Massachusetts Institute of Technology

Organic Chemistry 5.512

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Unit 7

Stereocontrolled Reduction of Ketones

- ★ Substrate Control: 1,2-Asymmetric Induction
- ★ Substrate Control: 1,3-Asymmetric Induction
- ★ Reagent Control Strategies
- ★ Retrosynthetic Analysis: Chiral Secondary Alcohols

General Reviews

"Enantioselective Reduction of Ketones" Itsuno, S. *Organic Reactions* **1998**, *52*, 395

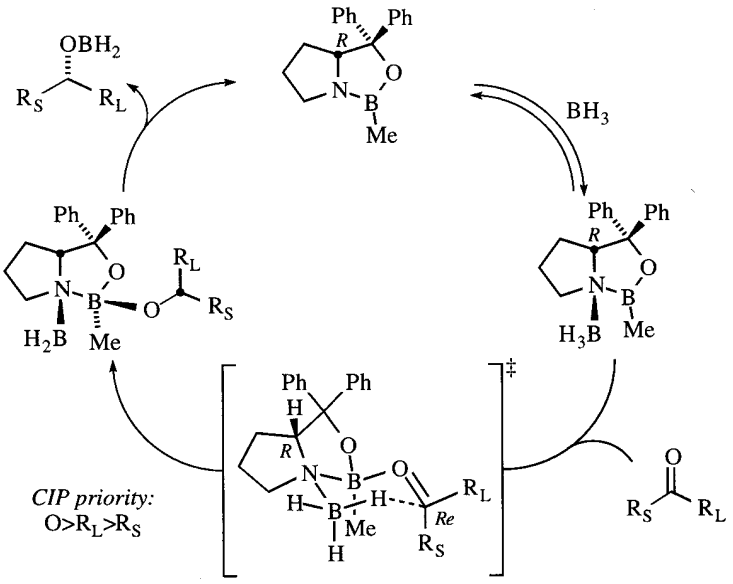
Reagent Control Strategies

(1) Itsuno-Corey Reduction ("CBS Reduction")

Review:

"Reduction of Carbonyl Compounds with Chiral Oxazaborolidine Catalysts: A New Paradigm for Enantioselective Catalysis and a Powerful Synthetic Method" Corey, E. J.; Helal, C. J. *Angew. Chem. Int. Ed.* **1998**, *37*, 1987

"Recent Advances in the Synthetic Applications of the Oxazaborolidine-Mediated Asymmetric Reduction" Cho, B. T. *Tetrahedron* **2006**, *62*, 7621



Scheme 7.3. Catalytic cycle for the asymmetric reduction of a ketone with an oxazaborolidine catalyst [29,35,36].

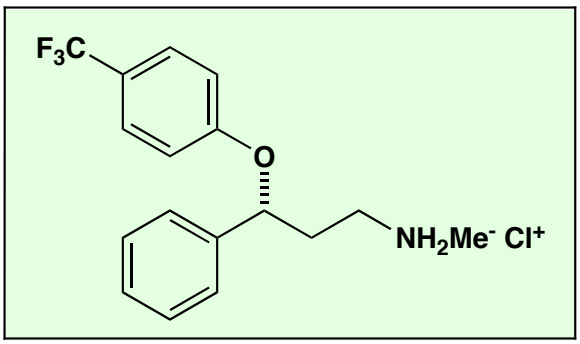
E. J. Corey

See Merck Process, *Org. Synth.* **1996**, *74*, 50

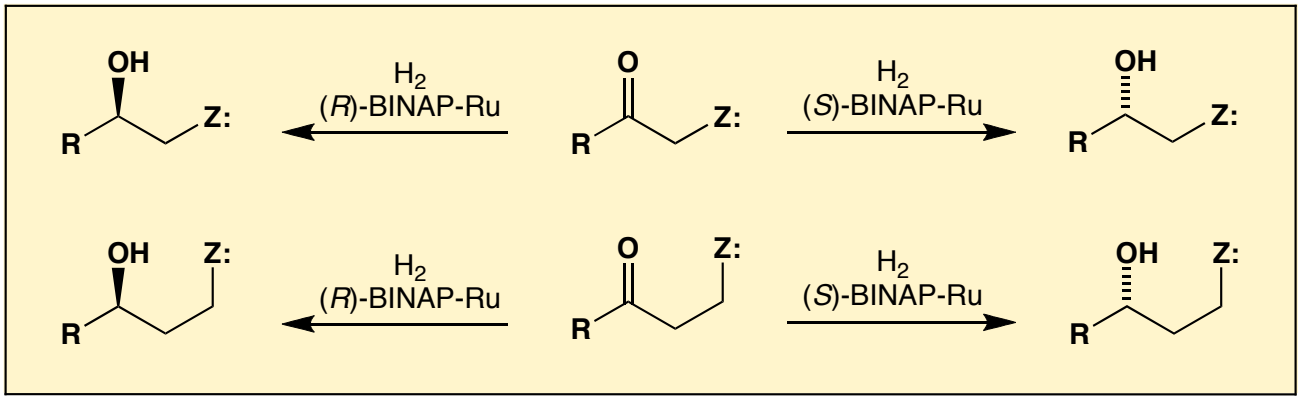
Case Study

Synthesis of
(*R*)-Fluoxetine (Prozac)

Corey, E. J.; Reichard, G. A.
Tetrahedron Lett. **1989,** *30*, 5207



(2) Noyori Asymmetric Hydrogenation



R. Noyori et al. *J. Am. Chem. Soc.* **1988,** *110*, 629

Also see R. Noyori et al. *Org. Synth.* **1992**, *71*,1

Table I. Catalytic Asymmetric Hydrogenation of Functionalized Ketones Using BINAP–Ru Complexes[a]

			conditions		product		
substrate	catalyst	S/C	H_2, atm	time, h	% yield[b]	% ee[c]	config[c]
$CH_3COCH_2N(CH_3)_2$	$Ru(OCOCH_3)_2[(S)$-binap]	780	50[d,e]	12	72	96	*S*
$(CH_3)_2CHCOCH_2N(CH_3)_2$	$Ru(OCOCH_3)_2[(S)$-binap]	390	100[d,e]	24	83	95	*S*
$C_6H_5COCH_2N(CH_3)_2$	$RuBr_2[(S)$-binap]	490	100[d,e]	24	85	95	*S*
$C_6H_5COCH_2N(CH_3)_2$	$Ru(OCOCH_3)_2[(S)$-tolbinap][f]	530	100[d,e]	8	92	93	*S*
CH_3COCH_2OH	$RuCl_2[(R)$-binap]	230	93[d]	32	100	92	*R*
$CH_3COCO_2CH_3$	$RuCl_2[(R)$-binap]	780	96[d]	46	97	83	*R*
$CH_3COCH_2CH_2OH$	$RuCl_2[(R)$-binap]	900	70	42	100	98	*R*
$CH_3COCH_2CO_2C_2H_5$	$RuBr_2[(R)$-binap]	1260	86	51	100	>99	*R*
$CH_3COCH_2CON(CH_3)_2$	$RuBr_2[(S)$-binap]	680	63	86	100	96	*S*
$CH_3COCH_2COSC_2H_5$	$RuCl_2[(R)$-binap]	540	95	86	42[g]	93	*R*
$(i\text{-}C_3H_7)_3SiOCH_2COCH_2CO_2C_2H_5$	$RuBr_2[(S)$-binap]	290	100[h]	86	100	95	*R*
$C_6H_5CH_2OCH_2CH_2COCH_2CO_2CH_3$	$RuBr_2[(S)$-binap]	370	50[d]	185	94	99	*S*
o-$CH_3COC_6H_4CO_2H$	$Ru_2Cl_4[(R)$-binap$]_2(C_2H_5)_3N$	220	43[i]	15	100[g]	92	*R*
o-$BrC_6H_4COCH_3$	$RuBr_2[(R)$-binap]	1100	100	62	97	92	*R*
$CH_3COCOCH_3$	$RuBr_2[(S)$-binap]	680	80	61	100[j]	100[k]	*S,S*
$CH_3COCH_2COCH_3$	$RuCl_2[(R)$-binap]	2000	72[j]	89	100, 95[g,m]	100[k]	*R,R*
$CH_3COCH(CH_3)COCH_3$	$RuCl_2[(S)$-binap]	2200	94	62	100[m]	99	*S,S*

[a] Reaction was carried out at 20–32 °C in 1–4 M ethanol solution of the substrate (3–21 mmol). [b] Determined by 270-MHz or 400-MHz ^1H NMR analysis. [c] The enantiomeric excesses and absolute configurations of the products were determined by combination of HPLC and ^1H NMR analysis of the appropriate MTPA esters and rotation measurement. The details are given in the Supplementary Material. [d] Methanol as solvent. [e] The substrate concentration was 0.15–0.3 M. [f] Tolbinap = 2,2′-bis(di-*p*-tolylphosphino)-1,1′-binaphthyl. [g] Isolated yield. [h] The substrate concentration was 0.5 M. [i] A 5:2 methanol–tetrahydrofuran mixture as solvent. [j] dl:meso = 26:74. [k] The minor isomer was not detectable by HPLC analysis of the MTPA ester. [l] A 10 M solution of the substrate (0.2 mol) was used. [m] dl:meso = 99:1.

(2) Noyori Asymmetric Hydrogenation

Case Study

Synthesis of C-D Spiroketal Unit of Spongistatin 1

Holson, E. B.; Roush, W. R. *Org. Lett.* **2002,** *4*, 3719

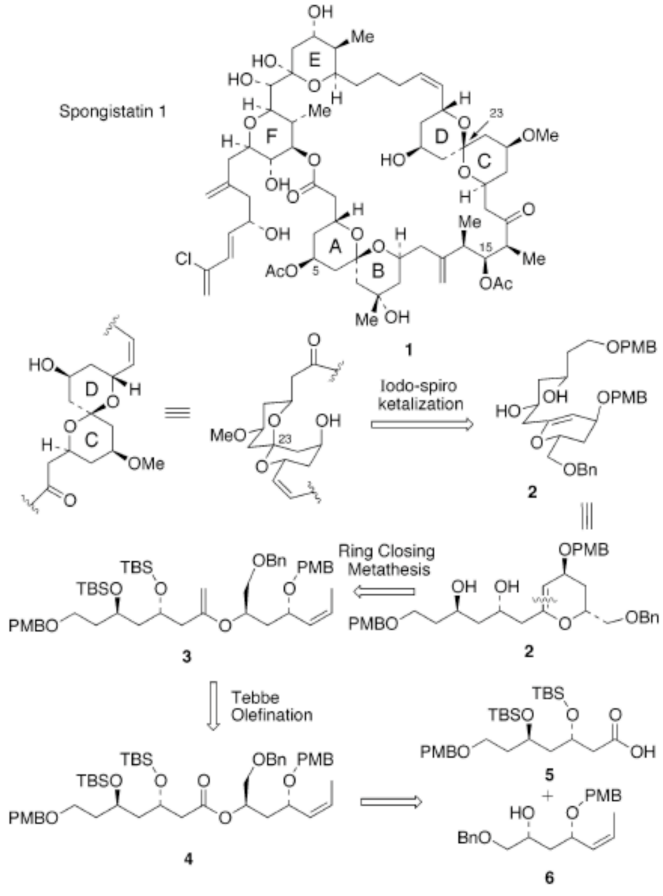


Figure 1. Retrosynthetic Analysis of the C−D Spiroketal.