

Massachusetts Institute of Technology
Organic Chemistry 5.512

May 5, 2006
Prof. Rick L. Danheiser

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 Review

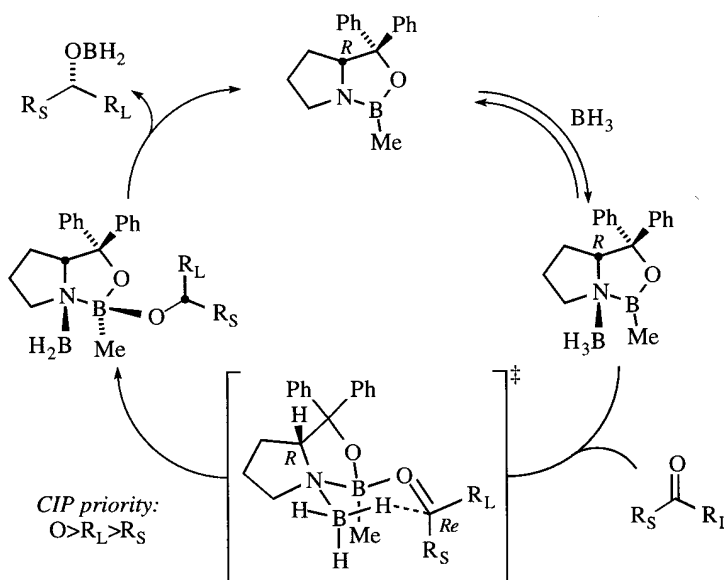
"Enantioselective Reduction of Ketones" Itsuno, S. *Organic Reactions* **1998**, 52, 395

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

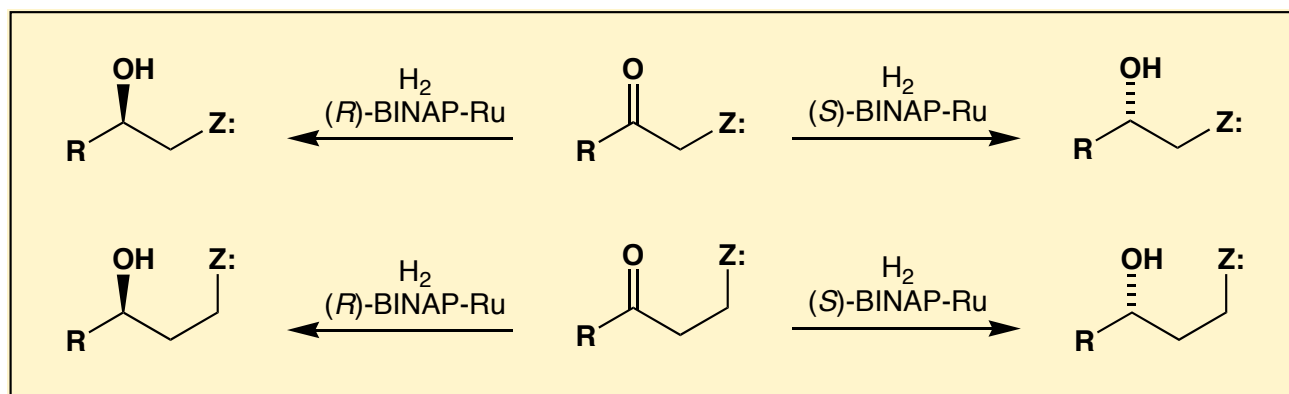


E. J. Corey

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

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

(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

substrate	catalyst	S/C	conditions		product		
			H ₂ , atm	time, h	% yield ^b	% ee ^c	config ^c
CH ₃ COCH ₂ N(CH ₃) ₂	Ru(OCOCH ₃) ₂ [(<i>S</i>)-binap]	780	50 ^{d,e}	12	72	96	<i>S</i>
(CH ₃) ₂ CHCOCH ₂ N(CH ₃) ₂	Ru(OCOCH ₃) ₂ [(<i>S</i>)-binap]	390	100 ^{d,e}	24	83	95	<i>S</i>
C ₆ H ₅ COCH ₂ N(CH ₃) ₂	RuBr ₂ [(<i>S</i>)-binap]	490	100 ^{d,e}	24	85	95	<i>S</i>
C ₆ H ₅ COCH ₂ N(CH ₃) ₂	Ru(OCOCH ₃) ₂ [(<i>S</i>)-tolbinap] ^f	530	100 ^{d,e}	8	92	93	<i>S</i>
CH ₃ COCH ₂ OH	RuCl ₂ [(<i>R</i>)-binap]	230	93 ^d	32	100	92	<i>R</i>
CH ₃ COCOCH ₃	RuCl ₂ [(<i>R</i>)-binap]	780	96 ^d	46	97	83	<i>R</i>
CH ₃ COCH ₂ CH ₂ OH	RuCl ₂ [(<i>R</i>)-binap]	900	70	42	100	98	<i>R</i>
CH ₃ COCH ₂ CO ₂ C ₂ H ₅	RuBr ₂ [(<i>R</i>)-binap]	1260	86	51	100	>99	<i>R</i>
CH ₃ COCH ₂ CON(CH ₃) ₂	RuBr ₂ [(<i>S</i>)-binap]	680	63	86	100	96	<i>S</i>
CH ₃ COCH ₂ COSi(CH ₃) ₃	RuCl ₂ [(<i>R</i>)-binap]	540	95	86	42 ^g	93	<i>R</i>
(<i>i</i> -C ₄ H ₉) ₃ SiOCH ₂ COCH ₂ CO ₂ C ₂ H ₅	RuBr ₂ [(<i>S</i>)-binap]	290	100 ^h	86	100	95	<i>R</i>
C ₆ H ₅ CH ₂ OCH ₂ CH ₂ COCH ₂ CO ₂ CH ₃	RuBr ₂ [(<i>S</i>)-binap]	370	50 ^d	185	94	99	<i>S</i>
<i>o</i> -CH ₃ COC ₆ H ₄ CO ₂ H	Ru ₂ Cl ₄ [(<i>R</i>)-binap] ₂ (C ₂ H ₅) ₃ N	220	43 ⁱ	15	100 ^g	92	<i>R</i>
<i>o</i> -BrC ₆ H ₄ COCH ₃	RuBr ₂ [(<i>R</i>)-binap]	1100	100	62	97	92	<i>R</i>
CH ₃ COCOCH ₃	RuBr ₂ [(<i>S</i>)-binap]	680	80	61	100 ^j	100 ^k	<i>S,S</i>
CH ₃ COCH ₂ COCH ₃	RuCl ₂ [(<i>R</i>)-binap]	2000	72 ^j	89	100, 95 ^{k,m}	100 ^k	<i>R,R</i>
CH ₃ COCH(CH ₃)COCH ₃	RuCl ₂ [(<i>S</i>)-binap]	2200	94	62	100 ^m	99	<i>S,S</i>

^aReaction was carried out at 20–32 °C in 1–4 M ethanol solution of the substrate (3–21 mmol). ^bDetermined by 270-MHz or 400-MHz ¹H NMR analysis. ^cThe 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. ^dMethanol as solvent. ^eThe substrate concentration was 0.15–0.3 M. ^fTolbinap = 2,2'-bis(di-*p*-tolylphosphino)-1,1'-binaphthyl. ^gIsolated yield. ^hThe substrate concentration was 0.5 M. ⁱA 5:2 methanol-tetrahydrofuran mixture as solvent. ^jdl:meso = 26:74. ^kThe minor isomer was not detectable by HPLC analysis of the MTPA ester. ^lA 10 M solution of the substrate (0.2 mol) was used. ^mdl:meso = 99:1.