Preliminary Note

Preparation of optically active 2-(trifluoromethyl)alkan-1-ols by catalytic asymmetric hydrogenation

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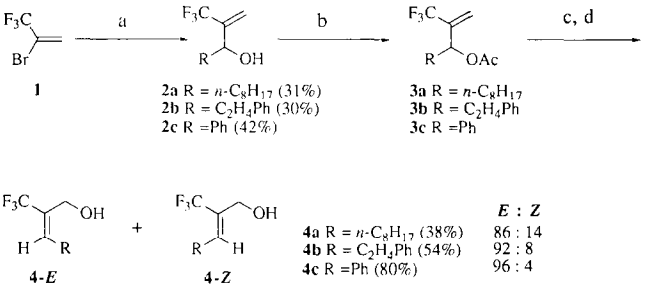

(a) *n*-BuLi, RCHO, -95°C; (b) Ac_2O, cat. DMAP in pyridine, room temperature; (c) $Pd(PPh_3)_4$ in THF, room temperature; (d) K_2CO_3 in methanol, room temperature.

Scheme 1. Preparation of 2-(trifluoromethyl)alk-2-en-1-ol (**4**).

Abstract

The hydrogenation of (*E*)-2-(trifluoromethyl)alk-2-en-1-ols catalyzed by Ru–BINAP and Rh–BINAP has been carried out with good enantiomeric excess (71%–83% ee). Ru–BINAP-catalyzed hydrogenation converted 2-trifluoromethylacrylic acid to the corresponding saturated acid, the esterification and reduction of which gave optically active 2-(trifluoromethyl)propan-1-ol in 80% ee.

The synthesis of chiral fluorinated molecules is an important aspect of organofluorine chemistry in relation to analytical and medicinal chemistry and optoelectric substances such as liquid crystal [1]. Some catalytic asymmetric hydrogenation reactions have been shown as useful for obtaining optically active fluorinated compounds [2]. The synthesis of chiral 2-(trifluoromethyl)alkan-1-ols (**5**) using stoichiometric amounts of chiral auxiliaries has recently been reported [3]. This paper presents the preparation of optically active **5** by catalytic asymmetric hydrogenation.

As shown in Scheme 1, 2-(trifluoromethyl)alk-2-en-1-ol (**4**) was prepared in four steps starting from 2-bromo-3,3,3-trifluoropropene (**1**). The conversion of **1** into the allylic alcohol **2** was carried out according to the method of Drakesmith *et al.* [4] in moderate yield while the acetylation of **2** with acetic anhydride in pyridine at room temperature gave the acetate **3** quantitatively. Treatment of **3** with tetrakis(triphenylphosphine)palladium in tetrahydrofuran at room temperature brought about allylic rearrangement followed by deacetylation with K_2CO_3 in methanol at room temperature to give a separable mixture of **4**-*E* and its *Z* isomer (**4**-*Z*) (38%–80% yield in two steps) together with compound **2**.

The hydrogenation of **4** was conducted using 10 mol% of either [(*R*)-2,2′-bis(diphenylphosphino)-1,1′-binaphthyl]ruthenium diacetate (Ru–(*R*)-BINAP, A) [5] or [(*R*)-2,2′-bis(diphenylphosphino)-1,1′-binaphthyl]rhodium(I) trifluoromethanesulfonate (Rh-(*R*)-BINAP, B) [6] as a catalyst as shown in Table 1. Enantiomeric excess was determined by GLC analysis of the Mosher ester of **5** [7]. Although the enantiomeric purity of 2-(trifluoromethyl)undecan-1-ol (**5a**) from **4a**–*E* (Entry 1) exceeded that from **4a**-*Z* (Entry 2), that the same enantiomer is preferentially formed from **4a**-*E* and **4a**-*Z* is a point of interest. The hydrogenation of a mixture of **4a**-*E* and **4a**-*Z* (45:55) (Entry 3) recovered 56% of the starting material in a ratio of 14:86, indicating **4a**-*E* to have been hydrogenated faster than **4a**-*Z*. Only in the hydrogenation of (*E*)-2-(trifluoromethyl)cinnamyl alcohol (**4c**-*E*) was Rh–(*R*)-BINAP (B) superior to Ru–(*R*)-BINAP (A) as a catalyst (Entries 5 and 6).

The hydrogenation rate of **4** was very low. Only 33% of **4a**-*E* was hydrogenated after 26 h under the same conditions as in Entry 1. In a control experiment with (*E*)-2-methylundec-2-en-1-ol, 100% conversion was observed in the same reaction time. The bulkiness and lipophilicity of the trifluoromethyl group may prevent the catalyst (Ru–BINAP) from coordinating **4**.

Treatment of 2-(trifluoromethyl)acrylic acid (**6**) with H_2 in the presence of 1 mol% of Ru–(*R*)-BINAP (C) [8] and 1.1 equiv. of triethylamine in methanol at 0 °C and 7 atm for 48 h afforded optically active 2-(trifluoromethyl)propionic acid (**7**) in 100% conversion. The esterification of **7** with diazomethane in ether at 0 °C followed by reduction with $LiAlH_4$ at 0 °C in tetrahydrofuran gave (*S*)-2-(trifluoromethyl)propan-1-ol (**8**) [3]. Enantiomeric excess of **8** was determined

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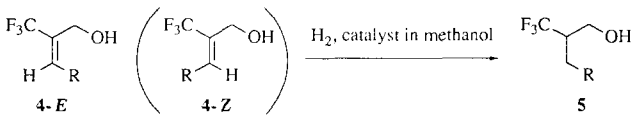
TABLE 1. Asymmetric hydrogenation of 2-(trifluoromethyl)alk-2-en-1-ol (**4**)

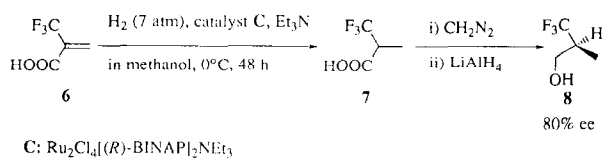


Entry	2-Trifluoromethylalk-2-en-1-ol		Catalyst[a] (mol%)	H_2 (atm)	Time (h)	Temp. (°C)	Product **5**	
	4	R					Conv. (%)	ee (%)
1	**4a**-*E*	n-C_8H_{17}	A (10)	18	240	30	94	83
2	**4a**-*Z*	n-C_8H_{17}	A (10)	18	48	30	21	15
3	**4a**-*E*/*Z*	(45:55)	A (10)	18	72	30	44	68
4	**4b**-*E*	C_2H_4Ph	A (10)	18	240	30	46	71
5	**4c**-*E*	Ph	A (10)	18	240	30	16	42
6	**4c**-*E*	Ph	B (10)	5	18	22	32	83

[a]A = Ru(OAc)$_2$[(*R*)-BINAP], [(*R*)-2,2′-bis(diphenylphosphino)-1,1′-binaphthyl]ruthenium diacetate; B = Rh^+[(*R*)-BINAP]OTf^-, [(*R*)-2,2′-bis(diphenylphosphino)-1,1′-binaphthyl]rhodium(I) triflate.

to be 80% ee by GLC analysis of the corresponding Mosher ester [7] (Scheme 2).

In conclusion, the hydrogenation of (*E*)-2-(trifluoromethyl)alk-2-en-1-ols (**4**-*E*) catalyzed by Ru–(*R*)-BINAP (A) and Rh–(*R*)-BINAP (B) has been carried out with good enantiomeric excess (71%–83% ee). Ru–(*R*)-BINAP (C)-catalyzed hydrogenation converted 2-(trifluoromethyl)acrylic acid (**6**) to the corresponding saturated acid **7** whose esterification and reduction provided optically active (*S*)-2-(trifluoromethyl)propan-1-ol (**8**) in 80% ee. Means are presently being sought to improve the hydrogenation rate of **4** and the optical yield of **5** through further investigation on this and related hydrogenations.



Scheme 2. Preparation of (*S*)-2-(trifluoromethyl)propan-1-ol (**8**).

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