Pergamon

Tetrahedron Letters, Vol. 38, No. 5, pp. 849-852, 1997

0040-4039/97 $17.00 + 0.00

PII: S0040-4039(96)02465-3

Pronounced Enhancement of Stereoselectivity in Asymmetric Hydrogenation of 2-Substituted 2-Propen-1-ols by Transient Acylation

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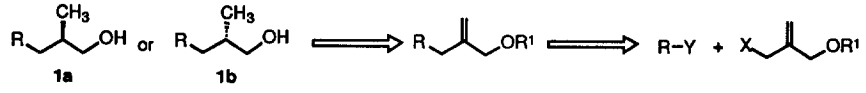
Abstract: In the hydrogenation using a chiral catalyst, $Ru_2Cl_4[(R)\text{-}(+)\text{-BINAP}]_2NEt_3$, aroylation of the allylic hydroxyl group of 2-(hydroxymethyl)-4-hydroxy-4-methyl-1-pentene (**2b**) and 2-(hydroxymethyl)-3-(1-hydroxycyclohexyl)-1-propene (**3b**) resulted in pronounced enhancement of asymmetric induction.

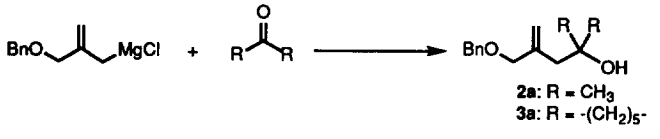
The chiral carbon atom bearing a methyl group or a hydroxyl group is widespread in natural products such as polypropionate derived compounds.[1] For the construction of the carbon framework of this class of compounds, a primary alcohol having a stereogenic center at the position 2 (**1a** or **1b**) would be a fundamental building block.

In this communication, we wish to report preparation of 2-substituted 2-propen-1-ols and their transformation into the chiral primary alcohol **1a** or **1b** by asymmetric hydrogenation (Scheme 1).[2,3]



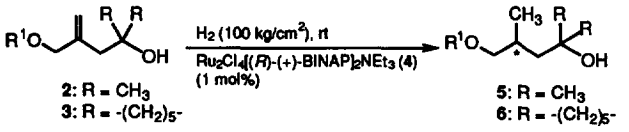
Scheme 1

As model substrates, 2-(benzyloxymethyl)-4-hydroxy-4-methyl-1-pentene (**2a**) and 2-(benzyloxymethyl)-3-(1-hydroxycyclohexyl)-1-propene (**3a**) were prepared by the reaction of 2-benzyloxymethyl-2-propenylmagnesium chloride with acetone and with cyclohexanone (Scheme 2).[4] In the subsequent asymmetric hydrogenation, the catalyst of our choice was $Ru_2Cl_4[(R)\text{-}(+)\text{-BINAP}]_2NEt_3$ (**4**), because it is readily prepared using the standard benchtop technique from commercially available reagents.[5] The reduction was conducted under pressure of 100 kg/cm^2 and at room temperature by the use of 1 mol% of the catalyst **4** in THF-ethanol (1 : 1 v/v; standard conditions) (Scheme 3). The enantiomer ratio was determined by HPLC analysis.[6]



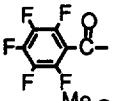
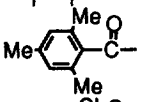
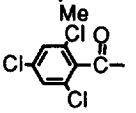
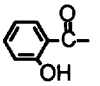
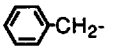
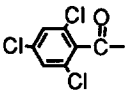
Scheme 2

At the outset, benzyl ethers **2a** and **3a** were respectively hydrogenated under standard conditions, where 4-benzyloxymethyl-2-methylpentan-2-ol (**5a**) and 2-benzyloxymethyl-1-(1-hydroxycyclohexyl)propane (**6a**) were obtained in 63% and 55% yields as racemic mixtures (Table 1, entries 1 and 8). In the hope of achieving effective stereodifferentiation through hydroxyl-coordination to Ru,[3a] **2a** and **3a** were converted into diol **2b** and **3b** by treatment with Li in ammonia. Contrary to our expectation, however, only a low level of enantioselectivity was again observed in the hydrogenation of **2b** and **3b** (Table 1, entries 2 and 9).



Scheme 3 (For R^1, see Table 1)

Table 1. Hydrogenation of **2** and **3**

Entry	Starting material (**2** or **3**) and product (**5** or **6**)				Yield of **5** or **6**	Selectivity
	R	R^1			%	% ee ( )[a]
1	CH_3		**2a**	**5a**	63	0
2	CH_3	H	**2b**	**5b**	90	9 (*R*)
3	CH_3		**2c**	**5c**	95	60 (*S*)
4	CH_3		**2d**	**5d**	>99	42 (*S*)
5	CH_3		**2e**	**5e**	98	75 (*S*)
6	CH_3		**2f**	**5f**	95	85 (*S*)
7	CH_3		**2g**	**5g**	93	36 (*S*)
8	$-(CH_2)_5-$		**3a**	**6a**	55	0
9	$-(CH_2)_5-$	H	**3b**	**6b**	72	0
10	$-(CH_2)_5-$		**3c**	**6c**	91	28 (*S*)
11	$-(CH_2)_5-$		**3f**	**6f**	88	68 (*S*)

a) Configuration of the major isomer.

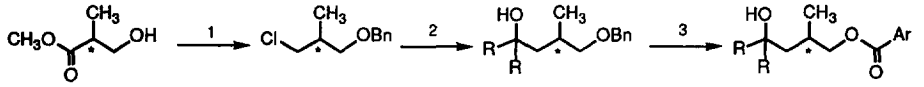
The catalyst **4** has been reported to be successfully utilized in the asymmetric hydrogenation of 2-acylaminoacrylic acid,[5] 2-acylaminocinnamic acid,[5b] methylenesuccinic acid,[5b] and β-keto esters.[7] These facts

suggest that the carboxyl and alkoxycarbonyl groups function as an efficient directing group in these reaction systems. Thus, diol **2b** and **3b** were acylated to give a series of esters **2c**, **2d**, **2e**, **2f**, **2g**, **3c**, and **3f**.

As expected, hydrogenation of **2c** (1 mmol) in THF (7.5 ml) and ethanol (7.5 ml) with 1 mol% of **4** at room temperature for 6 h (H_2: 100 kg/cm^2), followed by silica gel column chromatography (hexane/ethyl acetate = 4 : 1) afforded **5c** in 95% yield with 60% ee (Table 1, entry 3). Under similar conditions, pentafluorobenzoate **2d** and 2,4,6-trimethylbenzoate **2e** afforded the corresponding saturated esters **5d** and **5e** in 42% ee and 75% ee, respectively (Table 1, entries 4 and 5). On employing 2,4,6-trichlorobenzoate **2f**, much higher discrimination (85% ee) was achieved, while hydrogenation of 2-hydroxybenzoate showed a lower level of selectivity (36% ee) (Table 1, entries 6 and 7).

In the hydrogenation of cyclohexyl derivatives **3c** and **3f**, the benzoyl and 2,4,6-trichlorobenzoyl groups again play a role in the discrimination of the prochiral π-face (Table 1, entries 10 and 11).

The configurations of the newly produced chiral centers (see Table 1) were determined by comparison of the retention times (HPLC) with those obtained by a stereochemically unambiguous route from methyl (*R*)- and (*S*)-3-hydroxy-2-methylpropionates [(*R*)-**7** and (*S*)-**7**] as depicted in Scheme 4.[8]

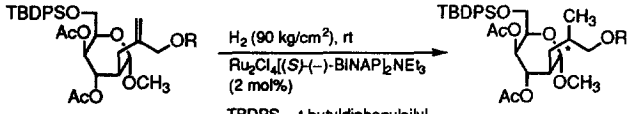


(*R*)-**7** (*S*)-**7** | (*R*)- and (*S*)-**5a** (*R*)- and (*S*)-**6a** | (*R*)- and (*S*)-**5c~5g** (*R*)- and (*S*)-**6c**, **6f**

Reagents and conditions: 1. (a) $BnOC(=NH)CCl_3$, TfOH (cat.), cycloC_6H_{12}-CH_2Cl_2 (2 : 1 v/v) rt, 1 h. (b) $LiAlH_4$, Et_2O, 0 °C, 1 h. (c) CCl_4, Ph_3P, CH_2Cl_2, rt, 1 d. For (*R*)-isomer, 55%, for (*S*)-isomer, 54%. 2. Mg, acetone or cyclohexanone, THF, rt, 1 d. 53%~>99%. 3. (a) H_2 (1 atm), Pd-C, EtOH, rt, 92%~98%. (b) Acylation, 64%~>99%.

Scheme 4

Next, stereochemistry of the reduction of the functionalized 2-propenyl group introduced into the hexopyranoside skeleton was investigated.[9] Thus, hydrogenation of carbohydrate derivatives **8a**, **8b**, and **8c** with Ru_2Cl_4[(*S*)-(−)-BINAP]$_2$NEt$_3$ at 90 kg/cm^2 in THF-ethanol (1 : 1 v/v) at room temperature gave **9a**, **9b**, and **9c** in 57-78% de (Scheme 5). Although the effect of the transient acylation of the hydroxyl group was not so pronounced as was observed in the case of the acyclic system, the installed benzoyl group again played a role in the discrimination of the π-face.

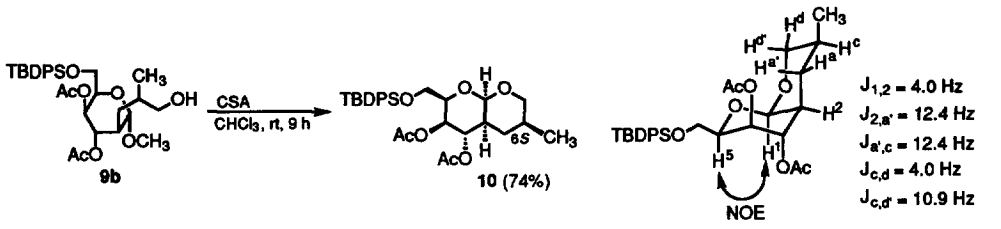


8a, b, c | **9a, b, c**

8, 9	R	Yield/%	%de
a	Bn	94	57
b	H	80	67
c	Bz	96	78

Scheme 5

The configuration of the newly introduced chiral center was determined to be *S*. Thus, the reaction of diastereomeric mixture **9b** (67% de) with a catalytic amount of D-camphor-10-sulfonic acid afforded fused ring cyclic acetals **10** as the major product in 74% yield.[10] The NMR examination (1D, COSY, and NOESY) revealed that **10** has 6*S* configuration (Scheme 6). The configuration of the major isomer of diastereomers (**9c**) obtained by the hydrogenation of **8c** (78% de) was also determined to be *S* by comparison of the retention time (HPLC) with that of benzoates derived from diastereomeric mixture **9b**.



NMR parameter for major isomer **10**

Scheme 6

Since the acyl groups could be removed at a suitable stage of the synthesis, the transient acylation procedure described in this paper would provide a useful method for the asymmetric hydrogenation of prochiral allylic alcohols which, otherwise, would proceed with low selectivity.

This work was partially supported by Grant-in-Aid for Scientific Research from the Ministry of Education, Science, Sports and Culture, Japan.

References and Notes

1. See for example, a) Omura, S. "*Macrolide Antibiotics*," Academic Press: Orlando, Florida, 1984, b) Cane, D. E.; Celmer,W. D.; Westley, J. W. *J. Am. Chem. Soc.*, **1983**, *105*, 3594-3600.
2. An alternative route to prepare **1a** and **1b**, see Mitsunobu, O. "*Regioselective Introduction of Allylic Groups into Carbohydrate Matrices*," in "*Organic Synthesis in Japan; Past, Present, and Future*," Noyori, R. Ed.-in-Chief; Tokyo Kagaku Dojin: Tokyo, 1992, pp 215-226.
3. For asymmetric hydrogenation by the use of homogeneous catalysts, see for example, a) Brown, J. M. *Angew. Chem. Int. Ed. Engl.*, **1987**, *26*, 190-203. b) Noyori, R. *Tetrahedron*, **1994**, *50*, 4259-4292. c) For the hydroxyl-directed hydrogenations, see for example, Evans, D. A. and Morrissey, M. M. *Tetrahedron Lett.*, **1984**, *25*, 4637-4640.
4. a) Van der Louw, J.; Van der Baan, J. L.; Bickelhaupt, F.; Klumpp, G. W. *Tetrahedron Lett.*, **1987**, *28*, 2889-2892. b) Van der Louw, J.; Van der Baan, J. L.; Stichter, H.; Out, G. J. J.; Bickelhaupt, F.; Klumpp, G. W. *Tetrahedron Lett.*, **1988**, *29*, 3579-3580.
5. a) Ikariya, T.; Ishii, Y.;Kawano, H.; Arai, T.; Saburi, M.; Yoshikawa, S.; Akutagawa, S. *J. Chem. Soc., Chem. Commun.*, **1985**, 922-924. b) Kawano, H.; Ikariya, T.; Ishii, Y.; Saburi, M.; Yoshikawa, S.; Uchida, Y.; Kumobayashi, H. *J. Chem. Soc. Perkin Trans. 1*, **1989**, 1571-1575.
6. Enantiomer excess (ee) of the chiral products was determined by HPLC on a Daicel Chiralcel column eluted with hexane-isopropanol under the following conditions [type of column, solvent ratio (flow rate; ml/min) retention times (min) of *S*-isomer and *R*-isomer]. For **5a**; OD, 50 : 1 (0.5), 23.9 and 25.2. **5c**; OD, 50 : 1, (0.5), 29.8 and 31.8. **5d**; OD, 50 : 1 (0.6), 30.4 and 34.2. **5e**; OD, 40 : 1 (0.6), 21.4 and 17.6. **5f**; OJ, 25 : 1 (0.5), 18.7 and 30.7. **6a**; OD, 50 : 1 (0.5), 14.9 and 16.1. **6c**; OD, 100 : 1 (0.6), 31.7 and 34.6. **6f**; OJ, 100 : 1 (0.6), 17.6 and 23.2. The configurations of **5b** and **5g** were determined after conversion into benzoates.
7. a) Taber, D. F.; Silverberg, L. J. *Tetrahedron Lett.*, **1991**, *32*, 4227-4230. b) King, S. A.; Thompson, A. S.; King, A. O.; Verhoeven, T. R. *J. Org. Chem.*, **1992**, *57*, 6689-6691.
8. The (*R*)-**7** and (*S*)-**7** were purchased from Tokyo Kasei Kogyo Co. Ltd. and Sigma-Aldrich Japan K. K., respectively. For the transformation, see for example, a) Branca, Q.; Fischli, A. *Helv. Chim. Acta*, **1977**, *60*, 925-944. b) White, J. D.; Reddy, G. N.; Spessard, G. O. *J. Am. Chem. Soc.*, **1988**, *110*, 1624-1626.
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(*Received in Japan* 8 *November* 1996; *revised* 9 *December* 1996; *accepted* 16 *December* 1996)