Tetrahedron Letters, Vol.32, No.34, pp 4227-4230, 1991
Printed in Great Britain

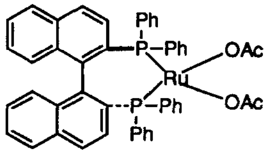
0040-4039/91 $3.00 + .00
Pergamon Press plc

ENANTIOSELECTIVE REDUCTION OF β-KETO ESTERS

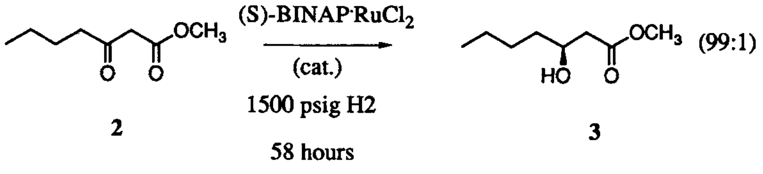
Douglass F. Taber* and Lee J. Silverberg
Department of Chemistry & Biochemistry, University of Delaware, Newark, DE 19716 USA

Summary: Highly enantioselective reduction of β-keto esters with BINAP·Ru catalyst can be effected at 50 psig H_2 and 80°, using a Parr shaker. A simplified preparation of the BINAP·Ru catalyst is reported.

In 1987 the Nagoya and Takasago groups, working in collaboration, reported [1,2] that a catalyst prepared by treating BINAP ruthenium diacetate **1** with methanolic HCl would effect the hydrogenation of a β-keto ester **2** to the corresponding alcohol **3** with excellent turnover and stunning enantioselectivity (99:1).



1

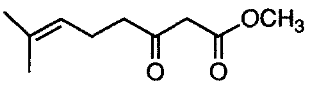
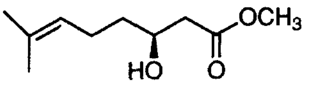
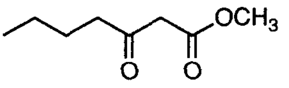
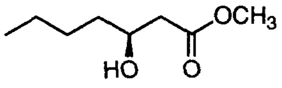
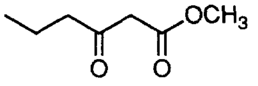
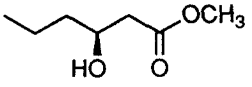
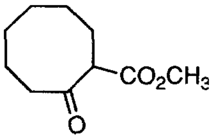
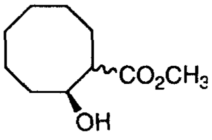
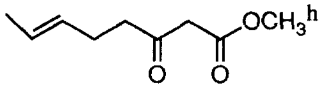
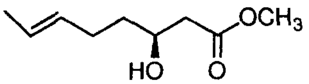


2 **3**

In the more than three years since the initial publication, only two[3] other research groups have reported the use of this procedure in a target-directed synthesis. The reasons for this are easy to understand. Ruthenium complex **1** must be prepared (three steps) and stored under controlled atmosphere conditions (Schlenkware or glove box). Further, the hydrogenation is carried out at 1500 psig, a pressure not routinely available to the organic synthesis chemist.

We have found that the direct product from combination of commercially available BINAP and $(RuCl_2\cdot cyclooctadiene)_n$ in the presence of triethylamine [1,3] is a very active catalyst that shows good selectivity in the hydrogenation. This observation makes it possible to carry out these hydrogenations without purifying $BINAP\cdot RuCl_2]_2\cdot Et_3N$ and $BINAP\cdot Ru(OAc)_2$, two very air sensitive substances.[4]

Table 1. Enantioselective Hydrogenation of Selected β-Keto Esters

Starting Ester[a]	Method[b]	Product[c]	Yield, %[d,e]	e.e.,%
 **4**	A	 **5**	96	98[f]
 **6**	B	 **7**	90	97[f]
 **8**	B	 **9**	86	98[f]
 **10**	B	 **11**	80[g]	96[f]
 **12**	A	 **13**	73	98[i]

a). All β-keto esters, except for **12**, were prepared by carbomethoxylation of the corresponding ketones (NaH, methyl carbonate), and were purified by distillation. b). See text for hydrogenation procedures c). The absolute stereochemistry of **5**, **7**, and **9** was established by correlation with material prepared following ref. 7. The other absolute configurations were assigned by analogy with these results, and with ref. 2b. d). Yields are for pure distilled materials. e). Each product was >95% pure by ^{13}C NMR, and gave ^{13}C NMR, ^{1}H NMR, IR, and MS consistent with the assigned structure. f). Enantiomeric excess determined by europium shift of methyl ester in ^{1}H NMR. g). Alcohol **11** was a 1:1 mixture of diastereomers. h). Prepared by alkylation of the dianion of methyl acetoacetate (ref. 8) with crotyl chloride. The hydrogenation was terminated after 30 min. i). Enantiomeric excess assigned by europium shift of the alcohol methine in the ^{13}C NMR.

We have also found that it is possible to effect ketone reduction without alkene hydrogenation. Under the high pressure conditions originally reported,[1,2] we observed that even the relatively unreactive trisubstituted alkene of **4** **(Table 1)** is *totally* reduced. As we lowered the hydrogen overpressure, an increasing fraction of the alkene survived. Concomitantly, the overall reaction slowed down. By raising the reaction temperature to 80°, we were able to regain reasonable reaction rates. Under the optimal conditions we have developed, 50 psig H_2, 80° (modified[5] Parr shaker), ester **4** is cleanly reduced to **5**, without alkene hydrogenation. Using this approach **(Table I, Method A)**, the turnover is somewhat lower than with the procedure originally reported.[1,2] Ruthenium catalyst derived from 40 mg of BINAP will reduce **(Table I, entry 1)** 5.2 grams of **4** to **5** in six hours, in 96% yield.

The catalyst originally reported was somewhat acidic. We found that by adding a little washed Dowex-50 resin to our reaction mixtures, we could increase catalyst turnover to the level originally reported. Thus, in the presence of washed Dowex-50 resin **(Table I, Method B)** ruthenium catalyst derived from 20 mg of BINAP will reduce five grams of **6** to **7** in six hours, in 90% yield. The alkene-containing β-keto ester **4** does not reduce cleanly under these more acidic conditions.

The disubstituted alkene of **12** is more reactive toward hydrogenation than the trisubstituted alkene of **4**. We were gratified to find that with Method B, but with a thirty minute reaction time, the conversion of **12** to **13** can be cleanly accomplished. In contrast, a terminal vinyl group (not shown) is reduced *more* rapidly than a ketone.

The key question was whether reducing the hydrogen overpressure and raising the reaction temperature had eroded the enantioselectivity of the reduction. In fact **(Table I)**, we find that enantioselectivity is fully maintained. We have prepared β-hydroxy esters both by this procedure, and by that originally described.[1,2] Analyzing the alcohols by ^1H and ^{13}C NMR, using enantiomerically pure shift reagents, we could see *no* difference in enantiomer ratios between the two sets of products.

It is clear that the substantial hydrogen overpressure reported by the original authors [1,2] is not critical for high enantioselectivity in the reduction of a β-keto ester. Further, under the alternative conditions of reduced pressure but slightly elevated temperature, it becomes possible to effect ketone reduction while avoiding alkene hydrogenation. Especially coupled with the highly diastereoselective Frater alkylation,[6] Ru·BINAP-mediated hydrogenation should become a powerful method for the preparation of enantiomerically pure materials.

Catalyst Preparation: *All manipulations were carried out under an N_2 atmosphere.* Following a modification of the published procedures, [1-3] a 5 mL reactivial was charged with a stir vane, $(RuCl_2\cdot cyclooctadiene)_n$ (39 mg), S-(-)-2,2'-bis (diphenylphosphino)-1,1'-binaphthyl (100 mg), triethylamine (0.275 mL), and toluene (about 4 mL). The vial was capped securely, then heated in a 140° bath until the solution was a clear homogeneous red (2-4 h). The contents of the flask were transferred to a 100 mL round-bottom flask with toluene. The toluene was removed in vacuo, and the resulting red oil was taken up in THF. The brown THF suspension was divided into 5 x 2 mL portions, which were stored in stoppered vials under N_2.

Procedure A: Under N_2, a modified[5] Parr bottle was charged with methyl 3-oxo-7-methyl-6-octenoate (**4**, 6.0 g, 32.6 mmol), methanol (22.5 mL), and catalyst as prepared above (4 mL; from 40 mg BINAP). The resulting solution was clear dark green. Hydrogenation was carried out at 50 psig H_2 and 80° for 6 h. The solvent was removed, and the residue was distilled bulb-to-bulb (bath = 100°, 0.5 mm) to give 6.08 g of colorless oil. This oil (0.501 g) was chromatographed on silica gel to give recovered starting material (0.066 g) and product **5**, 0.414 g, 96% yield at 87% conversion.

Procedure B: Under N_2, the modified[5] Parr bottle was charged with methyl 3-oxo-heptanoate (**6**, 5.0 g, 35.2 mmol), methanol (20 mL), catalyst as prepared above (2 mL; from 20 mg BINAP), and Dowex-50 resin (350 mg; washed with water, methanol, diethyl ether, and methanol, then pressed to remove most of the methanol). Hydrogenation was carried out at 50 psig H_2 and 80° for 5.5 h. After cooling, the methanol solution was filtered through glass wool and concentated *in vacuo*. The residue was distilled bulb-to-bulb at 0.5 mm (bath = 85°) to give **7** as a colorless oil (4.57 g, 31.7 mmol, 90% yield from **6**).

Acknowledgments: This work was supported by the Center for Catalytic Science and Technology of the University of Delaware. We thank Professor Henry C. Foley for his assistance. D. F. T. thanks the Du Pont Central Research and Development Department for their hospitality during a sabbatical year.

References and Notes

(1) Noyori, R.; Ohkuma, T.; Kitamura, M.; Takaya, H.; Sayo, N.; Kumobayashi, H.; Akutagawa, S. *J. Am. Chem. Soc.* **1987**, *109*, 5856.

(2) (a) Kitamura, M.; Ohkuma, T.; Inoue, S.; Sayo, N.; Kumobayashi, H.; Akutagawa, S.; Ohta, T.; Takaya, H. and Noyori, R. *J. Am. Chem. Soc.* **1988**, *110*, 629. (b) Kitamura, M.; Ohkuma, T.; Takaya, H. and Noyori, R. *Tetrahedron Lett.* **1988**, *29*, 1555. (c) Nishi, T.; Kitamura, M.; Ohkuma, T. and Noyori, R. *Tetrahedron Lett.* **1988**, *29*, 6327. (d) Noyori, R.; Ikeda, T.; Ohkuma, T.; Widhalm, M.; Kitamura, M.; Takaya, H.; Akutagawa, S.; Sayo, N.; Saito, T.; Taketomi, T. and Kumobayashi, H. *J. Am. Chem. Soc.* **1989**, *111*, 9134.

(3) (a) Schreiber, S. L.; Kelly, S.E.; Porco, J. A., Jr.; Sammakia, T. and Suh, E.M. *J. Am. Chem. Soc.* **1988**, *110*, 6210. (b) Jones, B.A.; Yamaguchi, M.; Patten, A.; Danishefsky, S.J.; Ragan, J.A.; Smith, D.B. and Schreiber, S.L. *J. Org. Chem.* **1989**, *54*, 17. (c) Oppolzer, W.; Wills, M.; Starkmann, C. and Bernardinelli, G. *Tetrahedron Lett.* **1990**, *31*, 4117.

(4) It should be stressed that the *crystallized* product from the initial exchange, $\mathrm{BINAP{\cdot}RuCl_2)_2{\cdot}Et_3N}$, is *not* an effective hydrogenation catalyst.

(5) The Parr shaker bottle was modified by replacing the rubber stopper (not compatible with Ru) with a 24/40 female joint having an outside thread, into which was inserted a 24/40 male straight gas inlet tube having a threaded plastic retaining ring. Complete sets are available from Douglas A. Nixon of this department. Heating mantles for Parr bottles are available from Fisher.

(6) (a) Frater, G. *Helv. Chim. Acta* **1979**, *62*, 2825. (b) Frater, G. *Helv. Chim. Acta* **1980**, *63*, 1383. (c) Frater, G. *Tetrahedron Lett.* **1981**, *22*, 425.

(7) Taber, D.F.; Deker, P.B.; Fales, H.M.; Jones, T.H.; Lloyd, H.A. *J. Org. Chem.* **1988**, *53*, 2968.

(8) Huckin, S.N.; Weiler, L. *J. Am. Chem. Soc.* **1974**, *96*, 1082.

(Received in USA 29 April 1991)