Available online at www.sciencedirect.com
SCIENCE DIRECT®
Tetrahedron Letters 45 (2004) 1015–1017
Tetrahedron Letters

Asymmetric synthesis of γ-perfluoroalkyl(aryl) butyrolactones via organoboranes

P. Veeraraghavan Ramachandran,* Kamlesh J. Padiya, Vivek Rauniyar, M. Venkat Ram Reddy and Herbert C. Brown

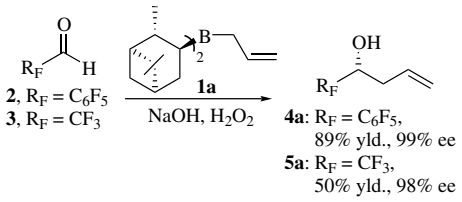
Department of Chemistry, Herbert C. Brown Center for Borane Research, Purdue University, 560 Oval Drive, West Lafayette, IN 47907-2084, USA

Received 28 October 2003; accepted 12 November 2003

Abstract—Asymmetric 'allyl'boration of fluorinated aldehydes with α-pinene-based 'allyl' boranes provides the corresponding homoallylic alcohols in high ee and de, which upon hydroboration, followed by oxidation with TPAP/NMO furnish γ-perfluoroalkyl(aryl)-γ-butyrolactones.

Lactones are important synthons in organic chemistry.[1] They are also present in a large number of natural products.[2] The unique properties of fluoroorganic molecules in biological and medicinal chemistry[3,4] inspired us to synthesize fluorine-containing lactones. We have recently reported several asymmetric syntheses of chiral lactones via organoboranes.[5] Even though several syntheses of lactones are available in the literature,[1] there have been only scarce reports of the syntheses of fluoro-analogs.[6]

Although we have reported on the unique nature of the asymmetric reduction of fluoroketones,[3a] and hydroboration of fluoro-olefins,[7] asymmetric allylboration of fluoroaldehydes[8] with (*B*)-allyldiisopinocampheylborane (**1a**),[9] did not reveal any surprises. For example, allylboration of two representative fluorinated aldehydes pentafluorobenzaldehyde (**2**) and trifluoroacetaldehyde (**3**) with reagent **1a** was relatively straightforward at −100 °C providing the products **4a** and **5a** in 99% and 98% ee, respectively (Scheme 1).

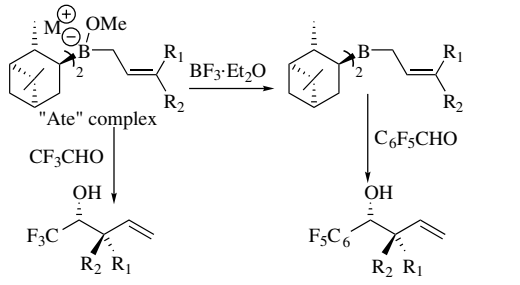


Scheme 1.

The success of the allylboration of fluoroaldehydes, coupled with the possibility of the formation of functionalized fluorinated lactones, persuaded us to undertake the asymmetric crotyl- and alkoxylallylboration as well with (*B*)-(*Z*)-crotyldiisopinocampheylborane (**1b**),[10] (*B*)-(*E*)-crotyldiisopinocampheylborane (**1c**),[10] and (*B*)-γ-2-methoxyethoxymethoxyallyldiisopinocampheylborane (**1d**).[11] We envisaged that the homoallylic alcohols obtained in high ee and de can be converted to the diols via hydroboration–oxidation, followed by further oxidation of the primary alcohols should provide γ-lactones. The secondary alcohol at the α-carbon to a perfluoroalkyl(aryl) group is deactivated and should not undergo oxidation to ketones. Herein we discuss the successful synthesis of γ-fluoroalkyl(aryl) β-substituted γ-lactones via allylboration, hydroboration, and oxidation.

Keywords: α-Pinene; Allylboration; Homoallylic alcohol; Hydroboration; Fluorolactones.
* Corresponding author. Tel.: +1-765-4945303; fax: +1-765-4940239; e-mail: chandran@purdue.edu

0040-4039/$ - see front matter © 2003 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2003.11.050



5b, R_1 = H, R_2 = OMEM
75% yld. >95% de, 96% ee

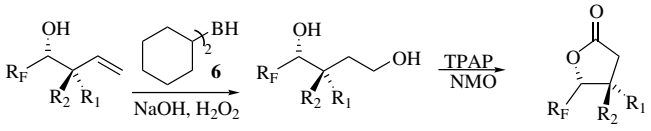
4b, R_1 = Me, R_2 =H
75% yld. >95% de, 94% ee
4c, R_1 = H, R_2 = Me
72% yld. >95% de, 92% ee
4d, R_1 = H, R_2 = OMEM
65% yld. >95% de, 95% ee

Scheme 2.

The reaction of **2** with all of the other three 'allyl' borane reagents **1b**, **1c**, and **1d** took place smoothly and the product homoallylic alcohols **4b**,[12] **4c**, and **4d** were obtained in excellent de and ee. The de was determined based on ^{1}H NMR analysis of the crude product mixture and the ee of the pure sample was ascertained using an HPLC on a Chiralcel OD-H column. The reaction of fluoral **3** with all the three reagents **1b–d** posed an interesting challenge. 'Allyl'boration of **3** with **1b–d** resulted in the polymerization of fluoral even at −100 °C. Unlike **1a**, the higher order allylboranes **1b–d** have to be generated in situ at low temperature due to the borotropic shift.[10,11] They remain as 'ate' complexes and 1.33 equiv of $BF_3{\cdot}Et_2O$ is added to liberate the trialkylborane[13] (Scheme 2). We rationalized that the strong Lewis acid, $BF_3{\cdot}Et_2O$, initiated the polymerization. In an attempt to arrest the polymerization of **3**, the reaction was carried out directly with 'ate' complex.[14] However, the expected homoallylic alcohols from reagents **1b** and **1c** could not be obtained in pure form and in reliable yields. Fortunately, alkoxyallylboration with **1d** afforded the product alcohol **5b** in 75% yield, >95% de, and 96% ee (Scheme 2).

After achieving excellent diastereo- and enantioselectivities in the allylboration, we proceeded with the conversion of these homoallylic alcohols into diols via hydroboration–oxidation. To obtain the optimum yield of the diols, a model study was performed on **4a** with several boranes, such as $BH_3{\cdot}THF$, 9-BBN, dichloroborane, and dicyclohexylborane. Dicyclohexylborane **6** gave the best results in terms of yield and regioselectivity and was chosen as the hydroborating agent for the present study. All of the homoallylic alcohols **4a–d** and **5a–b** underwent hydroboration with **6** and the diols **7a–d** and **8a–b** were obtained in very good yields[15] following an alkaline hydrogen peroxide oxidation. The oxidation of the 1° alcohol in **7a–d** and **8a–b** with several oxidizing agents, such as PCC, PDC, Jones reagent, etc., resulted in poor to moderate yields of the product lactones.[16] However, oxidation of the diols **7a–d** and **8a–b** using TPAP/NMO[17] converted these diols into the corresponding γ-lactones **9a–d**[18] and **10a–b** in good yields (Scheme 3). This oxidizing system developed by Ley is very mild, typically provides good yields, and is applicable to sensitive substrates as well.[19] Thus, a combination of allylboration, hydroboration, and Ley's oxidation provides an excellent procedure for the preparation of γ-lactones, particularly sensitive fluorinated lactones.

In conclusion, we have studied allylboration of fluoroaldehydes with various α-pinene-based 'allyl' boranes and obtained homoallylic alcohols in excellent ee and de. In the case of fluoral, alkoxyallylboration has been achieved via the reaction of 'ate' complex to provide the product in good yield. We have converted these alcohols to fluorinated γ-lactones in two steps via hydroboration, followed by oxidation. Further work is in progress toward the application of this methodology for the synthesis of fluoro-analogs of biologically active molecules containing γ-lactones.



4 a-d
5 a,b

7 a-d
8 a,b

7a, $R_F = C_6F_5$, R_1 = H, R_2 = H, 79%
7b, $R_F = C_6F_5$, R_1 = Me, R_2 = H, 84%
7c, $R_F = C_6F_5$, R_1 = H, R_2 = Me, 85%
7d, $R_F = C_6F_5$, R_1 = OMEM, R_2 = H, 72%
8a, $R_F = CF_3$, R_1 = H, R_2 = H, 71%
8b, $R_F = CF_3$, R_1 = OMEM, R_2 = H, 82%

9 a-d
10 a,b

9a, $R_F = C_6F_5$, R_1 = H, R_2 = H, 64%
9b, $R_F = C_6F_5$, R_1 = Me, R_2 = H, 75%
9c, $R_F = C_6F_5$, R_1 = H, R_2 = Me, 72%
9d, $R_F = C_6F_5$, R_1 = OMEM, R_2 = H, 75%
10a, $R_F = CF_3$, R_1 = H, R_2 = H, 61%
10b, $R_F = CF_3$, R_1 = OMEM, R_2 = H, 68%

Scheme 3.

Acknowledgements

Financial support from the Herbert C. Brown Center for Borane Research[20] and the Aldrich Chemical Company is greatfully acknowledged.

References and notes

1. Collins, I. *J. Chem. Soc., Perkin Trans. 1* **1999**, *11*, 1377.
2. Hoffmann, H. M. R.; Rabe, J. *Angew. Chem., Int. Ed. Engl.* **1985**, *24*, 94.
3. (a) *Asymmetric Fluoroorganic Chemistry*; Ramachandran, P. V., Ed.; *ACS Symposium Series 746*; American Chemical Society: Washington, DC, 1999; (b) *EPC-Synthesis of Fluoroorganic Compounds: Stereochemical Challenges and Biomedical Targets*; Soloshonok, V. A., Ed.; John Wiley: Chichester, West Sussex, UK, 1999.
4. For recent reviews, see: (a) *Biomedical Frontiers of Fluorine Chemistry*; Ojima, I., McCarthy, J. R., Welch, J. T., Eds.; *ACS Symposium Series 639*; American Chemical Society: Washington, DC, 1996; (b) Kiselyov, A. S.; Strekowski, L. *Org. Prep. Proced. Int.* **1996**, *28*, 289.
5. For a review please see: Ramachandran, P. V. *Aldrichim. Acta* **2002**, *35*, 23.
6. (a) Seebach, D.; Renaud, P. *Helv. Chim. Acta* **1985**, *68*, 2342; (b) Komatsu, Y.; Sasaki, F.; Takei, S.; Kitazume, T. *J. Org. Chem.* **1998**, *63*, 8058; (c) Bravo, P.; Frigerio, M.; Melloni, A.; Panzeri, W.; Pesenti, C.; Viani, F.; Zanda, M. *Eur. J. Org. Chem.* **2002**, 1895.
7. (a) Ramachandran, P. V.; Jennings, M. P. *Org. Lett.* **2001**, *3*, 3789; (b) Brown, H. C.; Chen, G.-M.; Jennings, M. P.; Ramachandran, P. V. *Angew. Chem., Int. Ed. Engl.* **1999**, *38*, 2052.
8. Kumar, D. J. S.; Madhavan, S.; Ramachandran, P. V.; Brown, H. C. *Tetrahedron: Asymmetry* **2000**, *11*, 4629.
9. Brown, H. C.; Jadhav, P. K. *J. Am. Chem. Soc.* **1983**, *105*, 2092.
10. Brown, H. C.; Bhat, K. S. *J. Am. Chem. Soc.* **1986**, *108*, 5919.
11. (a) Ramachandran, P. V.; Prabhudas, B.; Pratihar, D.; Chandra, J. S.; Reddy, M. V. R. *Tetrahedron Lett.* **2003**, *44*, 3745; (b) Ramachandran, P. V.; Chandra, J. S.; Reddy, M. V. R. *J. Org. Chem.* **2002**, *67*, 7547.
12. (1*R*,2*S*)-2-Methyl-1-pentafluorophenyl-but-3-en-1-ol, **4b**: ^{1}H NMR (300 MHz) δ (ppm): 5.45–5.58 (m, 1H), 4.91–5.03 (m, 2H), 4.76 (d, $J = 4.86$ Hz, 1H), 2.56–2.82 (m, 1H), 2.45 (br s, 1H), 1.12 (d, $J = 7.20$ Hz, 3H); ^{13}C NMR (75.5 MHz) δ (ppm): 138.3, 136.1–146.2 (m, 5C), 117.0, 70.5, 44.8, 16.9; ^{19}F NMR (300 MHz) δ (ppm): −80.2, −92.9, −99.8; EI-MS: m/z 235 $(M-OH)^+$, 197 (100%); CI-MS: m/z 253 $(M+H)^+$, 235 $[(M+H-H_2O)^+$, 100%].
13. Brown, H. C.; Sinclair, J. A. *J. Organomet. Chem.* **1977**, *131*, 163.
14. Bratz, M.; Bullock, W. H.; Overman, L. E.; Takemoto, T. *J. Am. Chem. Soc.* **1995**, *117*, 5958.
15. (1*R*,2*S*)-2-Methyl-1-pentafluorophenyl-1,4-butanediol, **7b**: ^{1}H NMR (300 MHz) δ (ppm): 5.16 (d, $J = 5.1$ Hz, 1H), 4.77 (dd, $J = 4.95$, 9.45 Hz, 1H), 3.90 (br t, $J = 4.80$ Hz, 1H), 3.63–3.83 (m, 2H), 2.23–2.29 (m, 1H), 2.04–2.15 (m, 1H), 1.46–1.57 (m, 1H), 0.80 (d, $J = 6.90$ Hz, 3H); ^{13}C NMR (75.5 MHz) δ (ppm): 140.5–152.1 (m, 5C), 75.5, 64.8, 41.6, 41.0, 20.8; EI-MS: m/z 252 $(M-H_2O)^+$, 56 $[C_2H_5OH^+$, 100%]; CI-MS: m/z 271 $(M+H)^+$, 253 $[(M+H-H_2O)^+$, 100%]; HRMS-CI: $(M+H-H_2O)^+$ 252.0574 (actual), 252.0573 (calcd).
16. Brown, H. C.; Ramachandran, P. V.; Kumar, D. J. S.; Padiya, K. J. Unpublished results.
17. Ley, S. V.; Norman, J.; Griffith, W. P.; Marsden, S. P. *Synthesis* **1994**, *7*, 639.
18. (4*S*,5*R*)-4-Methyl-5-pentafluorophenyl-dihydrofuran-2-one, **9b**: ^{1}H NMR (300 MHz) δ (ppm): 5.29 (d, $J = 8.25$ Hz, 1H), 2.92 (dd, $J = 8.52$, 16.74 Hz, 1H), 2.72–2.86 (m, 1H), 2.37 (dd, $J = 9.51$, 16.88 Hz, 1H), 1.23 (d, $J = 6.60$ Hz, 3H); 174.8, 138.2–148.0 (m, 5C), 77.9, 36.7, 36.6; ^{19}F NMR (300 MHz) δ (ppm): −79.9, −89.5, −98.4; EI-MS: m/z 266 (M^+), 197 $[C_4H_5O^+$, 100%]; CI-MS: m/z 267 $[(M+H)^+$, 100%]; HRMS-CI: 266.0375 (actual), 266.0366 (calcd).
19. (a) Ley, S. V.; Humphires, A. C.; Eick, H.; Downham, R.; Ross, A. R.; Boyce, R. J.; Pavey, J. B. J.; Pietruszka, J. *J. Chem. Soc., Perkin Trans. 1* **1998**, 3907; (b) Lindsay, K. B.; Tang, M.; Pyne, S. G. *Synlett* **2002**, 731.
20. Contribution #31 from Herbert C. Brown Center for Borane Research.