Tetrahedron: Asymmetry Vol. 1, No. 1, pp. 1-4, 1990
Printed in Great Britain

0957-4166/90 $3.00+.00

Dynamic Kinetic Resolution in BINAP—Ruthenium(II) Catalyzed Hydrogenation of 2-Substituted 3-Oxo Carboxylic Esters

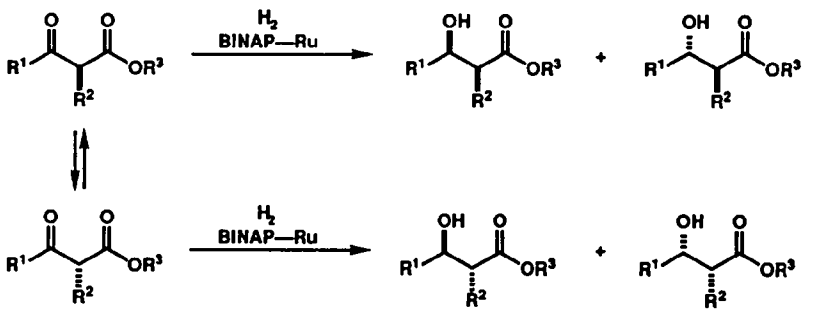
M. Kitamura, T. Ohkuma, M. Tokunaga, and R. Noyori*

Department of Chemistry, Nagoya University, Chikusa, Nagoya 464, Japan

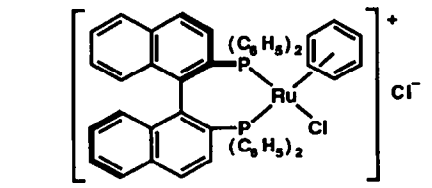
(*Received* 3 *November* 1989)

Abstract: BINAP—Ru catalyzed hydrogenation allows efficient dynamic kinetic resolution of certain 2-substituted 3-oxo carboxylic esters having cyclic structures to lead to the alcoholic products in high enantiomeric and diastereomeric excesses.

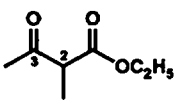
Kinetic resolution is a process in which one of the enantiomeric constituents of a racemate is more readily transformed into a product than is the other.[1] In ordinary kinetic resolution processes, the maximum yield of one enantiomer is 50% and the enantiomeric excess (ee) is affected by the extent of conversion. However, racemic compounds possessing a chirally labile stereogenic center, under certain conditions, may be converted to one major stereoisomer, where the chemical yield can be 100% and the ee is independent of conversion. Thus asymmetric hydrogenation of 2-substituted 3-oxo carboxylic esters provides an opportunity to obtain one stereoisomer among four possible isomers in a diastereo- and enantioselective manner. We here disclose stereoselective reaction of some cyclic substrates using BINAP—Ru(II) catalysts.[2]



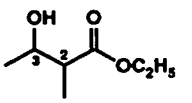
A systematic study, as summarized in Table I, has revealed that the steric course of hydrogenation of chiral oxo esters catalyzed by [RuCl(C_6H_6)(*R*)-binap)]Cl (**1**)[3] is markedly influenced by the structures of the substrates and reaction conditions including the choice of solvents. Formation of hydroxy ester **3** from the simple 2-alkylated substrate **2** is highly enantioselective but not diastereoselective regardless of the substrate conversion (entry 1 and 2).[4] Use of cyclic substrates, however, results in satisfactory diastereoselectivity, where annulation of the ester directive group and ketone moiety[5] provides equally distinct, but opposite, diastereomeric bias. Thus, under the influence of a catalytic amount of **1** in methanol,[6] hydrogenation of racemic keto lactone **4** proceeded in 98:2 2,3-syn/anti selectivity to form (2*S*,3*R*)-**5** (94% ee) and (2*R*,3*R*)-**5**



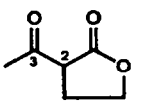
1



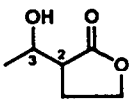
2



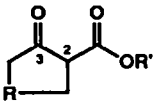
3



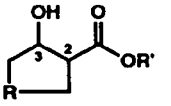
4



5



6



7

a, R = CH_2; R' = CH_3
b, R = $(CH_2)_2$; R' = C_2H_5
c, R = $(CH_3)_3$; R' = CH_3

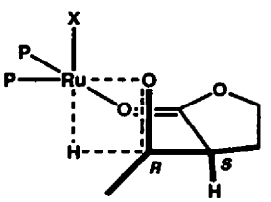
Table I. Stereoselective Hydrogenation of 2-Substituted 3-Oxo Carboxylic Esters[a]

			product,[b] % yield[c]			
			syn		anti	
entry	substrate	solvent	2*S*,3*R*	2*R*,3*S*	2*R*,3*R*	2*S*,3*S*
1	**2**	CH_2Cl_2	29.9[d]	2.2[d]	65.9[d]	2.0[d]
2	**2**	C_2H_5OH	49.9[d]	0.8[d]	48.9[d]	0.4[d]
3	**4**	CH_3OH	94.5[e]	3.2[e]	1.8[d]	0.5[d]
4	**6a**	CH_2Cl_2	1.35[f]	0.05[f]	94.5[g]	4.1[g]
5	**6a**	CH_3OH	18.4[f]	0.1[f]	76.7[g]	4.8[g]
6	**6b**	CH_2Cl_2	3.7[f]	1.4[f]	90.2[h]	4.7[h]
7	**6b**	C_2H_5OH	47.1[f]	1.5[f]	48.4[h]	3.0[h]
8	**6c**	CH_2Cl_2	5.5[f]	1.7[f]	89.5[i]	3.3[i]

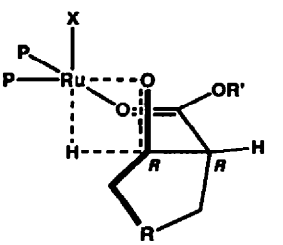
[a] Reactions were carried out in a 0.6—1.6 M solution of the substrate (1.9—4.6 mmol) under 100 atm of hydrogen at 50 °C for 60—80 h in the presence of 0.08—0.18 mol% of [RuCl(C_6H_6)((*R*)-binap)]Cl. Conversion was 100%. [b] Hydroxy ester numbering. [c] Combination of GLC analysis of the hydrogenation product and HPLC analysis of the (*R*)-MTPA ester or the *N*-[(*R*)-(1-naphthyl)ethylcarbamates. [d] A 91:9 mixture of (2*R*,3*R*)- and (2*S*,3*R*)-3 and methyl (2*S*,3*S*)-3-hydroxy-2-allylbutanoate were prepared by the known method [Fráter, G.; Müller, U.; Günther, W. *Tetrahedron* **1984**, *40*, 1269]. The latter was converted in 50% yield to (2*S*,3*S*)-5 (ozonolysis and $NaBH_4$ reduction). These (*R*)-MTPA esters were used for the peak assignment in the HPLC analysis. [e] HPLC analysis of the (*R*)-MTPA esters derived from a 26:74 mixture of the 2,3-syn and -anti products which was prepared by epimerization of (2*S*,3*S*)-5 (2 equiv LDA, H_2O). [f] HPLC analysis of the (*R*)-MTPA esters formed from an 11:89—21:79 mixture of the 2,3-syn and -anti isomers which was prepared from the hydrogenation product (1 equiv $NaOCH_3$ or $NaOC_2H_5$). [g] Rotation of *trans*-2-hydroxymethylcyclopentanol obtained by $LiAlH_4$ reduction of the hydrogenation product (synthetic, $[\alpha]_D^{25}$ −38.6° (*c* 1.28, CH_3OH); lit.[7] $[\alpha]_D^{20}$ +42.2° (*c* 0.37, CH_3OH) for the 1*S*,2*R* isomer in >99% ee). [h] Rotation of the hydrogenation product ($[\alpha]_D^{29}$ −47.3° (*c* 0.52, ether); lit.[7] $[\alpha]_D^{20}$ +58° (*c* 0.5, ether) for 1*S*,2*S* isomer). [i] ^{1}H-NMR analysis of the (*R*)-MTPA ester (see ref 11b).

(60% ee) (hydroxy ester numbering, entry 3). By contrast, reaction of racemic cyclic ketone of type **6** in dichloromethane containing the same catalyst proceeded with consistently high (up to 99:1) 2,3-anti selectivity to give the trans products [(2*R*,3*R*)-7] in excellent ee's (entry 4, 6 and 8).[7] For instance, hydrogenation of **6a** in dichloromethane afforded (1*R*,2*R*)-2-methoxycarbonylcyclopentan-1-ol in 92% ee and in 99% yield. In the reaction of **6**, the diastereoselectivity is decreased to some extent by increasing the ring size and by replacing the dichloromethane solvent by alcohols (entry 5 and 7), while ee's of the major products remain unchanged. These results obtained with the chiral substrates agree with the general sense of enantioselective hydrogenation of prochiral 3-oxo carboxylic esters.[4]

Thus ideal dynamic kinetic resolution[7,8] of 3-oxo carboxylic esters has been accomplished, because: (1) racemization of the substrates is sufficiently faster than hydrogenation, (2) stereochemical control by chiral BINAP—Ru catalyst is efficient, and (3) the cyclic structures of the substrates differentiate clearly between the syn and anti transition states. Chirality of the BINAP ligand is controlling the facial selectivity at the carbonyl function, whereas the cyclic constraints in the substrates determine the relative reactivities of the enantiomeric substrates. Overall, one of four possible diastereomeric transition states is selected, to realize a high level of enantio- and diastereoselective formation of the 2-substituted 3-hydroxy esters. The sterically restricted transition states leading to the major stereoisomers are visualized in structures **8** and **9**.

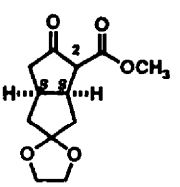


8

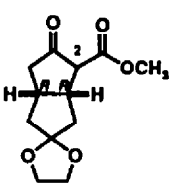


9

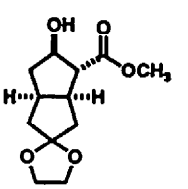
P—P = (*R*)-BINAP
X = Cl, H, H_2, or solvent



(*S*,*S*)-**10**



(*R*,*R*)-**10**



11

The bicyclic substrate **10**[9] contains one chirally labile and two stable stereogenic centers. When the racemate was subjected to hydrogenation using 0.36 mol% of the Ru catalyst **1** (100 atm, CH_2Cl_2, 50 °C, 42 h), the (*S*,*S*)-**10** was consumed at substantially higher rate than (*R*,*R*)-**10** and alcoholic product **11** among eight possible stereoisomers was obtained in 86% ee and in 32% yield.[10] Thus the 2*R* isomer of (*S*,*S*)-**10** appears to be hydrogenated preferentially from the convex face of the bicyclo[3.3.0]octane skeleton by way of the

transition state of type **9**. The product **11** serves as a chiral building block[11] for the synthesis of carbacyclins, stable analogues of prostacyclin.[12]

References and Notes

1. Review: Kagan, H. B.; Fiaud, J. C. *Top. Stereochem.* **1988**, *18*, 249.
2. Noyori, R. *Chem. Soc. Rev.* **1989**, *18*, 187.
3. Mashima, K.; Kusano, K.; Ohta, T.; Noyori, R.; Takaya, H., *J. Chem. Soc., Chem. Commun.* **1989**, 1208.
4. Noyori, R.; Ohkuma, T.; Kitamura, M.; Takaya, H.; Sayo, N.; Kumobayashi, H.; Akutagawa, S. *J. Am. Chem. Soc.* **1987**, *109*, 5856.
5. Sayo, N.; Saito, T.; Taketomi, T.; Kumobayashi, H.; Akutagawa, S.; Takaya, H.; Ikeda, T.; Ohkuma, T.; Widhalm, M.; Kitamura, M.; Noyori, R. *J. Am. Chem. Soc.*, submitted for publication.
6. Reaction was very slow in dichloromethane.
7. Buisson, D.; Azerad, R. *Tetrahedron Lett.* **1986**, *27*, 2631.
8. Biological: Fülling, G.; Sih, C. J. *J. Am. Chem. Soc.* **1987**, *109*, 2845. Buisson, D.; Sanner, C.; Larcheveque, M; Azerad, R. *Tetrahedron Lett.* **1987**, *28*, 3939. Buisson, D.; Henrot, S.; Larcheveque, M.; Azerad, R. *Tetrahedron Lett.* **1987**, *28*, 5033. Nakamura, K; Miyai, T.; Nozaki, K.; Ushio, K.; Oka, S.; Ohno, A. *Ibid.* **1986**, *27*, 3155. Yamada, H.; Shimizu, S.; Shimada, H.; Tani, Y.; Takahashi, S.; Ohashi, T. *Biochimie* **1980**, *62*, 395. Chemical: Hayashi, T.; Kanehira, K.; Hioki, T.; Kumada, M. *Tetrahedron Lett.* **1981**, *22*, 137.
9. A mixture of the epimers at C-2.
10. The relative and absolute configuration of **11** was confirmed by comparison of the ^{1}H NMR spectrum and optical rotaion value reported in ref 11a (synthetic: $[\alpha]_D^{28}$ +22.5° (*c* 0.46, chloroform); lit. $[\alpha]_D^{23}$ –27° (*c* 0.5, chloroform) for 1*R*,2*S*,3*S*,5*S* isomer). The ee value of **11** was determined by HPLC analysis of the (*R*)-MTPA ester (column, YMC 003-3 SIL (4.6 mm x 25 cm) and 002-3 SIL (4.6 mm x 15 cm); flow rate, 1 mL/min; eluent, 2:3 ether—hexane mixture; detection, 254-nm light; t_R of 1*S*,2*R*,3*R*,5*R* isomer, 23.0 min, t_R of 1*R*,2*S*,3*S*,5*S* isomer, 24.9 min). The recovered (*R*,*R*)-**10** (25% yield) was converted to the corresponding **11** by the known method[11e] and then the ee value was determined to be 65% ee. Several other products including 3,3,7,7-bisdiethylenedioxybicyclo[3.3.0]octane (15%) and 7,7-diethylenedioxy-3-oxobicyclo[3.3.0]octane (12%) were obtained under such conditions.
11. (a) Brooks, D. W.; Wilson, M.; Webb, M. *J. Org. Chem.* **1987**, *52*, 2244. (b) Xie, Z.-F.; Suemune, H.; Sakai, K. *J. Chem. Soc., Chem. Commun.* **1987**, 838. (c) Barco, A.; Benetti, S.; Pollini, G. P.; Baraldi, P. G.; Gandolfi, C. *J. Org. Chem.* **1980**, *45*, 4776. (d) Shibasaki, M.; Ueda, J.; Ikegami, S. *Tetrahedron Lett.* **1979**, 433. (e) Nicolaou, K. C.; Sipio, W. J.; Magolda, R. L. *J. Chem. Soc., Chem. Commun.* **1978**, 1067. (f) Kojima, K.; Sakai, K. *Tetrahedron Lett.* **1978**, 3743.
12. Reviews: Aristoff, P. A. in *Advances in Prostaglandin, Thromboxane, and Leukotriene Research*, Pike, J. E.; Morton, D. R. Jr., Eds.; Raven Press: New York, 1985; Vol 14. Bartmann, W.; Beck, G. *Angew. Chem., Int. Ed. Engl.* **1982**, *21*, 751. Ikegami, S.; Shibasaki, M. *J. Syn. Org. Chem. Jpn.* **1980**, *38* 1037. Mongelli, N.; Andreoni, A.; Faustini, F.; Gandolfi, C. In *Advances in Pharmacological Research and Practice, Prostanoids*; Kecskeméti, V., Ed.; Pergamon Press: Oxford, 1980; Vol 6.