Stereocontrolled OH Protection: Asymmetric Tetrahydrofuranylation

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(ON^+)(Salen)ruthenium(II) complex **1** was found to be an effective catalyst for asymmetric tetrahydrofuranylation of alcohols. The tetrahydrofuranylation of optically active alcohols was also successfully performed in a highly diastereoselective manner by taking advantage of double diastereodifferentiation.

Protection of hydroxy group as tetrahydrofuranyl (THF) or tetrahydropyranyl (THP) ether is widely used in various organic synthesis, because their protection and deprotection can be carried out under mild acidic conditions to which many functional groups are tolerable.[1] These protecting groups, however, possess one chiral carbon and, when hydroxy compound is chiral, the protection gives a mixture of diastereomeric THF or THP ether, because the etherification under usual acidic conditions generally proceeds with poor diastereoselectivity.[2] This makes spectroscopic analysis of the protected alcohol difficult, especially when the parent alcohol possesses a complex structure. Thus, stereoselective tetrahydrofuranylation (THFT) and tetrahydropyranylation (THPT) of hydroxy group have been strongly needed. To our knowledge, however, there are few reports on this subject.[3] Thus, we examined Lewis acid-catalyzed stereoselective THFT and THPT.

Recently, we and others have reported that optically active metallosalen complexes serve as chiral Lewis acid catalysts.[4,5] Therefore, we first examined asymmetric THFT and THPT of benzyl alcohol in chlorobenzene using various metallosalens (**1–5**)[5] as the catalyst (Table 1). THPT did not occur under the conditions examined, but THFT using (ON^+)(salen)ruthenium(II) complex **1** under irradiation or (salen)cromium(III) complex **2** as the catalyst proceeded smoothly. Especially, THFT using **1** as the catalyst showed high enantioselectivity of 85% ee.

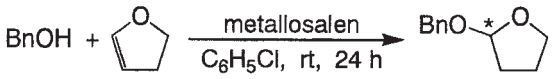
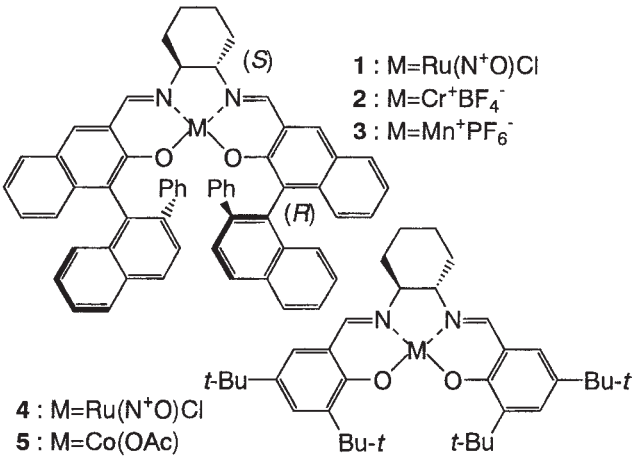


Table 1. Asymmetric THFT of benzyl alcohol with metallosalens as catalyst[a]

Entry	Metallosalen	Yield/%	% ee[b]
1[c]	**1**	89	85
2	**2**	91	2
3	**3**	0	—
4	**4**	10	1
5	**5**	0	—

[a]Reactions were carried out with molar ratio of alcohol: 2,3-dihydrofuran: catalyst = 1 : 3 : 0.02 at room temperature for 24 h. [b]Determined by HPLC analysis using optically active column (DAICEL CHIRALCEL OD-H, hexane/2-propanol = 400/1, flow rate = 0.5 ml/min). [c]Reaction was carried out under deaerated conditions with irradiation by a halogen lamp (Note 6).



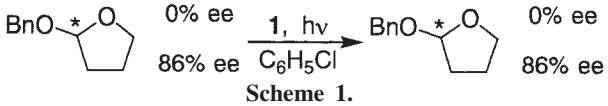
Enantioselectivity of the reaction was not affected so much by the solvent used but the reaction rate was reduced in polar solvents (Table 2, Entries 5–7).

Table 2. THFT of benzyl alcohol in various solvents[a]

Entry	Solvent	Yield/%[b]	% ee
1	chlorobenzene	89	85
2	CH_2Cl_2	88	86
3	toluene	83	84
4	$C_6H_5CF_3$	75	85
5	THF	trace	—
6	dioxane	27	85
7	acetone	49	75

[a]Reactions were carried out with molar ratio of alcohol: 2,3-dihydrofuran: **1** = 1 : 3 : 0.02 at room temperature for 24 h under irradiation with a halogen lamp. [b]Isolated yield.

In general, acetals are sensitive to acidic conditions. In order to explore whether tetrahydrofuranyl ether is stable under the present conditions or not, we exposed racemic and enantiomerically enriched (86% ee) benzyl tetrahydrofuranyl ethers to the reaction conditions. No change in enantiomeric excesses of the ethers was observed (Scheme 1). This indicates that stereochemistry of the present THFT is kinetically controlled.



Scheme 1.

THFT of other alcohols and phenols in chlorobenzene also proceeded with high enantioselectivity (Table 3), though the reaction of secondary alcohol, 2-indanol, showed somewhat diminished enantioselectivity (Entry 5).

Alcoholic synthetic intermediates in most of natural product syntheses are chiral. Therefore, stereochemistry of THFT of those intermediates is regulated not only by the chirality of the catalyst

Table 3. Asymmetric THFT of various phenols and alcohols with **1** as the catalyst

Entry	R-OH	Yield/%[a]	% ee
1	phenol	76	84[b]
2	3-phenylpropargyl alcohol	88	85[c]
3	β-naphthol	94	86[d]
4	cinnamyl alcohol	97	80[e]
5	2-indanol	96	71[f]

[a]Isolated yield. [b]Determined by HPLC analysis using optically active column (DAICEL CHIRALCEL OB-H, hexane/2-propanol = 400/1, flow rate = 0.5 ml/min). [c]Determined by HPLC analysis using optically active column (DAICEL CHIRALCEL OB-H, hexane/2-propanol = 15/1, flow rate = 0.5 ml/min). [d]Determined by HPLC analysis using optically active column (DAICEL CHIRALPAK AS, hexane/2-propanol = 400/1, flow rate = 0.5 ml/min). [e]Determined by HPLC analysis using optically active column (DAICEL CHIRALPAK AD-H, hexane/2-propanol = 100/1, flow rate = 0.5 ml/min). [f]Determined by HPLC analysis using optically active column (DAICEL CHIRALCEL OD-H, hexane/2-propanol = 400/1, flow rate = 0.5 ml/min).

but also by the chirality of substrate. If these two stereocontrolling factors match, stereoselectivity of the THFT is expected to become higher than the selectivity induced only by the catalyst **1**.[7] Thus, we examined THFT of optically active alcohols using **1** as the catalyst in dichloromethane or chlorobenzene (Table 4). As expected, high stereoselectivity greater than 90% de was observed in the matched reactions, except for the reaction of 2-octanol in which substrate control was considered to be small (Entries 3 and 4).

We also examined kinetic resolution of racemic phenethyl alcohol under the optimized conditions, but the observed relative reaction ratio was only modest (1.6).

Typical procedure was exemplified by THFT of benzyl alcohol: In a 5 ml Schlenk tube were placed complex **1**[5] (2.0 mg, 2.0 μmol) and chlorobenzene (1 ml). To the solution were successively added benzyl alcohol (10.3 μl, 0.1 mmol) and 2,3-dihydrofuran (22.8 μl, 0.3 mmol), and cooled by liquid nitrogen. The mixture was deaerated under vacuum and warmed to room temperature. The mixture was stirred for 24 h at the temperature under irradiation using a halogen lamp (150 W). The reaction mixture was directly submitted to column chromatography on silica gel (hexane/ethyl acetate = 19/1) to give 2-benzyloxytetrahydrofuran (15.8 mg, 85% ee) in 89% yield.

In conclusion, we were able to achieve highly stereoselective tetrahydrofuranylation of achiral and chiral alcohols.

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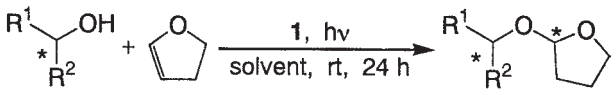
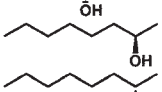
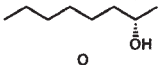
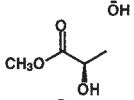
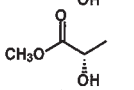
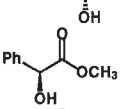
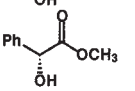
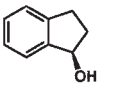
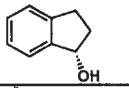


Table 4. Double diastereodifferentiation in THFT of secondary alcohols using **1** as the catalyst

Entry	Substrate	Solvent	Yield /%[a]	% de[b]
1		C_6H_5Cl	100	98
2		C_6H_5Cl	78	74
3		CH_2Cl_2	89	63
4		CH_2Cl_2	85	78
5		CD_2Cl_2	91[c]	92
6		CD_2Cl_2	79[c]	87
7		C_6H_5Cl	97	99
8		C_6H_5Cl	88	97
9		CH_2Cl_2	81	40
10		CH_2Cl_2	88	96

[a]Isolated yield. [b]Determined by ^{1}H NMR (400 MHz) analysis. [c]Reaction was carried out in dichloromethane-d_2 and the yield was determined by ^{1}H NMR (400 MHz) analysis using 1-bromonaphthalene as internal standard.

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