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Highly enantioselective synthesis of (+)- and (−)-perfluoroalkyl(aryl) homoallyl alcohols

Dileep J. S. Kumar,*,† Sridharan Madhavan,† P. Veeraraghavan Ramachandran and Herbert C. Brown*

H. C. Brown and R. B. Wetherill Laboratories of Chemistry, Purdue University, West Lafayette, IN 47907-1393, USA

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Abstract

Asymmetric allylboration of perfluoroaldehydes and fluorine substituted aromatic aldehydes with ^{d}Ipc$_2$BAll and 2-Icr$_2$BAll has been investigated. Both enantiomers of the fluorinated homoallyl alcohols were obtained in high yields and excellent enantiopurity (95–99% ee). © 2001 Elsevier Science Ltd. All rights reserved.

The synthesis of chiral fluorinated molecules has attracted continuous attention from chemists due to their potential applications in biological, pharmaceutical and liquid crystals etc.[1] Although a large body of information is available in the literature about the synthesis of fluorinated alcohols, there have been only very few reports concerning their asymmetric synthesis.[2] In our extensive efforts towards the development of asymmetric reduction, we have reported the utility of Ipc$_2$BCl (DIP-chloride) as a superior reducing agent for the reduction of various ketones.[3] While studying the effect of fluorine substitution, we observed that the reduction of pentafluoroacetophenone with DIP-chloride gives poor enantioselectivity (44% ee) compared to that of acetophenone.[4] This encouraged us to investigate the effect of fluorine substitution in the allylboration of perfluoroaldehydes, as well as fluorine substituted benzaldehydes using *B*-allyldiisopinocampheylborane (^{d}Ipc$_2$BAll) and *B*-allylbis(2-isocaranyl)borane (2-Icr$_2$BAll) which were introduced by us as highly enantioselective reagents for the synthesis of homoallyl alcohols.[5,6]

Initially we examined the allylboration of perfluoroaldehydes with *B*-allyldiisopinocampheylborane **1**. Perfluoroaldehydes were synthesized via the reduction of the corresponding acids using LiAlH$_4$, followed by decomposition of the isolated aldehyde–hydrate with P$_2$O$_5$–H$_2$SO$_4$ mixture

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* Corresponding authors. E-mail: dkumar@mednet.ucla.edu; hcbrown@chem.purdue.edu

† Post-doctoral research associate on grant from the Purdue Borane Research Foundation.

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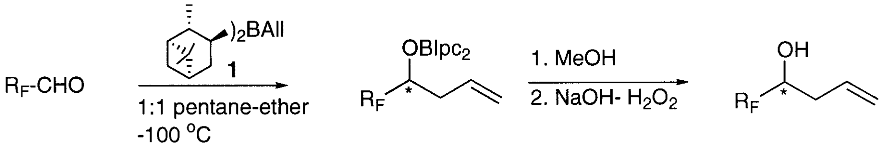
according to a procedure reported previously.[7] Thus for example, addition of fluoral **2**, (CF_3CHO) to a solution of ^{d}Ipc$_2$BAll at −100°C or below, followed by stirring the solution for 1 h at the same temperature and the usual work up yields 50% of 1,1,1-trifluoro-4-penten-2-ol **3** (Table 1).[8] The ee of the product was found to be >98.6% based on chiral GC analysis. Similarly, we attempted the allylboration of C_2F_5CHO and C_3F_7CHO to yield the corresponding homoallyl alcohols in 65 and 55% yields, respectively, with excellent ee (Table 1). The enantiopurity of **5** was determined by chiral GC analysis, whereas, that of **7** was estimated by chiral HPLC[9] analysis of the corresponding *p*-nitrobenzoyl (PNB) derivative. The configurations of the products reported in Table 1 were assigned as *R* based on the comparison of the specific rotation of the corresponding nonfluorinated homoallyl alcohols reported in literature.[5]

Table 1
Asymmetric allylation of perfluoroaldehydes with ^{d}Ipc$_2$BAll



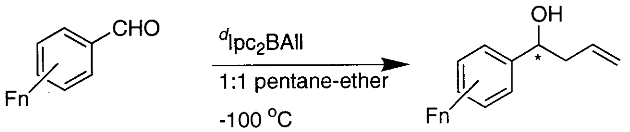
Entry	R_F	Yield (%)[a]	Configuration	ee (%)	$[\alpha]_D^{25}$ (CHCl$_3$)
1	**2** CF_3	**3** (50)	*R*	98.8[b]	+28.6 (*c* 2.2)
2	**4** C_2F_5	**5** (65)	*R*	99.7[b]	+23.8 (*c* 2.3)
3	**6** C_3F_7	**7** (55)	*R*	98.6[c]	+14.6 (*c* 2.1)

[a] Isolated yield.
[b] Determined by GC.
[c] Determined by HPLC analyses of *p*-nitrobenzoyl derivative.

Subsequently, we examined the allylboration of fluorine substituted benzaldehydes with ^{d}Ipc$_2$BAll. It has been observed in general, that the yields of fluorinated homoallyl alcohols from benzaldehyde derivatives (80–96%, Table 2) were better than that for the perfluoroaldehydes (50–65%) reported in Table 1. The enantiopurity analysis of the homoallyl alcohol derived from pentafluoro-, 2,6-difluoro-, 2-fluoro-, and 4-fluorobenzaldehyde provided excellent ee (entries 1, 2, 5 and 7, Table 2). Whereas, 3,5-difluoro-, 2,4-difluoro- and 3-fluorobenzaldehyde provided 95% ee for the corresponding homoallyl alcohol during the allylation process (entries 3, 4 and 6, Table 2). We also examined the effect of CF_3 substitution in the allylboration reactions of fluorinated benzaldehydes. It has been observed that *meta*-substituted trifluoromethyl benzaldehyde provided the homoallyl alcohol in 99.9% ee, whereas, *ortho*- and *para*- afforded the corresponding allyl alcohol in 96.8% and 95.2% ee, respectively (Table 2). The enantiomeric excess of the products were determined by chiral GC analyses for **9** and **15** (entries 1 and 4, Table 2), chiral HPLC[9] analyses for **11**, **13**, **17**, **19** and **21** (entries 2, 3 and 5–7, Table 2) and chiral HPLC analyses of the corresponding *p*-nitrobenzoyl derivatives for **23**, **25** and **27**, respectively (entries 8–10, Table 2). The configurations of the homoallyl alcohols reported in Table 2 were assigned as *R* based on the specific rotation of the phenyl-3-buten-1-ol previously reported.[5]

We also examined the allylboration of perfluoroaldehydes and fluorine substituted benzaldehydes using 2-Icr$_2$BAll as the allylating agent to synthesize the corresponding *S* enantiomer of the homoallyl alcohol. During our studies we found that perfluoroaldehydes, as well as fluorine

Table 2
Asymmetric allylboration reactions of fluorinated aldehydes with ^{d}Ipc$_2$BAll



Entry	Aldehyde (Fn & CF$_3$)	Product (yield %)[a]	Configuration	ee (%)	$[\alpha]_D^{25}$ (CHCl$_3$)
1	**8** (F=1,2,3,4,5)	**9** (86)	*R*	99.8[b]	+12.5 (*c* 2.7)
2	**10** (F=2,6)	**11** (88)	*R*	99.6[c]	+22.5 (*c* 2.2)
3	**12** (F=3,5)	**13** (90)	*R*	95.2[c]	+54.5 (*c* 1.7)
4	**14** (F=2,4)	**15** (86)	*R*	95.3[b]	+52.6 (*c* 1.9)
5	**16** (F=2)	**17** (80)	*R*	98.1[c]	+76.9 (*c* 1.25)
6	**18** (F=3)	**19** (85)	*R*	95.0[c]	+50.2 (*c* 2.1)
7	**20** (F=4)	**21** (90)	*R*	98.0[c]	+64.0 (*c* 1.0)
8	**22** (CF$_3$=2)	**23** (96)	*R*	96.8[d]	+69.4 (*c* 1.1)
9	**24** (CF$_3$=3)	**25** (80)	*R*	99.9[d]	+36.4 (*c* 2.1)
10	**26** (CF$_3$=4)	**27** (81)	*R*	95.2[d]	+56.9 (*c* 1.3)

[a] Isolated yield.

[b] Determined by GC.

[c] Determined by HPLC.

[d] Determined by HPLC analyses of *p*-nitrobenzoyl derivative.

substituted benzaldehydes, on reaction with 2-Icr$_2$BAll at −100°C, provided the corresponding homoallylic alcohols in 95–99% ee. The configurations of the products derived from 2-Icr$_2$BAll were assigned as *S* based on the comparison of their HPLC and GC data of the same products obtained on using ^{d}Ipc$_2$BAll as the allylating agent.

Table 3 summarizes our results of the enantiomeric excesses obtained in the allylboration of perfluoroaldehydes and fluorine substituted benzaldehydes using two chiral reagents at −100°C.

Table 3
Comparison of the enantiomeric excess in the allylboration of fluorinated aldehydes using ^{d}Ipc$_2$BAll and 2-Icr$_2$BAll at −100°C

Reagent	**3**	**5**	**7**	**9**	**11**	**13**	**15**	**17**	**19**	**21**	**23**	**25**	**27**
^{d}Ipc$_2$BAll (%ee)	98.8	>99	98.6	>99	>99	95.2	95.3	98	95	98	96.8	>99	95
2-Icr$_2$BAll (%ee)	>99	>99	>99	96	97	98	96	96	97	98	96	97	97

In summary, we have synthesized a series of fluorinated homoallyl alcohols from the corresponding perfluoroaldehydes or fluorine substituted benzaldehydes using ^{d}Ipc$_2$BAll and 2-Icr$_2$BAll as the chiral allylborating agents. Both the enantiomers were obtained in excellent enantiopurity. Further utilization of these optically active molecules is currently under investigation.

Acknowledgements

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8. In a typical experiment, a stirred solution of 20 ml (10 mmol, 1 M solution in 1:1 ether–pentane) ^{d}Ipc$_2$BAll **1** was cooled to −100°C and fluoral **2** (1 ml, 10 mmol) was added. The mixture was allowed to stir for 1 h at the same temperature and the ^{11}B NMR of the resulting solution after 1 h ($\delta = 52$ ppm) indicated the completion of the reaction. Methanol (1 ml) was added to the above solution and was warmed to rt, oxidized with 3N NaOH (6 ml) and 30% H_2O_2 (5 ml) and stirred for 6 h. The product was extracted with ether, washed with brine and dried over anhydrous $MgSO_4$. The solvent was distilled off and pure product was fractionally distilled at 103°C to yield 700 mg (50%) of 1,1,1-trifluoromethyl-4-penten-2-ol **3**. The enantiopurity of **3** was estimated as 98.6 based on chiral GC analysis. **3**: $[\alpha]_D^{25}$ ($CHCl_3$) = +28.6 (*c* 2.2); IR (neat) cm^{-1}, 3412 (OH), 1280 (CF_3); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.8–2.1 (2H, m, CH_2), 2.15–2.3 (1H, d, OH), 3.9–4.1 (1H, m, CH), 5.2–5.3 (2H, m, CH_2), 5.8–5.9 (1H, m, CH). ^{13}C NMR (75 MHz, $CDCl_3$) δ 34.4 (CH_2), 69.11, 69.53, 69.94, 70.35 ($\underline{CH}$-CF_3, q, $J = 31$ Hz), 119.82, 131.76 ($CH{=}CH_2$), 119.5, 123.9, 126.82, 130.58 (CF_3, q, $J = 282$ Hz). ^{19}F NMR (282.35 MHz, $CDCl_3$) δ −80.84, −80.86 (CF_3, d, $J = 6$ Hz); mass (EI, *m*/*z*, relative intensity) 140 (M^+, 55), 122 (14), 99 (14), 71 (100), 51 (50).
9. HPLC analyses was performed using Chiralcel OD-H column.