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Enantioselective Rhodium(I)-Catalyzed Hydrogenation of Trifluoromethyl Ketones

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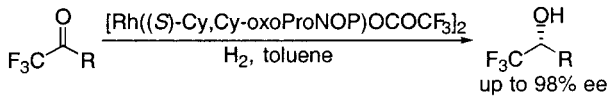
ABSTRACT



The asymmetric hydrogenation of trifluoromethyl ketones to yield chiral α-trifluoromethyl alcohols with enantiomeric excesses up to 98% was achieved in the presence of chiral rhodium-(amidephosphine-phosphinite) complexes.

The catalytic asymmetric synthesis of chiral organofluorine compounds has played an important role in the development of medicines and materials based on the influence of fluorine's unique properties.[1] Homochiral α-trifluoromethyl alcohols are versatile intermediates for the synthesis of antiferroelectric liquid crystalline molecules.[2] Although a few asymmetric catalyses for preparing the alcohols have been reported,[3] their synthesis has drawbacks such as insufficient levels of enantioselectivity, low catalytic efficiencies, and limited scope of the substrates. Recently, we reported that the highly enantioselective synthesis of 1,1,1-trifluoroalkan-2-ols can be successfully achieved by hydrogenating 1,1,1-trifluoroalkan-2-one enol acetates in the presence of chiral ruthenium catalysts.[4] This paper discloses the asymmetric hydrogenation of trifluoromethyl ketones catalyzed by chiral rhodium-(amidephosphine-phosphinite) complexes to provide chiral α-trifluoromethyl alcohols with up to 98% ee.

Recently, we found that chiral rhodium-(amidephosphine-phosphinite) complexes, prepared from $[Rh(COD)OCOCF_3]_2$ and oxoProNOP ligands,[5] catalyze the hydrogenation of 2,2-difluoro-3-oxocarboxylates and 4,4,4-trifluoroacetoacetate to give the corresponding β-hydroxy esters with good-to-excellent enantioselectivity.[6] The stereochemical outcome from the latter β-keto ester indicated that the trifluoromethyl group has a significant influence on the enantiotopic face selection, prompting us to examine the hydrogenation of the trifluoromethyl ketones using the chiral rhodium-(amidephosphine-phosphinite) complexes.

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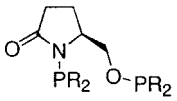
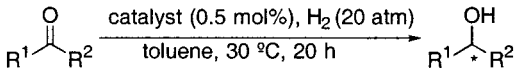


(*S*)-Cy,Cy-oxoProNOP: R = *c*-C_6H_{11}
(*S*)-*i*-Pr,*i*-Pr-oxoProNOP: R = *i*-Pr

1,1,1-Trifluoro-2-decanone was hydrogenated using 0.5 mol % [Rh((*S*)-Cy,Cy-oxoProNOP)$OCOCF_3]_2$ (**1**) or 0.1 mol % [Rh((*R*)-*i*-Pr,*i*-Pr-oxoProNOP)$OCOCF_3]_2$ (**2**) under 10 or 20 atm of hydrogen in toluene at 30 °C for 20 h to give 1,1,1-trifluoro-2-decanol[7] with 97% ee in a nearly quantitative yield (Table 1, entries 1 and 2). The reactions of 1,1-difluoro-2-decanone and 1-fluoro-2-decanone under the same conditions dramatically diminished the enantioselectivity despite the quantitative yields (entries 3 and 4). However, the catalyst **1** scarcely promoted the hydrogenation of 2-decanone (entry 5). A nonfluorinated aromatic ketone, acetophenone, was also hydrogenated into 1-phenylethanol with only 8% ee in only 2% yield (entry 6), while the reaction of α,α,α-trifluoroacetophenone led to a 93% yield of the corresponding (*R*)-product[8] with 73% ee (entry 7). 1,1,1,2,2-Pentafluoro-3-dodecanone underwent hydrogenation to yield the corresponding α-pentafluoroethyl alcohol with 97% ee in quantitative yield (entry 8).

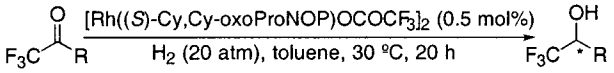
Table 1. Asymmetric Hydrogenation of Ketones Using Rhodium-(Amidephosphine-phosphinite) Complexes (**1** and **2**)



entry	R^1	R^2	catalyst [a]	yield (%)[b]	ee (%)
1	CF_3	C_8H_{17}	**1**	99	97[c] (*R*)[d]
2[e]	CF_3	C_8H_{17}	**2**	100	97[c] (*S*)[d]
3	CHF_2	C_8H_{17}	**1**	100	27[c]
4	CH_2F	C_8H_{17}	**1**	100	15[c]
5	CH_3	C_8H_{17}	**1**	<1	
6	CH_3	Ph	**1**	2	8[f]
7	CF_3	Ph	**1**	93	73[f] (*R*)[d]
8	C_2F_5	C_9H_{19}	**1**	100	97[g] (*R*)[h]

[a] **1**, [Rh((*S*)-Cy,Cy-oxoProNOP)$COCF_3]_2$; **2**, [Rh((*R*)-*i*-Pr,*i*-Pr-oxoProNOP)$COCF_3]_2$. [b] Isolated yield. [c] Determined by GLC analysis of the corresponding acetate with CP-Cyclodex-β-236M. [d] Assigned by comparing the sign of the optical rotations with literature data. See refs 7 and 8. [e] Carried out using 0.1 mol % of **2** under 10 atm H_2. [f] Determined by HPLC analysis with CHIRALCEL OD-H. [g] Determined by HPLC analysis of the corresponding 3,5-dinitrobenzoate with CHIRALCEL OD-H. [h] Assigned by the modified Mosher method.[9]

Table 2. Asymmetric Hydrogenation of Trifluoromethyl Ketones



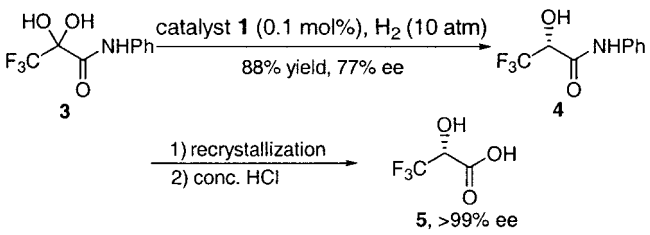
entry	R	yield (%)[a]	ee (%)
1	C_6H_{13}	98	97[b] (*R*)[c]
2	*c*-C_6H_{11}	90	97[d] (*R*)[c]
3	*c*-$C_6H_{11}CH_2$	97	98[b]
4	$PhCH_2$	97	97[e]
5	$PhCH_2CH_2$	99	96[e]
6	$PhCH_2OCH_2$	100	86[b]
7	*p*-ClPh	8	38[e]
8	*p*-CH_3OPh	100	83[e]

[a] Isolated yield. [b] Determined by GLC analysis of the corresponding acetate with CP-Cyclodex-β-236M. [c] Assigned by comparing the sign of the optical rotations with literature data. See refs 7 and 10. [d] Determined by HPLC analysis of the corresponding 3,5-dinitrobenzoate with CHIRALCEL OD-H. [e] Determined by HPLC analysis with CHIRALCEL OD-H.

A variety of trifluoromethyl ketones were hydrogenated in the presence of 0.5 mol % of the catalyst **1** under 20 atm of hydrogen in toluene at 30 °C for 20 h (Table 2). The hydrogenations of 1,1,1-trifluoro-2-octanone and cyclohexyl trifluoromethyl ketone provided the (*R*)-products[7,10] with 97% ee in 98% and 90% yields, respectively (entries 1 and 2). The cyclohexylmethyl trifluoromethyl ketone was also hydrogenated with high enantioselectivity and good catalyst activity (entry 3). While the reactions of the two ketones having a benzene ring also proceeded with high enantiomeric excesses (entries 4 and 5), the catalyst **1** failed in high asymmetric induction (86% ee) with 1,1,1-trifluoro-5-phenyl-4-oxa-2-pentanone (entry 6). The introduction of a chlorine atom into the *p*-position of α,α,α-trifluoroacetophenone drastically reduced the chemical and optical yields (entry 7 vs Table 1, entry 7), while the hydrogenation of α,α,α-trifluoro-*p*-methoxyacetophenone significantly improved the enantioselectivity (entry 8).

Finally, the asymmetric hydrogenation of 3,3,3-trifluoro-2,2-dihydroxypropionanilide (**3**), prepared from hexafluoropropene oxide,[11] using 0.1 mol % of the catalyst **1** was also examined in toluene under 10 atm H_2 at 70 °C for 20 h, and (*R*)-3,3,3-trifluoro-2-hydroxypropionanilide (**4**) was obtained in 77% ee and 88% yield. A single recrystallization of **4** afforded (*R*)-**4** with >99% ee. Hydrolysis of the amide (*R*)-**4** with concentrated HCl at 80 °C provided (*R*)-trifluorolactic acid (**5**) in 84% yield and >99% ee (Scheme 1).

Scheme 1



In summary, the catalytic asymmetric hydrogenation of trifluoromethyl ketones has been accomplished using the rhodium-oxoProNOP catalysts, providing a variety of opti-

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cally active α-trifluoromethyl alcohols with up to 98% ee. Applications of this method to the synthesis of versatile chiral fluorinated molecules are currently under investigation.

Supporting Information Available: Detailed experimetal procedures and characterization data for chiral α-trifluoromethyl alcohols. This material is available free of charge via the Internet at http://pubs.acs.org.

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