation is listed in brackets).