

Reviews:

Ager, D. J.; Laneman, S. A. *Tetrahedron: Asymmetry* **1997**, 8, 3327–3355.

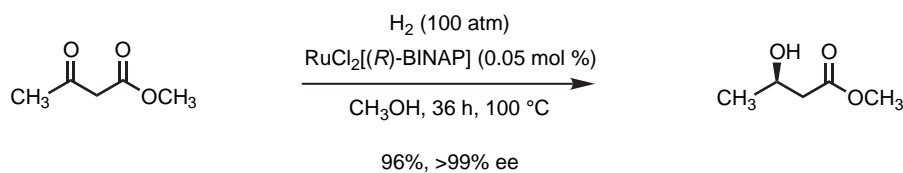
Noyori, R. *Acta. Chem. Scand.* **1996**, 50, 380–390.

Genet, J. P. In *Reductions in Organic Synthesis*, Abdel-Magid, A. F., Ed.; ACS Symposium Series, 641; American Chemical Society: Washington, D.C., **1996**, pp. 31–51.

Noyori, R. *Asymmetric Catalysis in Organic Synthesis*, John Wiley & Sons: New York, **1993**, pp. 56–82.

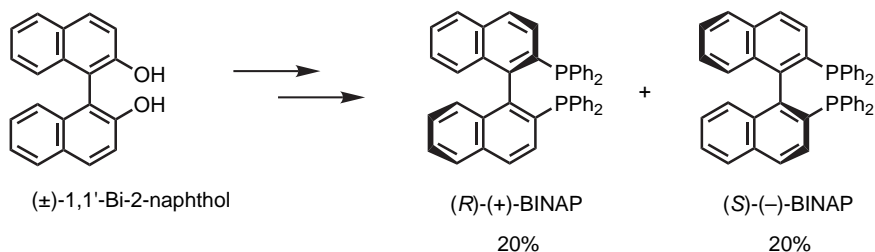
Noyori, R.; Tokunaga, M.; Kitamura, M. *Bull. Chem. Soc. Jpn.* **1995**, 68, 36–56.

Original Report:



Noyori, R., Okhuma, T.; Kitamura, M.; Takaya, H.; Sayo, N.; Kumobayashi, H.; Akuragawa, S. *J. Am. Chem. Soc.* **1987**, 109, 5856–5858.

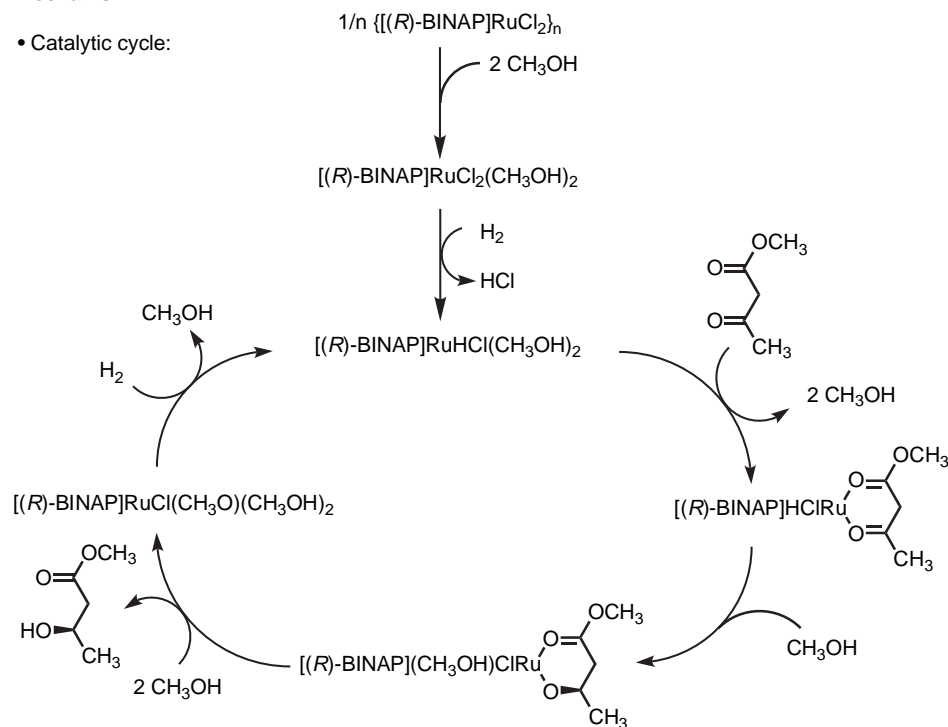
- Both enantiomers of BINAP are commercially available. Alternatively, both enantiomers can be prepared from the relatively inexpensive (\pm)-1,1'-bi-2-naphthol.



Takaya, H.; Akutagawa, S.; Noyori, R. *Org. Synth.* **1989**, 67, 20–32.

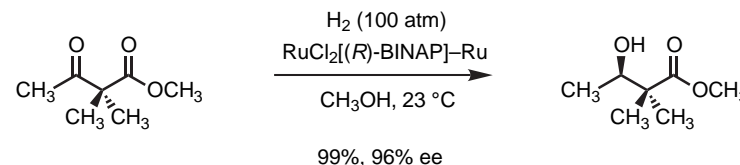
Mechanism:

- Catalytic cycle:



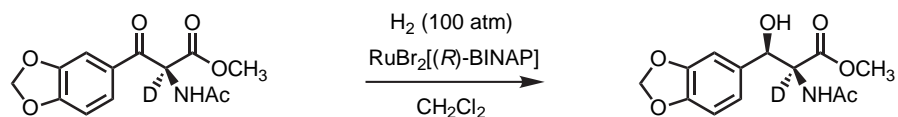
Noyori, R. *Asymmetric Catalysis in Organic Synthesis*, John Wiley & Sons: New York, **1993**, pp. 56–82.

- Evidence that the reduction proceeds through the keto form of the β -keto ester is the fact that the reduction of methyl 2,2-dimethyl-3-oxobutanoate occurs with high yield and high enantioselectivity. However, pathways that involve hydrogenation of the enol form of other β -keto esters cannot be ruled out.



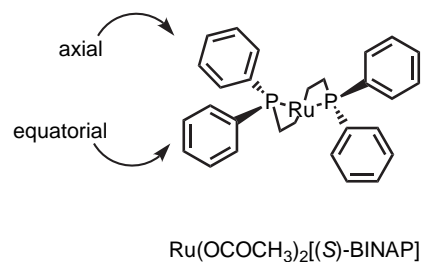
Noyori, R.; Takaya, H. *Acc. Chem. Res.* **1990**, 23, 345–350.

- The use of a deuterated substrate provides further evidence that the reduction proceeds through the keto tautomer. Enolization is rapid, so the deuterium is lost quickly. However, when the reaction was stopped at 1.3% conversion, the hydroxy ester product retained 80% of the deuterium at C-2, and no deuterium was incorporated at C-3.



Noyori, R.; Ikeda, T.; Okhuma, T.; Widhalm, M.; Kitamura, M.; Takaya, H.; Akutagawa, S.; Sayo, N.; Saito, T.; Taketomi, T.; Kumobayashi, H. *J. Am. Chem. Soc.* **1989**, *111*, 9134–9135.

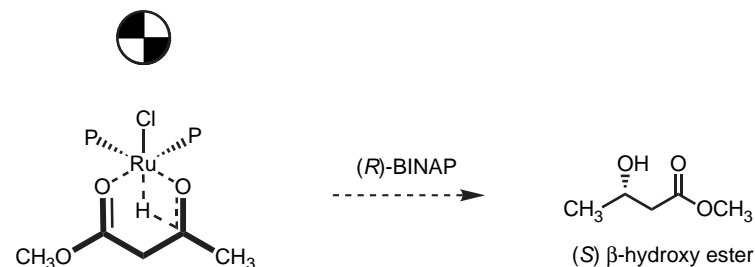
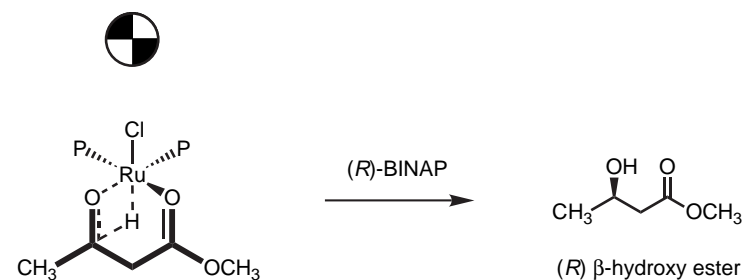
- A crystal structure of $\text{Ru}(\text{OCOCH}_3)_2[(S)\text{-BINAP}]$ revealed that the rigid BINAP backbone forces the phenyl rings attached to phosphorous to adopt the conformation depicted here (the naphthyl rings are omitted for clarity).



- The two protruding equatorial *P*-phenyl groups allow a coordinating ligand access to only two quadrants on the accessible face of Ru (the other face is blocked by BINAP's naphthyl rings). This situation is represented by a circle with two black quadrants where no coordination can occur.

Ohta, T.; Takaya, H.; Noyori, R. *Inorg. Chem.* **1988**, *27*, 566–569.

- Of the two possible diastereomeric transition states for complexes with (*R*)-BINAP shown below, the one leading to the (*R*) β-hydroxy ester allows the approach of the ketone at an unhindered quadrant (as represented by the light lower left quadrant of the circle).



Noyori, R.; Tokunaga, M.; Kitamura, M. *Bull. Chem. Soc. Jpn.* **1995**, *68*, 36–56.

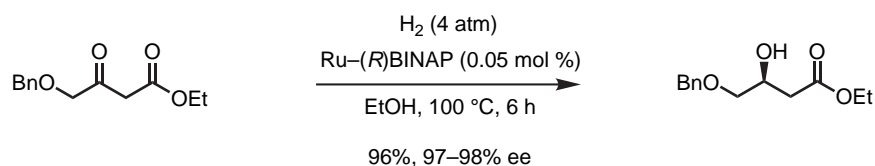
Reaction Conditions:

- Noyori has published conditions to prepare the active Ru-BINAP catalyst in one step from commercially available $[\text{RuCl}_2(\text{benzene})_2]_2$, and it can be used without a purification step. Also, the reaction can be run at 4 atm/100 °C or 100 atm/23 °C.

Note: 1 atm = 14.7 psi

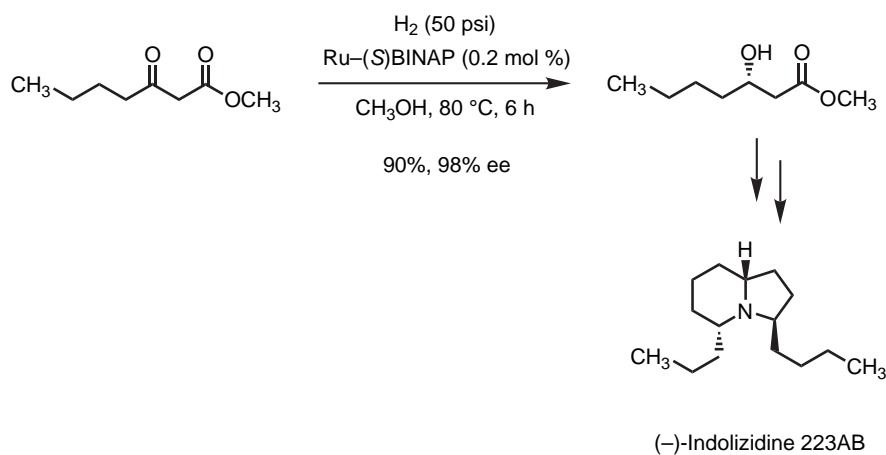
Kitamura, M.; Tokunaga, M.; Okhuma, T.; Noyori, R. *Org. Synth.* **1993**, *71*, 1–13.

- This in situ procedure of catalyst generation was found to be much more reliable. Also, reactions with this catalyst were more enantioselective and required less catalyst. The following reaction was done on a 10 kg scale. Note the benzyl group is not removed.



Beck, G.; Jendralla, H.; Kessler, K. *Synthesis* **1995**, 1014–1018.

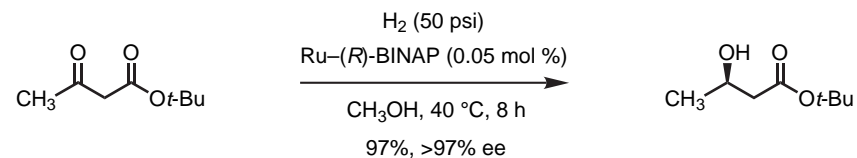
- A simplified, milder set of conditions that also features a catalyst available in one step from commercially available BINAP and RuCl₂•cyclooctadiene has been published. The reaction proceeds at a sufficiently low H₂ pressure (50 psi) to avoid reduction of trisubstituted olefins, but not terminal olefins.



Taber, D. F.; Silverberg, L. J. *Tetrahedron Lett.* **1991**, 32, 4227–4230.

Taber, D. F.; Dekker, P. B.; Silverberg, L. J. *J. Org. Chem.* **1992**, 57, 5990–5994.

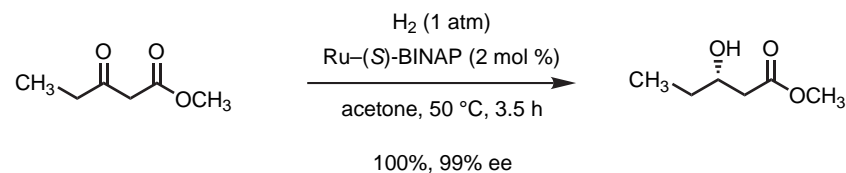
- These conditions have been improved on even further, with milder reaction conditions and lower catalyst loadings.



- The authors present kinetic data to show the dramatic increase in reaction rate that occurs in the presence of a catalytic amount of strong acid, and they suggest that failed reactions may result from low levels of basic impurities. Note that the acid-sensitive *t*-Bu ester is not cleaved under these conditions.

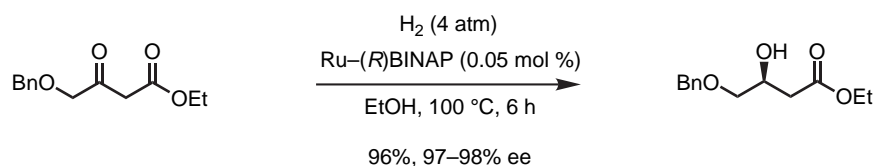
King, S. A.; Thompson, A. S.; King, A. O.; Verhoeven, T. R. *J. Org. Chem.* **1992**, 57, 6689–6691.

- Reduction of β -keto esters has been achieved at 1 atm of hydrogen using a catalyst prepared in situ from BINAP, (COD)Ru(2-methylallyl)₂, and HBr, all of which are commercially available. No special reaction apparatus is necessary for this procedure; however, the catalyst loading is unusually high.



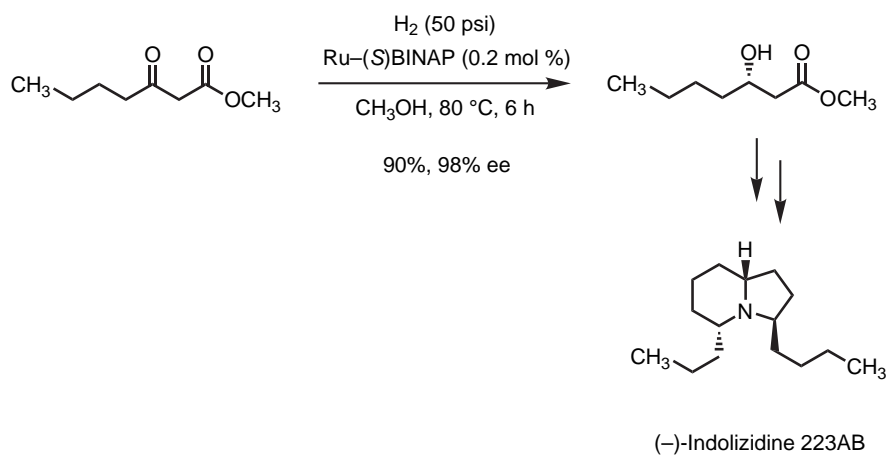
Genet, J. P.; Ratovelomanana-Vidal, V.; Caño de Andrade, M. C.; Pfister, X.; Guerreiro, P.; Lenoir, J. Y. *Tetrahedron Lett.* **1995**, 36, 4801–4804.

- This in situ procedure of catalyst generation was found to be much more reliable. Also, reactions with this catalyst were more enantioselective and required less catalyst. The following reaction was done on a 10 kg scale. Note the benzyl group is not removed.



Beck, G.; Jendralla, H.; Kessler, K. *Synthesis* **1995**, 1014–1018.

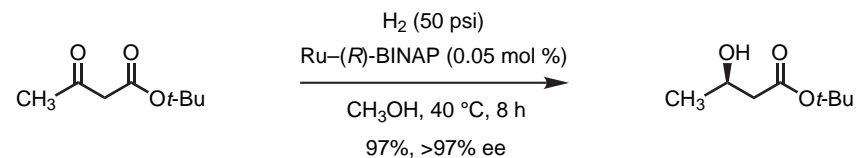
- A simplified, milder set of conditions that also features a catalyst available in one step from commercially available BINAP and $\text{RuCl}_2 \cdot \text{cyclooctadiene}$ has been published. The reaction proceeds at a sufficiently low H_2 pressure (50 psi) to avoid reduction of trisubstituted olefins, but not terminal olefins.



Taber, D. F.; Silverberg, L. J. *Tetrahedron Lett.* **1991**, 32, 4227–4230.

Taber, D. F.; Deker, P. B.; Silverberg, L. J. *J. Org. Chem.* **1992**, 57, 5990–5994.

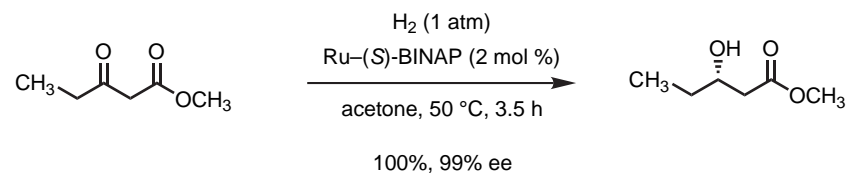
- These conditions have been improved on even further, with milder reaction conditions and lower catalyst loadings.



- The authors present kinetic data to show the dramatic increase in reaction rate that occurs in the presence of a catalytic amount of strong acid, and they suggest that failed reactions may result from low levels of basic impurities. Note that the acid-sensitive *t*-Bu ester is not cleaved under these conditions.

King, S. A.; Thompson, A. S.; King, A. O.; Verhoeven, T. R. *J. Org. Chem.* **1992**, 57, 6689–6691.

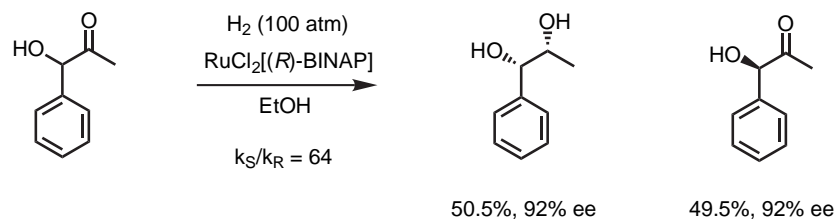
- Reduction of β -keto esters has been achieved at 1 atm of hydrogen using a catalyst prepared in situ from BINAP, $(\text{COD})\text{Ru}(2\text{-methylallyl})_2$, and HBr, all of which are commercially available. No special reaction apparatus is necessary for this procedure; however, the catalyst loading is unusually high.



Genet, J. P.; Ratovelomanana-Vidal, V.; Caño de Andrade, M. C.; Pfister, X.; Guerreiro, P.; Lenoir, J. Y. *Tetrahedron Lett.* **1995**, 36, 4801–4804.

Dynamic Kinetic Resolution:

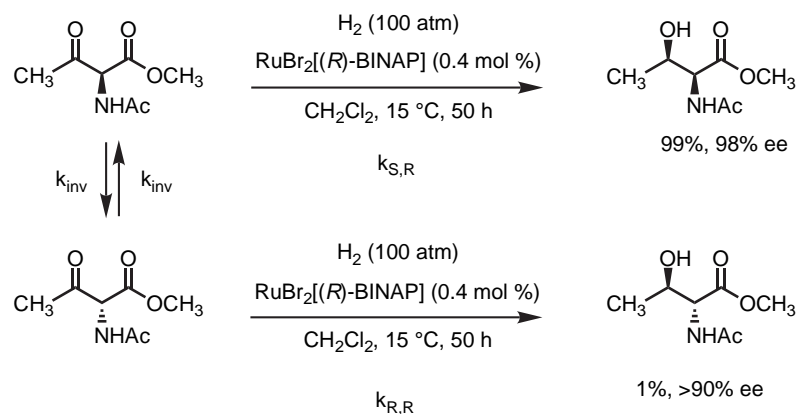
- Kinetic resolution of enantiomers occurs when the chiral catalyst reacts with one enantiomer much more rapidly than the other.



- An inherent drawback to kinetic resolution is the fact that the maximum yield is 50% of enantiopure material.

Noyori, R. *Asymmetric Catalysis in Organic Synthesis*, John Wiley & Sons: New York, **1993**, pp. 56–82.

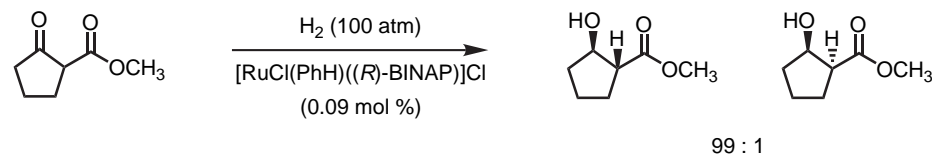
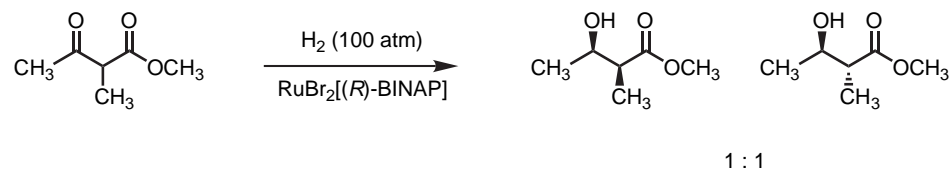
- If the initially present stereocenter can be epimerized under the reaction conditions, i.e., the enantiomer that does not react can be transformed into the one that does react, then the theoretical yield is 100%. This is a dynamic kinetic resolution.



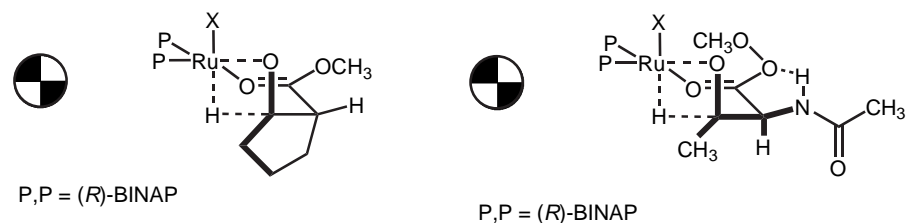
- For yields approaching 100% of the desired enantiomer, rapid isomerization between the two enantiomeric β -keto esters must occur ($k_{inv} > k_{S,R}$ and $k_{R,R}$).

Noyori, R.; Ikeda, T.; Okhuma, T.; Widhalm, M.; Kitamura, M.; Takaya, H.; Akutagawa, S.; Sayo, N.; Saito, T.; Taketomi, T.; Kumobayashi, H. *J. Am. Chem. Soc.* **1989**, *111*, 9134–9135.

- The stereochemistry of the secondary alcohol is determined by the choice of catalyst, but the stereochemistry at the α -position is substrate dependent.



- The preference for one diastereomer over the other can be rationalized by examining the likely transition states for carbonyl reduction. If the reduction of the α -amino compound is carried out in methanol instead of dichloromethane, the diastereoselectivity drops from 99 : 1 to 82 : 18.



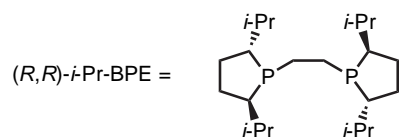
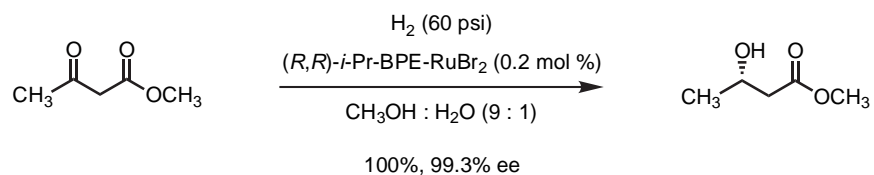
Noyori, R.; Ikeda, T.; Okhuma, T.; Widhalm, M.; Kitamura, M.; Takaya, H.; Akutagawa, S.; Sayo, N.; Saito, T.; Taketomi, T.; Kumobayashi, H. *J. Am. Chem. Soc.* **1989**, *111*, 9134–9135.

- A detailed mathematical model of the dynamic kinetic resolution process has been published.

Kitamura, M.; Tokunaga, M.; Noyori, R. *J. Am. Chem. Soc.* **1993**, *115*, 144–152.

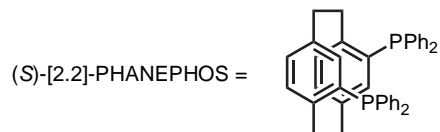
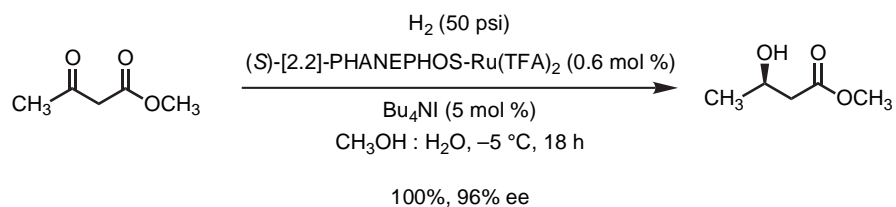
Other Ligands:

- Burk's 1,2-bis(*trans*-2,5-diisopropylphospholano)ethane (*i*-Pr-BPE) is a useful ligand for the reduction of many β -keto esters, and the reaction conditions are milder than those originally reported by Noyori.



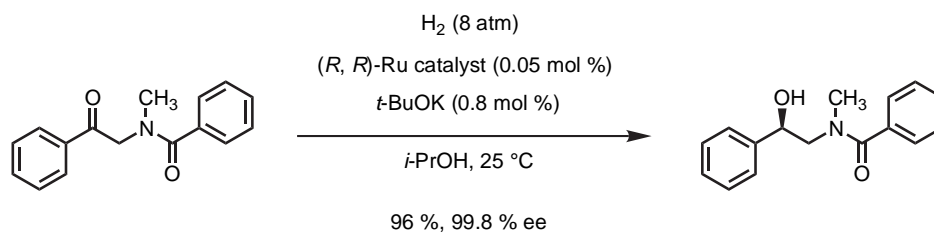
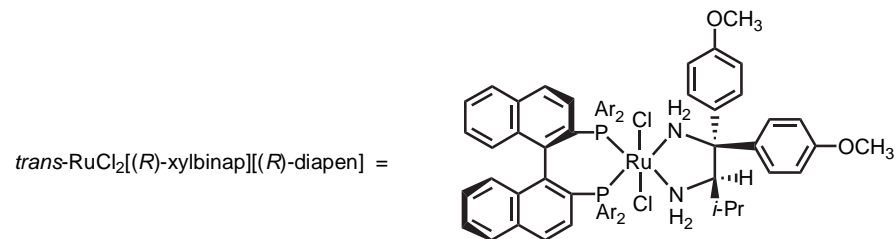
Burk, M. J.; Harper, T. G. P.; Kalberg, C. S. *J. Am. Chem. Soc.* **1995**, *117*, 4423–4424.

- Using the novel [2.2]-PHANEPHOS ligand, extremely mild, neutral conditions for the reduction of β -keto esters have been developed.

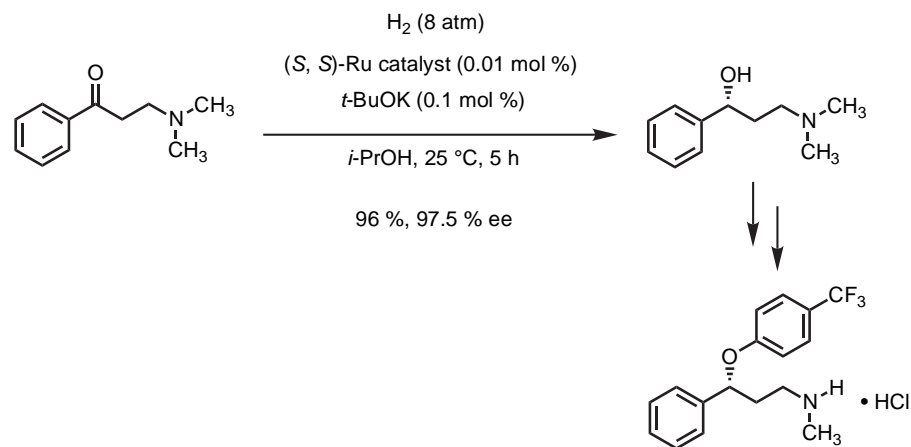


Pye, P. J.; Rossen, K.; Reamer, R. A.; Volante, R. P.; Reider, P. J. *Tetrahedron Lett.* **1998**, *39*, 4441–4444.

- Noyori has discovered a Ru-based catalyst, *trans*-RuCl₂[(*R*)-xylbinap][(*R*)-diapen], that efficiently reduces α -, β -, and γ -amino ketones in a highly enantioselective fashion under mild conditions.



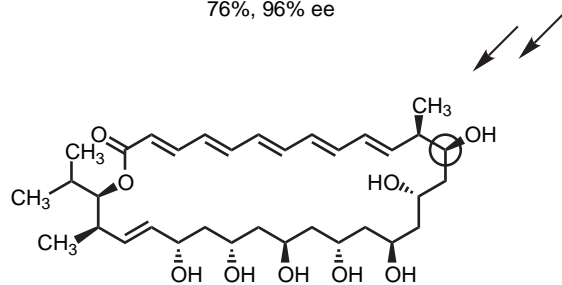
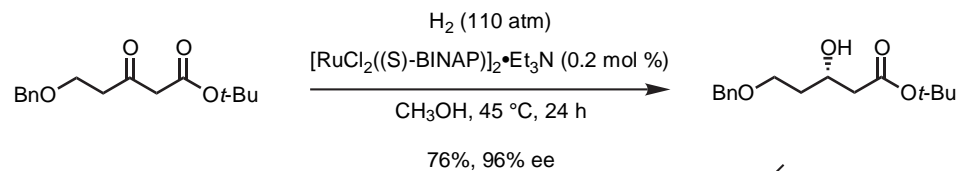
- The mechanism of this reduction differs from the Ru-BINAP catalyst in that the adjacent nitrogen is believed not to ligate to the Ru center.
- This method allows for a practical synthesis of the antidepressant (*R*)-fluoxetine without the need for any chromatographic separations.



Ohkuma, T.; Ishii, D.; Takeno, H.; Noyori, R. *J. Am. Chem. Soc.* **2000**, *122*, 6510–6511.

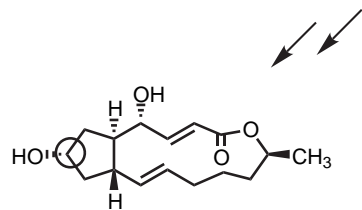
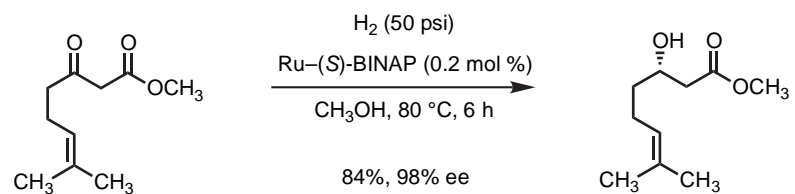
Examples in Total Synthesis:

- In all of the examples, the carbonyl carbon that is initially reduced is circled in the final product.



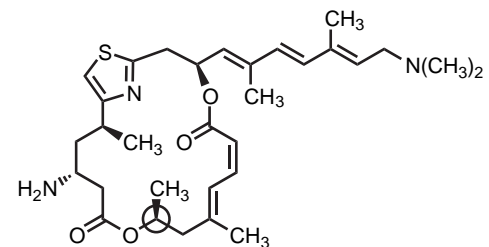
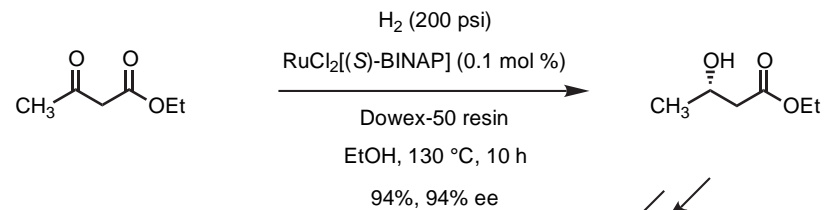
(-)-Roxaticin

Rychnovsky, S. D.; Hoye, R. C. *J. Am. Chem. Soc.* **1994**, *116*, 1753–1765.



(+)-Brefeldin A

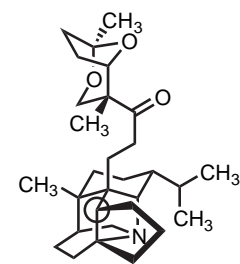
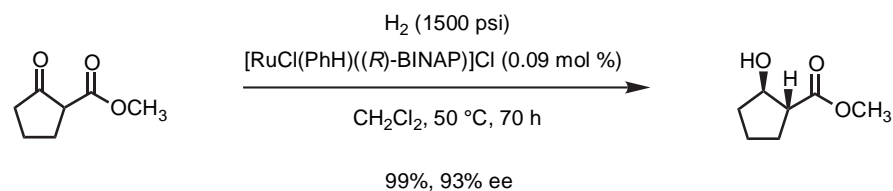
Taber, D. F.; Silverberg, L. J.; Robinson, E. D. *J. Am. Chem. Soc.* **1991**, *113*, 6639–6645.



Pateamine A

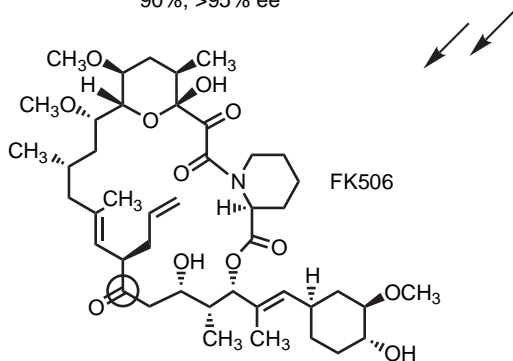
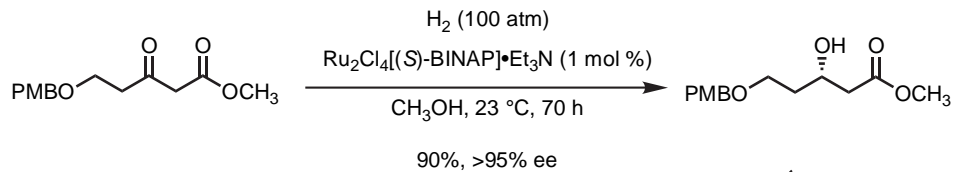
Romo, D.; Rzasa, R. M.; Shea, H. A.; Park, K.; Langenhan, J. M.; Sun, L.; Akhiezer, A.;

Liu, J. O. *J. Am. Chem. Soc.* **1998**, *120*, 12237–12254.

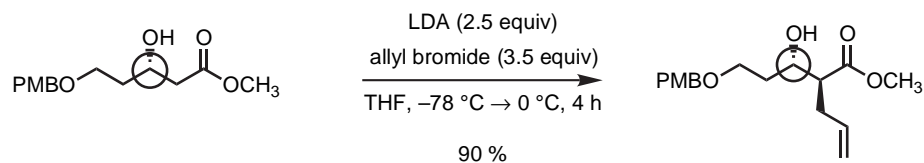


(+)-Codaphniphylline

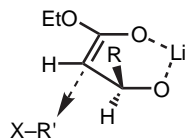
Heathcock, C. H.; Kath, J. C.; Ruggeri, R. B. *J. Org. Chem.* **1995**, *60*, 1120–1130.



- Although the chirality of the β -hydroxy ester is lost in the final product, it is used to set two other stereocenters.



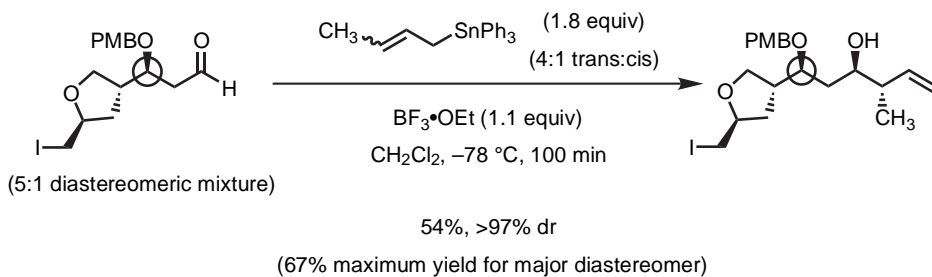
- Chelation control and steric shielding explain the high diastereoselectivity of the allylation reaction.



(from the work of Fráter and Seebach)

Fráter, G.; Müller, U.; Günther, W. *Tetrahedron* **1984**, *40*, 1269–1277.

Seebach, D.; Aebi, J.; Wasmuth, D. *Org. Synth.* **1984**, *63*, 109–120.



Nakatsuka, M.; Ragan, J. A.; Sammakia, T.; Smith, D. B.; Uehling, D. E.; Schreiber, S. L. *J. Am. Chem. Soc.* **1990**, *112*, 5583–5601.