Reviews:

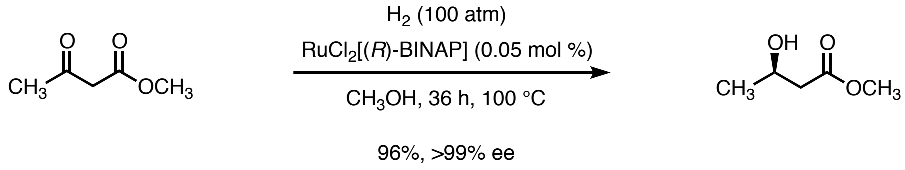
Noyori, R. *Angew. Chem. Int. Ed.* **2013**, *52*, 79–92.

Kitamura, M.; Nakatsuka, H. *Chem. Commun.* **2011**, *47*, 842–846.

Tang, W.; Zhang, X. *Chem. Rev.* **2003**, *103*, 3029–3069.

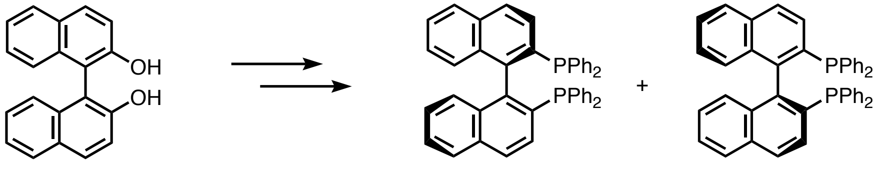
Noyori, R.; Ohkuma, T. *Angew. Chem. Int. Ed.* **2001**, *40*, 40–73.

Original Report by the Noyori Group:



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 (±)-1,1'-bi-2-naphthol.



(±)-1,1'-Bi-2-naphthol

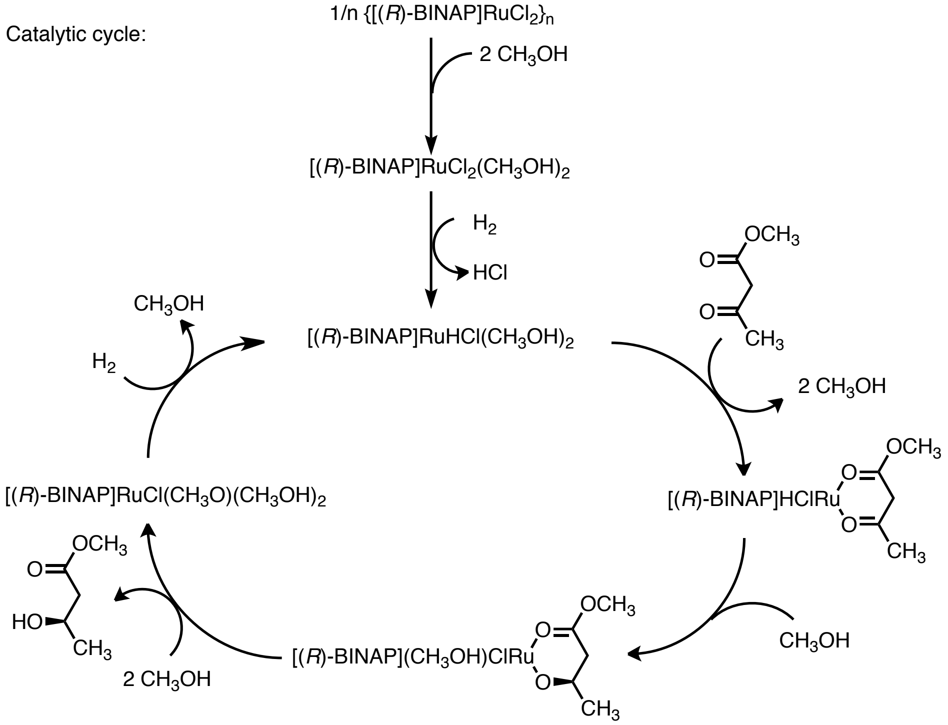
(*R*)-(+)-BINAP
20%

(*S*)-(–)-BINAP
20%

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

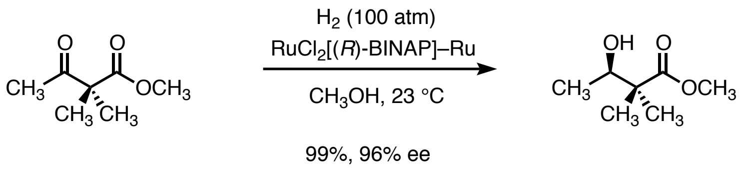
Mechanism:

- Catalytic cycle:



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

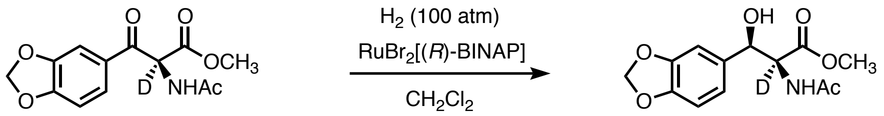
- The reduction of methyl 2,2-dimethyl-3-oxobutanoate proceeds in high yield and with high enantioselectivity, providing evidence that the reduction proceeds through the keto form of the β-keto ester. However, pathways that involve hydrogenation of the enol form of other β-keto esters cannot be ruled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



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

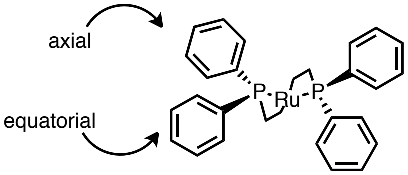
Andrew Haidle

- 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.

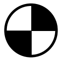


Noyori, R.; Ikeda, T.; Okhuma, T.; Widhalm, M.; Kitamura, M.; Takaya, H.; Akutagawa, S.; Sayo, N.; Saito, T.; Taketomi, T.; Kumobayashi, H. *J. Am. Chem. Soc.* **1989**, *111*, 9134–9135.

- A crystal structure of $Ru(OCOCH_3)_2$[(*S*)-BINAP] revealed that the rigid BINAP backbone forces the phenyl rings attached to phosphorous to adopt the conformation depicted here (the napthyl rings are omitted for clarity).



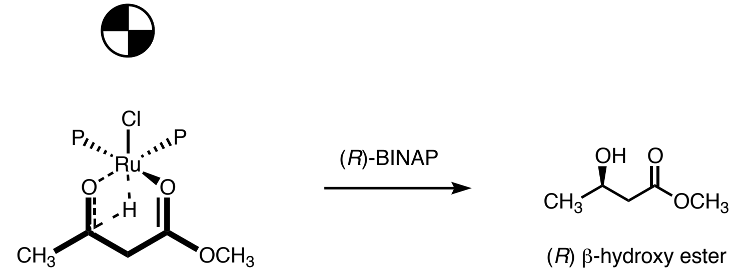
$Ru(OCOCH_3)_2$[(*S*)-BINAP]

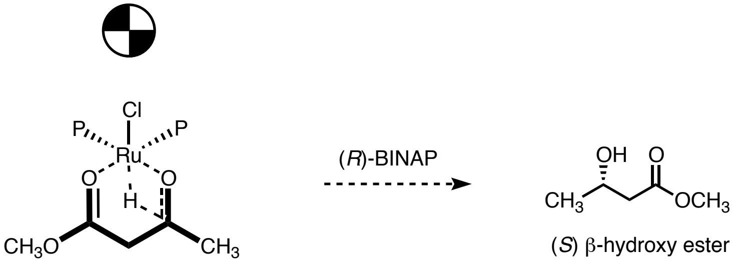


- The two protruding equatorial *P*-phenyl groups allow a coordinating ligand access to only two quadrants on the accessible face of Ru (the other face is blocked by BINAP's napthyl rings). This situation is represented by a circle with two black quadrants where no coordination can occur.

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 $[RuCl_2(benzene)]_2$, 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.

$$^1/_2\ [RuCl_2(\text{benzene})]_2 \ + \ (R)\text{-BINAP} \xrightarrow{\text{DMF, 100 °C}} (R)\text{-BINAP-Ru(II)}$$

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

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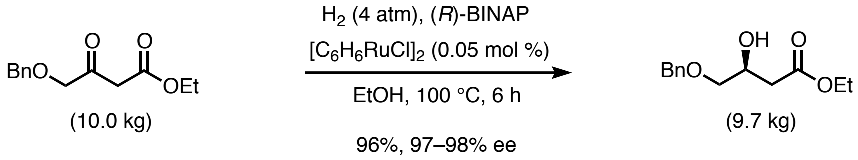
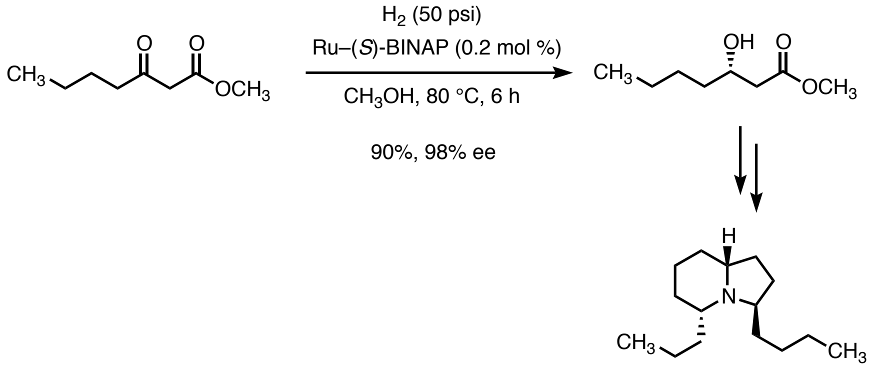
- The procedure involving *in situ* catalyst generation was found to be much more reliable. Also, reactions with this catalyst were more enantioselective and required less catalyst. The following reaction was done on a 10-kg scale. Note the benzyl group is not removed.



Beck, G.; Jendralla, H.; Kesseler, 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 $RuCl_2$•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.

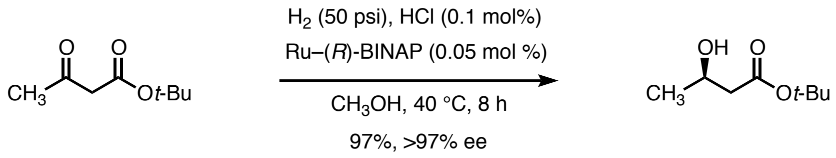


(–)-Indolizidine 223AB

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.

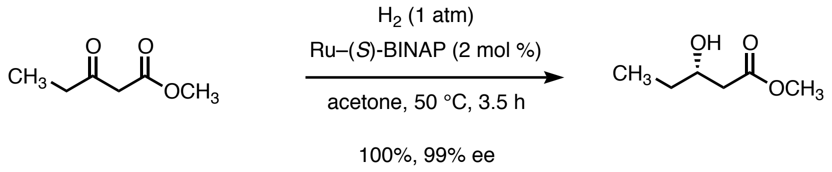
- These conditions have been improved on even further, with milder reaction conditions and lower catalyst loadings.



- 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 be a result of 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.

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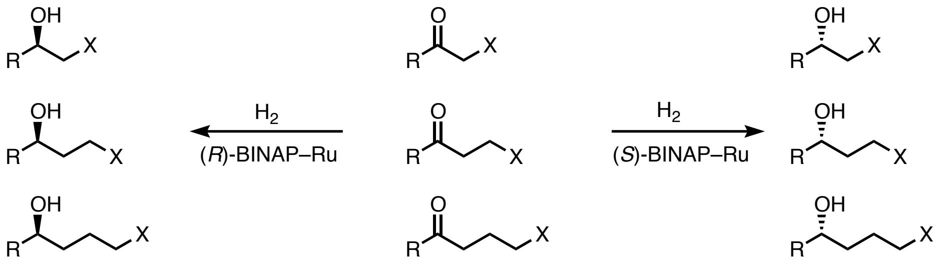
Substrates:

- β-Keto esters are typically the best substrates. However, nearly any substrate that has an ether or amine separated from a ketone by 1–3 carbons will be reduced to the corresponding secondary alcohol with high yields and high enantioselectivities.

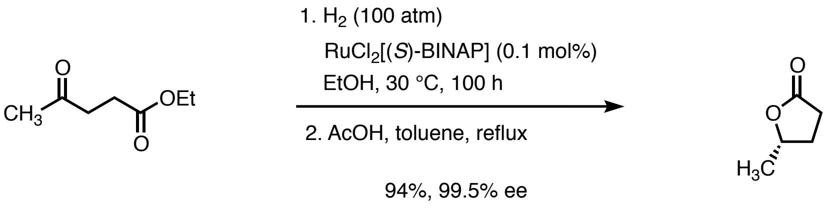


X = OR, NR_2

- The authors propose that the heteroatom is necessary because the substrate must function as a bidentate ligand for Ru.

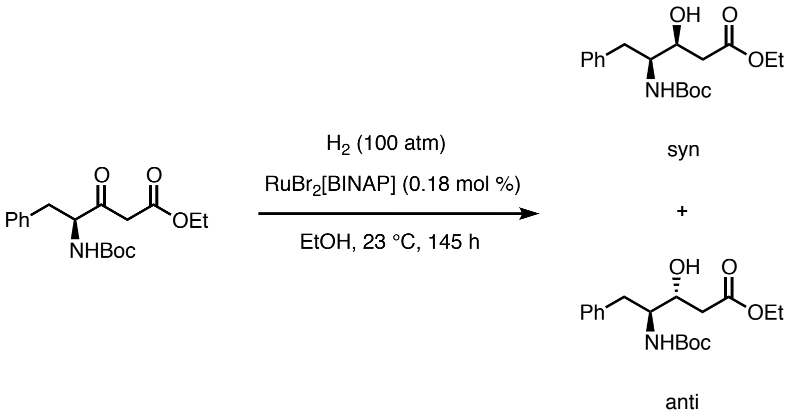
Kitamura, M.; Ohkuma, T.; Inoue, S.; Sayo, N.; Kumobayashi, H.; Akutagawa, S.; Ohta, T.; Takaya, H.; Noyori, R. *J. Am. Chem. Soc.* **1988**, *110*, 629–631.

- Example:



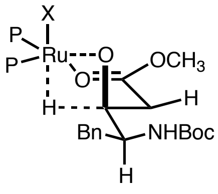
Okhuma, T.; Kitamura, M.; Noyori, R. *Tetrahedron Lett.* **1990**, *31*, 5509–5512.

- Chiral substrates:



configuration of BINAP	% yield	syn : anti
R	98	>99:1
S	96	9:91

- The (*R*)-BINAP case represents a stereochemically matched case, while the (*S*)-BINAP catalyzed case has to override the inherent syn selectivity of the substrate:



proposed T.S.‡

- Analysis of the results show that for this substrate, catalyst control is >32:1, while the substrate control is only 3:1.

Nishi, T.; Kitamura, M.; Okhuma, T.; Noyori, R. *Tetrahedron Lett.* **1988**, *29*, 6327–6330.

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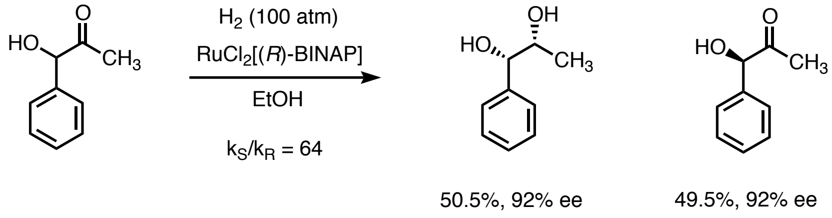
Dynamic Kinetic Resolution:

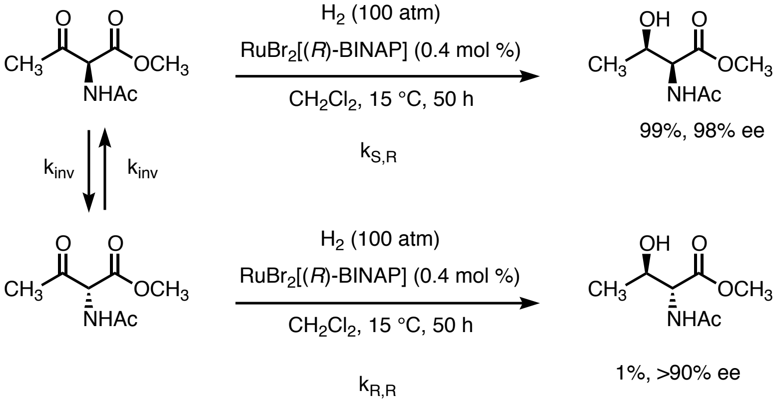
- Kinetic resolution of enantiomers occurs when the chiral catalyst reacts with one enantiomer much more rapidly than the other.



- 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.

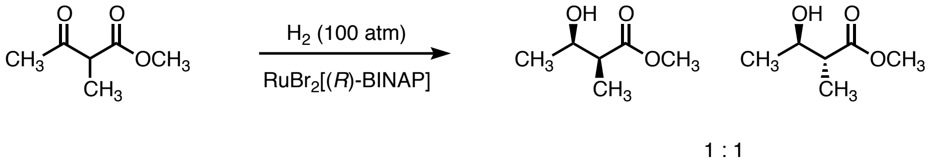
- Epimerizing systems can give rise to a dynamic kinetic resolution, where the maximum theoretical yield is 100%.

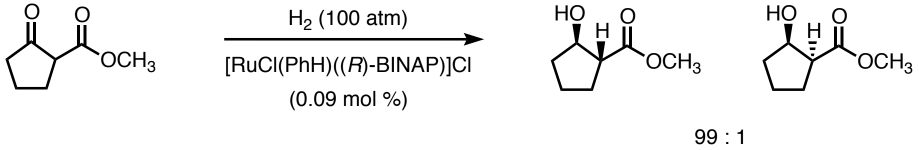


- To achieve yields approaching 100%, isomerization must be rapid relative to reduction ($k_{inv} > k_{S,R}$ and $k_{R,R}$).

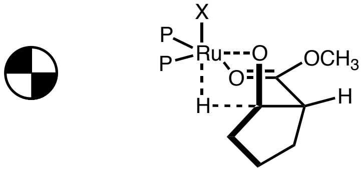
Noyori, R.; Ikeda, T.; Okhuma, T.; Widhalm, M.; Kitamura, M.; Takaya, H.; Akutagawa, S.; Sayo, N.; Saito, T.; Taketomi, T.; Kumobayashi, H. *J. Am. Chem. Soc.* **1989**, *111*, 9134–9135.

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

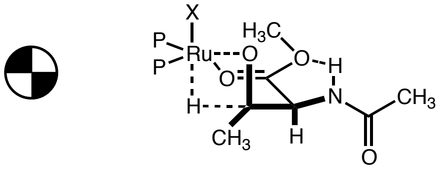




- The preference for one diastereomer over the other can be rationalized by examining the likely transition states for carbonyl reduction. If the reduction of the α-amino compound, below right, is carried out in methanol instead of dichloromethane, the diastereoselectivity drops from 99 : 1 to 82 : 18.



P,P = (R)-BINAP



P,P = (R)-BINAP

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.

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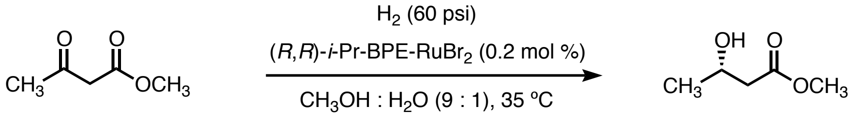
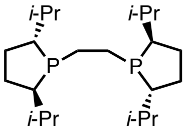
Other Ligands:

- 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.



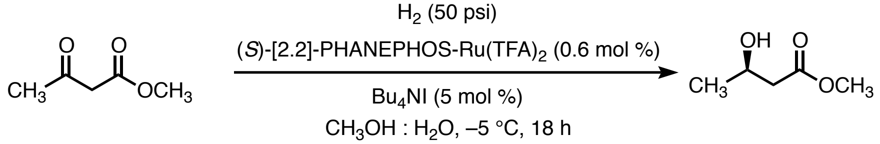
100%, 99.3% ee

(*R*,*R*)-*i*-Pr-BPE =



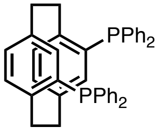
Burk, M. J.; Harper, T. G. P.; Kalberg, C. S. *J. Am. Chem. Soc.* **1995**, *117*, 4423–4424.

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



100%, 96% ee

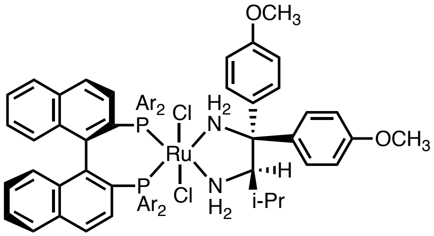
(*S*)-[2.2]-PHANEPHOS =



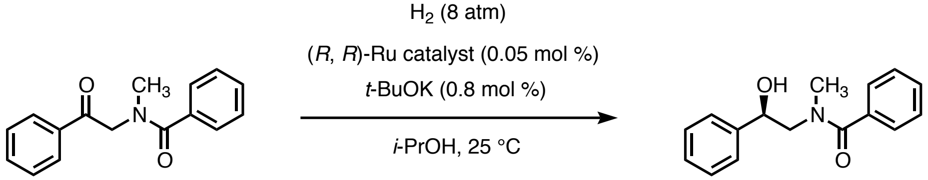
Pye, P. J.; Rossen, K.; Reamer, R. A.; Volante, R. P.; Reider, P. J. *Tetrahedron Lett.* **1998**, *39*, 4441–4444.

- Noyori has discovered a Ru–based catalyst, *trans*-$RuCl_2$[(*R*)-xylbinap][(*R*)-diapen], that efficiently reduces α-, β-, and γ-amino ketones in a highly enantioselective fashion under mild conditions.

trans-$RuCl_2$[(*R*)-xylbinap][(*R*)-diapen] =



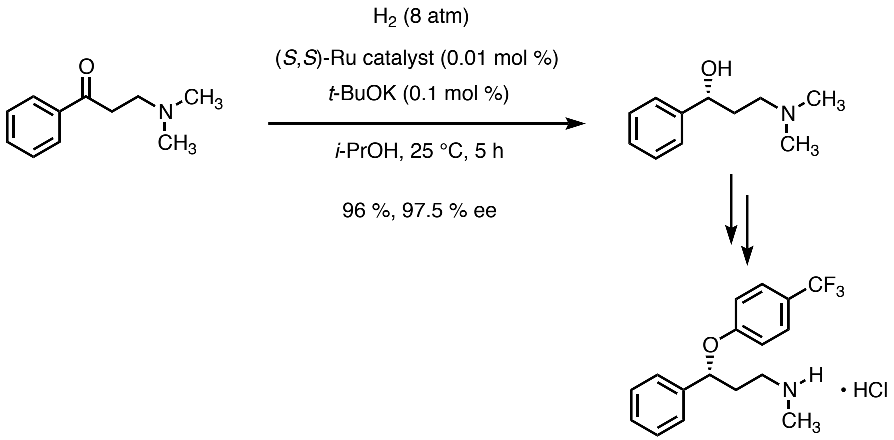
Ar = 3,5-$(CH_3)_2$-C_6H_3



96 %, 99.8 % ee

- 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 antidepressent (*R*)-fluoxetine without the need for any chromatographic separations.



96 %, 97.5 % ee

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

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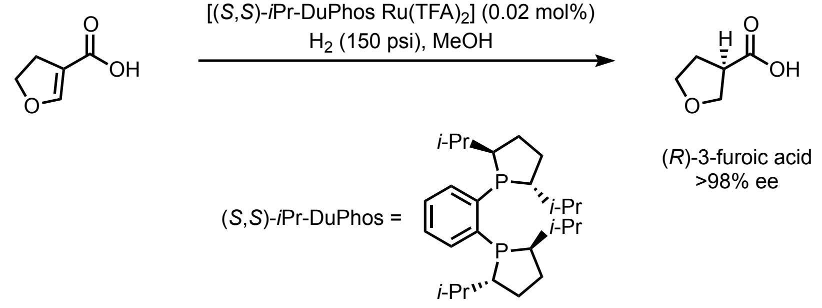
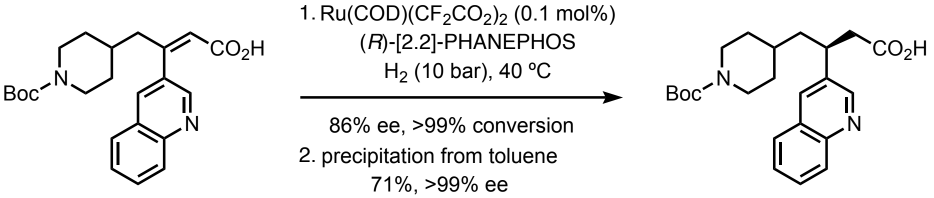
Other Ligands and Other Substrates:

- Ru catalysts have been applied to asymmetric reduction of acrylate derivatives.
- Production of 3-furoic acid using (*S,S*)-*i*-Pr-DuPhos:



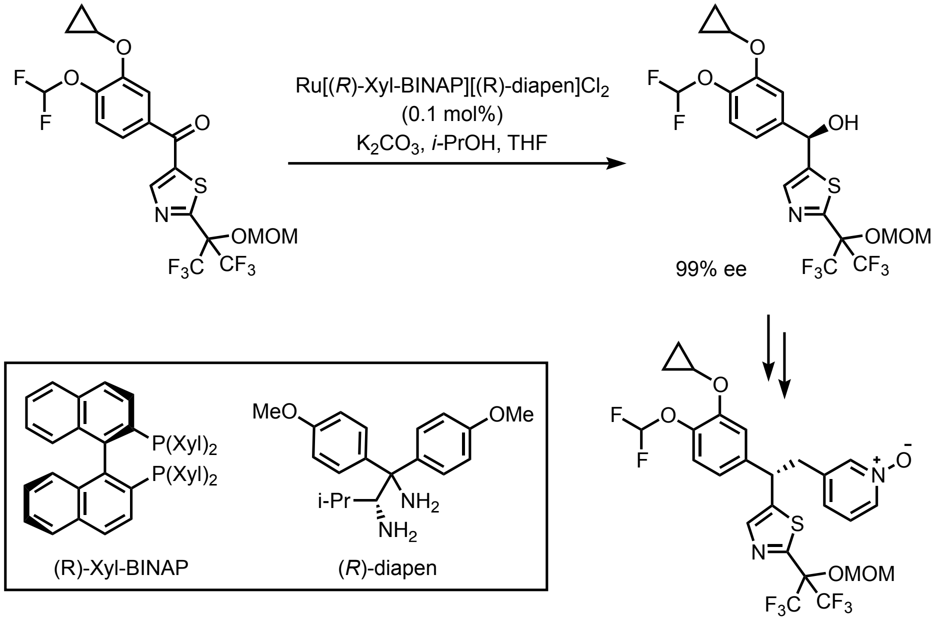
Johnson, N. B.; Lennon, I. C.; Moran, P. H.; Ramsden, J. A. *Acc. Chem. Res.* **2007**, *40*, 1291–1299.

- A reduction of an α,β-unsaturated cabroxylic acid using (*R*)-[2.2]-PHANEPHOS enabled the large-scale synthesis of the integrin inhibitor JNJ-26076713:



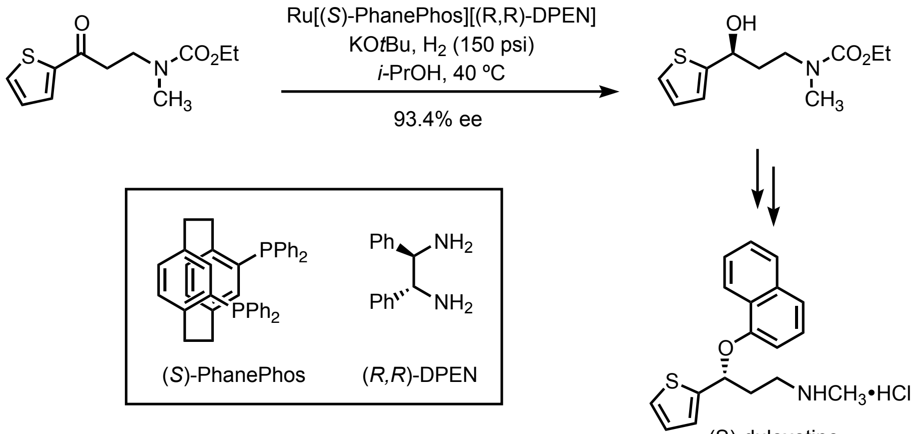
Kinney, W. A.; Teleha, C. A.; Thompson, A. S.; Newport, M.; Hansen, K.; Ballentine, S.; Ghosh, S.; Mahan, A. Grasa, G.; Zanotti-Gerosa, A.; Dinegen, J.; Schubert, C.; Zhou, Y.; Leo, G. C.; McComsey, D. F.; Santulli, R. J.; Maryanoff, B. E. *J. Org. Chem.* **2008**, *73*, 2302–2310.

- Seminal reports on the use of ruthenium based catalysts for the asymmetric reduction of ketones focused on the use of a chiral diamine in combination with BINAP derived bis-phosphine ligands.
- Application to the synthesis of a PDE-IV inhibitor:



Chen, C.-Y.; Reamer, R. A.; Chilenski, J. R.; McWilliams, C. J. *Org. Lett.* **2003**, *5*, 5039–5042.

- A similar system was used in the production of the antidepressant, (*S*)-duloxetine.



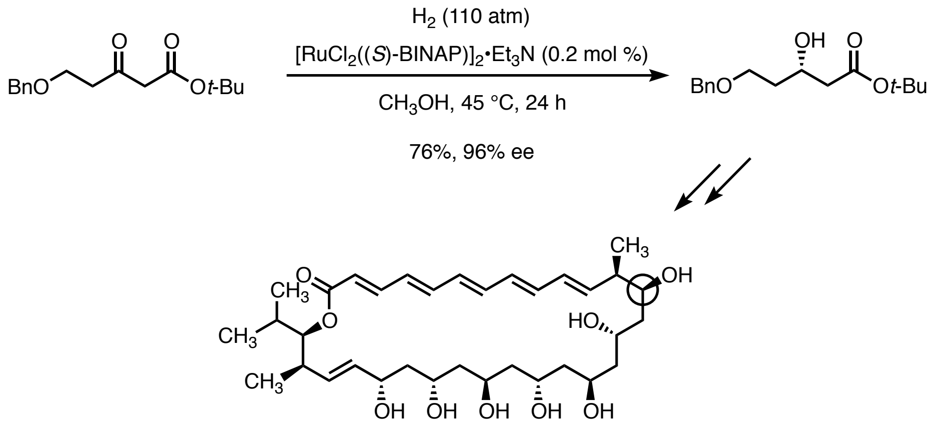
(S)-duloxetine

Hems, W.; Rossen, K.; Reichert, D.; Kohler, K.; Perea, J. J. US Patent 0272390, 2005

Joseph Tucker

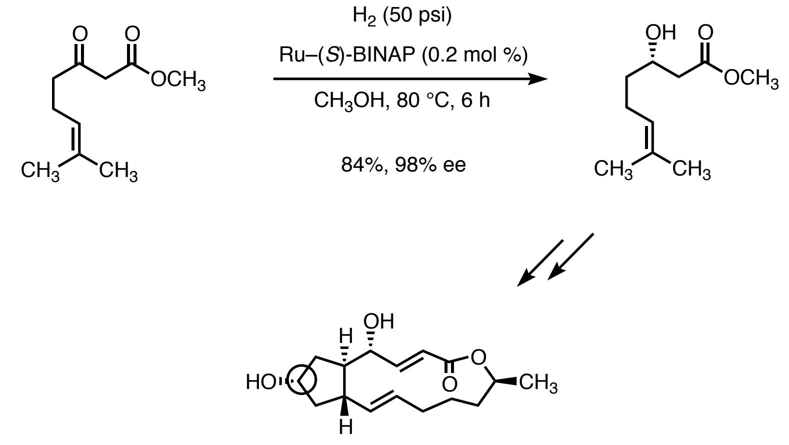
Examples in Total Synthesis:

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



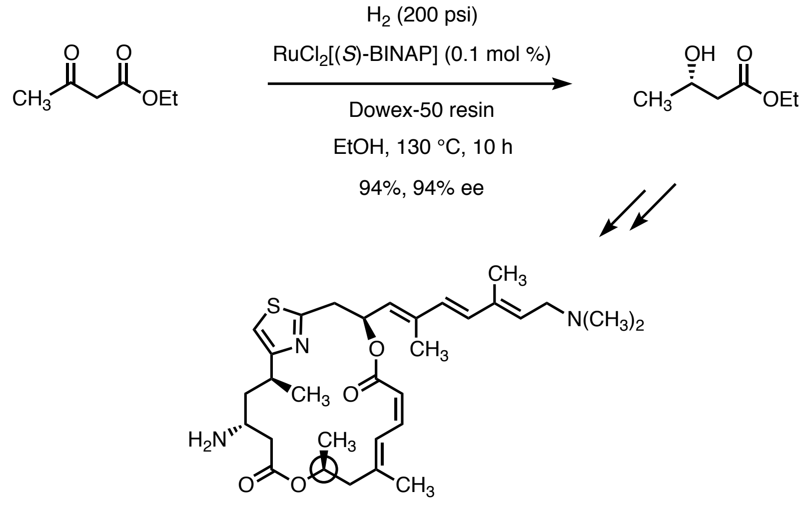
(–)-Roxaticin

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



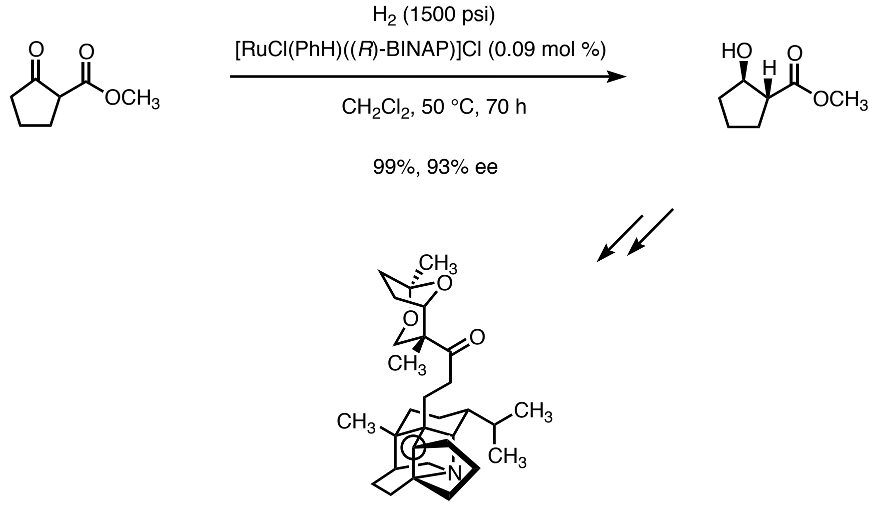
(+)-Brefeldin A

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



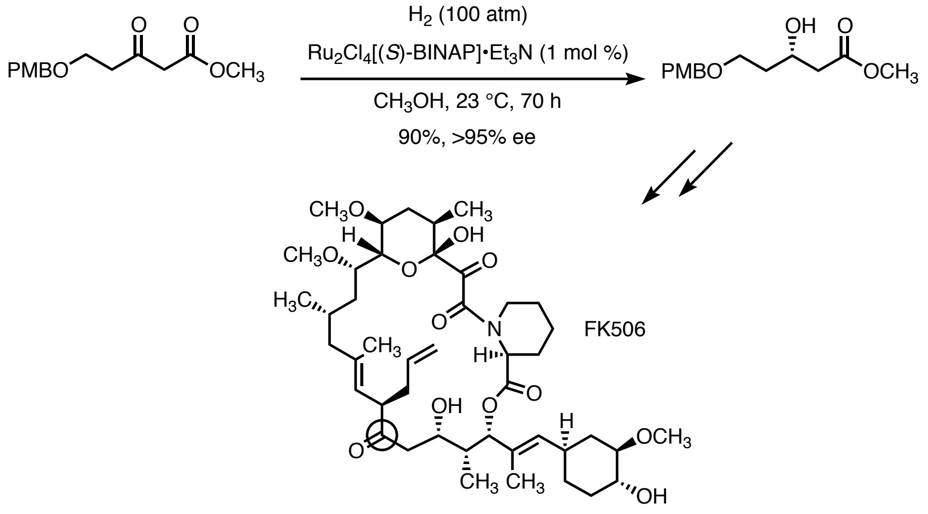
Pateamine A

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.

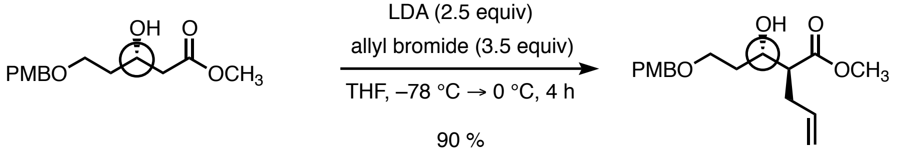


(+)-Codaphniphylline

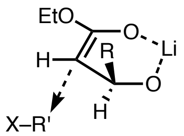
Heathcock, C. H.; Kath, J. C.; Ruggeri, R. B. *J. Org. Chem.* **1995**, *60*, 1120–1130.



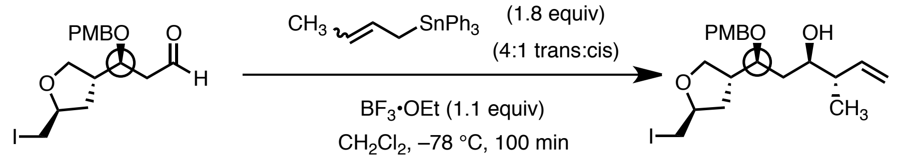
- Although the chirality of the β-hydroxy ester is lost in the final product, it is used to set two other stereocenters.



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



Fráter, G.; Müller, U.; Günther, W. *Tetrahedron* **1984**, *40*, 1269–1277.
Seebach, D.; Aebi, J.; Wasmuth, D. *Org. Synth.* **1984**, *63*, 109–120.

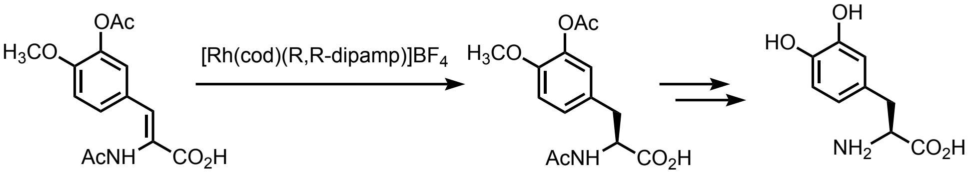


(5:1 diastereomeric mixture)

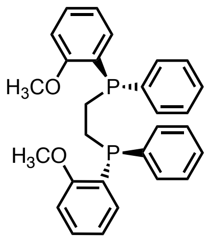
54%, >97% dr
(67% maximum yield for major diastereomer)

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

L-DOPA: First Industrial Application of Asymmetric Hydrogenation



L-DOPA



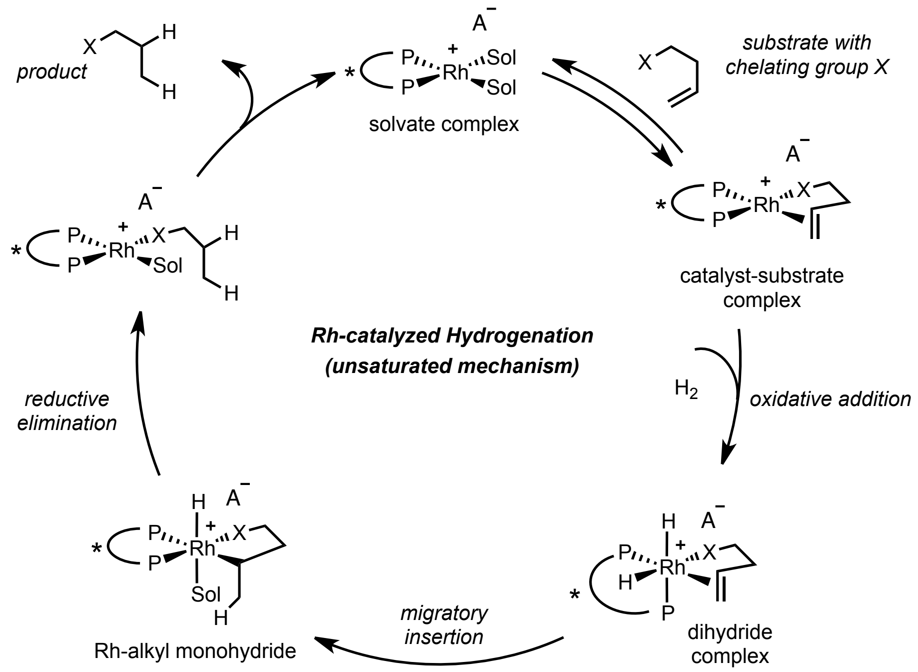
(*R,R*)-DiPAMP

- (S)-3',4'-dihydroxyphenylalanine (L-DOPA) is used in the treatment of Parkinson's disease.
- This is the first successful industrial application of a homogeneous catalytic asymmetric hydrogenation.
- William Knowles had developed the Rh-catalyzed enantioselective hydrogenation using (*R,R*)-DiPAMP as a chiral ligand while working at Monsanto in the late 1970s.
- Knowles was awarded the 2002 Nobel Prize in Chemistry for this discovery.

Knowles, W. S. *Angew. Chem. Int. Ed.* **2002**, *41*, 1998–2007.
Knowles, W. S. *Adv. Synth. Catal.* **2003**, *345*, 3–13.

Andrew Haidle, Danica Rankic

Mechanism:



- Evidence suggests that Rh-catalyzed hydrogenations operate through a mechanism by which substrate chelation occurs prior to hydrogen oxidative addition, although recently, studies with bulky diphosphines have shown that oxidative addition can occur prior to substrate association.

Gridnev, I. D.; Imamoto, T. *Acc. Chem. Res.* **2004**, *37*, 633.

- The solvate complex, catalyst-substrate complex, and Rh-alkyl monohydride complexes have all been observed and characterized.

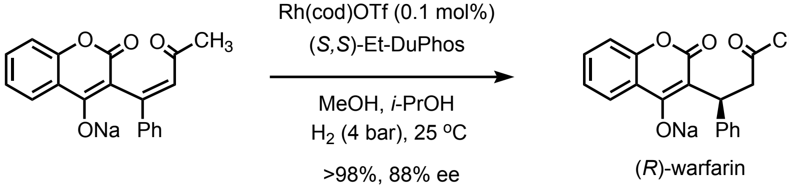
- Enantioselectivity is highly dependent on temperature and H_2 pressure.

- Curtin-Hammett kinetics is operating under the reaction conditions: the minor diastereomer of the catalyst-substrate complex undergoes hydrogenation to afford the major enantiomer of product.

Halpern, J. *Science* **1982**, *217*, 401–407.

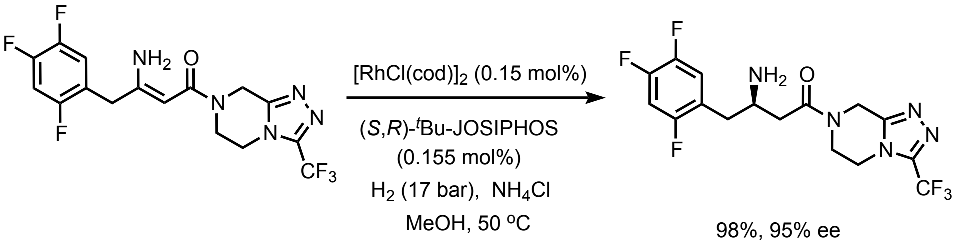
Application in Industry

- **(*R*)-Warfarin synthesis:**
- An asymmetric hydrogenation was employed in the synthesis of (*R*)-warfarin, one of the most commonly prescribed oral anticoagulant drugs in North America.
- Enantiomeric excess could be improved from 88% to 98% ee by recrystallization.



Robinson, A.; Li, H.-Y.; Feaster, J. *Tetrahedron Lett.* **1996**, *37*, 8321–8324.

- **Sitagliptin:**
- Sitagliptin (Januvia®) is a potent and selective DPP IV inhibitor for the treatment of type 2 diabetes mellitus.
- The second-generation process route involves the hydrogenation of an unprotected β-(amino)acrylamide.
- A catalytic amount of NH_4Cl is required for high ee and turnover numbers.
- Hydrogenation occurs through the imine tautomer.

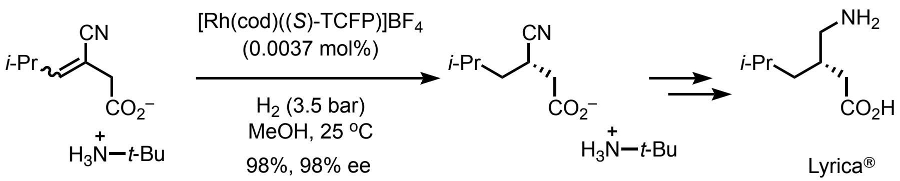


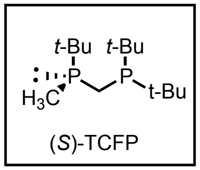
98%, 95% ee
(>99.9% ee after recrystalization)

Desai, A. A. *Angew. Chem. Int. Ed.* **2011**, *50*, 1974–1976.
Hansen, K. B.; Hsiao, Y.; Xu, F.; Rivera, N.; Clausen, A.; Kubryk, M.; Krska, S.; Rosner, T.; Simmons, B.; Balsells, J.; Ikemoto, N.; Sun, Y.; Spindler, F.; Malan, C.; Grabowski, E. J. J.; Armstrong, J. D. *J. Am. Chem. Soc.* **2009**, *131*, 8798–8804.

Danica Rankic

- **Pregabalin:**
- Pregabalin (Lyrica®) is an anti-convulsive agent marketed for the treatment of a number of nervous system disorders, including epilepsy, neuropathic pain, anxiety and social phobia.

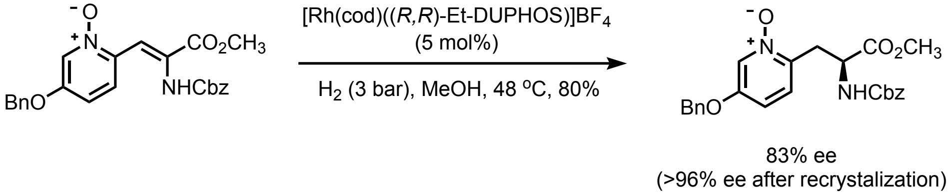


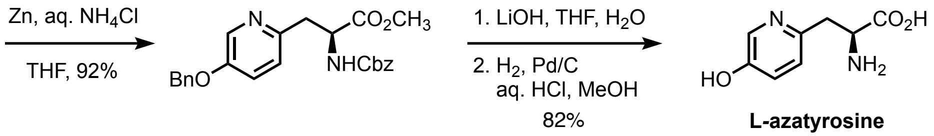


- Rh-catalyzed asymmetric hydrogenation replaced an enzymatic resolution (lower cost of reagents, waste reduction and higher throughput)
- Trichickenfootphos (TCFP) is a P-chiral phosphine designed and developed at Pfizer that allowed for high turnover numbers (> 27000) and high ee.

Hoge, G.; Wu, H.-P.; Kissel, W. S.; Pflum, D. A.; Greene, D. J.; Bao, J. *J. Am. Chem. Soc.* **2004**, *126*, 5966–5967.

- **Anti-tumor antibiotic *L*-azatyrosine:**
- An *N*-oxide was found to be necessary to prevent catalyst inhibition through pyridine coordination.





Adamczyk, M.; Akireddy, S. R.; Reddy, R. E. *Org. Lett.* **2001**, *3*, 3157–3159.