Massachusetts Institute of Technology

Organic Chemistry 5.512

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Prof. Rick L. Danheiser

Unit 3

Stereocontrolled Conjugate Addition

- ★ Intrinisic Stereochemistry in the Michael Reaction
- ★ Substrate Control: Asymmetric Induction by Molecular Framework
- ★ Substrate Control: Asymmetric Induction via Chiral Auxiliaries
- ★ Catalytic Asymmetric Conjugate Addition I: *Unstabilized Nucleophiles*
- ★ Catalytic Asymmetric Conjugate Addition II: *Conjugate Reduction*
- ★ Catalytic Asymmetric Conjugate Addition III:
  Stabilized Nucleophiles (Michael Additions)

Definitions

Conjugate Addition

Addition of a nucleophile to an alkene conjugated with an electron-withdrawing group

Michael Reaction

Addition of an enolate or related "stabilized" carbanionic species to an a,b-unsaturated carbonyl compound or related electron-deficient alkene or alkyne

General References

Conjugate Addition Reactions in Organic Synthesis", P. Perlmutter, Pergamon Press, 1992

Reviews:

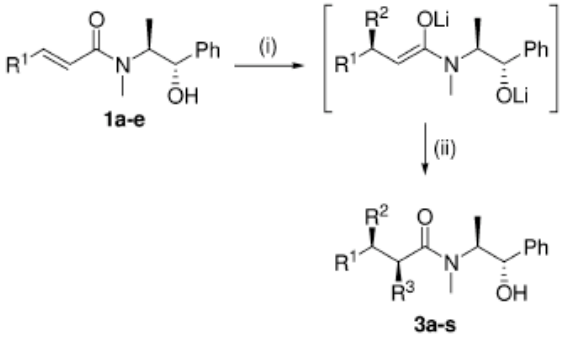
"Enantioselective Conjugate Additions"; M. P. Sibi; S. Manyem *Tetrahedron* **2000,** *56,* 8033.
"Recent Advances in Catalytic Enantioselective Michael Additions";
N. Krause; A. Hoffmann-Röder *Synthesis* **2001,** 171

Review Reading Assignment

Carey and Sundberg "Advanced Organic Chemistry" Part B
Section 1.10 (Alkylation of Carbon Nucleophiles by Conjugate Addition)
Section 7.3.1 (Organozinc Compounds)
Section 8.1 (Organocopper Intermediates)
Section 9.1.1 (Synthesis of Organoboranes)

Chiral Auxiliaries: Conjugate Addition to α,β-Unsaturated Amides

D. Badia et al. *J. Org. Chem.* **2006,** *71,* 7763



[a] Reagents and conditions: (i) R^2Li, LiCl, THF, −105 °C; (ii) (1) R^3X, THF, 0 °C, (2) NH_4Cl_{aq}.

TABLE 3. Asymmetric Tandem Conjugate Addition/α-Alkylation with α,β-Unsaturated Amides 1a−d

entry	enamide	product	R^1	R^2	R^3	yield[a] (%)	dr[b,c]
1	**1a**	**3a**	Me	Ph	Me	77	93:4:3:<1
2	**1a**	**3b**	Me	Ph	Et	96	95:5:<1:<1
3	**1a**	**3c**	Me	Ph	allyl	70	93:4:2:1
4	**1a**	**3d**	Me	Ph	Bn	78	94:4:<1:<1
5	**1a**	**3e**	Me	*n*-Bu	Me	67	91:5:3:<1
6	**1a**	**3f**	Me	*n*-Bu	Et	73	91:6:2:<1
7	**1a**	**3g**	Me	*n*-Bu	allyl	71	86:10:4:<1
8	**1a**	**3h**	Me	*n*-Bu	Bn	63	89:8:3:<1
9	**1b**	**3i**	Et	Ph	Me	75	95:4:<1:<1
10	**1b**	**3j**	Et	Ph	Et	80	97:2:<1:<1
11	**1b**	**3k**	Et	Ph	allyl	77	95:4:1:<1
12	**1b**	**3l**	Et	Ph	Bn	67	99:<1:<1:<1
13	**1c**	**3m**	*n*-Pr	Ph	Me	86	99:<1:<1:<1
14	**1c**	**3n**	*n*-Pr	Ph	Et	82	95:4:1:<1
15	**1c**	**3o**	*n*-Pr	Ph	allyl	70	96:4:<1:<1
16	**1c**	**3p**	*n*-Pr	Ph	Bn	73	>99:<1:<1:<1
17	**1c**	**3q**	*n*-Pr	*n*-Bu	allyl	77	96:3:<1:<1
18	**1d**	**3r**	*t*-Bu	Ph	Me	70	96:3:2:<1
19	**1d**	**3s**	*t*-Bu	*n*-Bu	Me	35	97:2:<1:<1
20	**1a**		Me	Ph	*i*-Pr	<5[d]	-

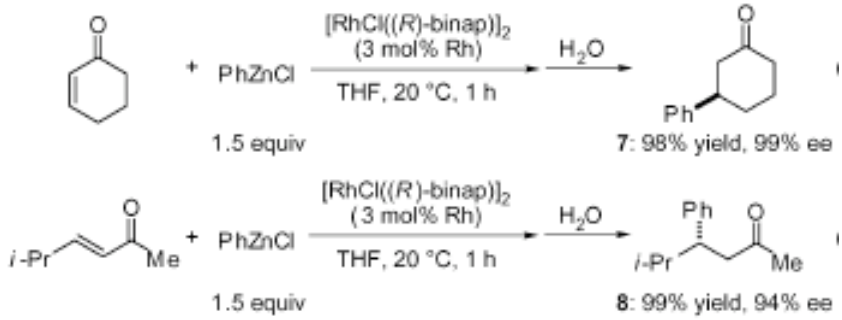
Hayashi-Miyaura Rh-Catalyzed Conjugate Addition Reactions

Reviews

T. Hayashi et al.
Chem. Rev. **2003,** *103,* 2829, *Bull. Chem. Soc. Jpn.* **2004,** *77,* 13,
Modern Rhodium-Catalyzed Reactions, Evans, P. A., Ed., Wiley-VCH, 2005, pp 55-77
See also *Org. Synth.* **2002**, *79*, 84

Recent variant using arylzinc compounds:

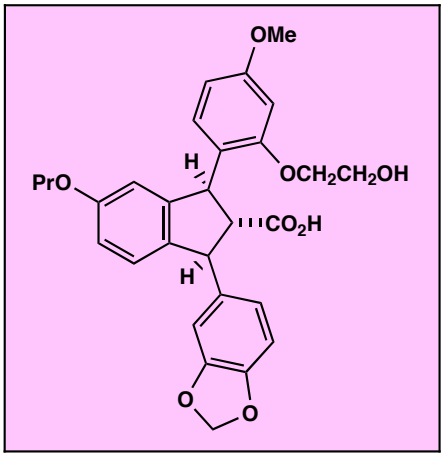
Hayashi, T. et al**.** *J. Am. Chem. Soc.* **2004,** *126,* 6240



Recent variant using bicyclo[2.2.2]octadiene ligands:

Hayashi, T. et al. *J. Org. Chem.* **2005,** *70,* 2503; Carreira, E. M. *J. Am. Chem. Soc.* **2005**, *127,* 10,850; and refs cited therein.

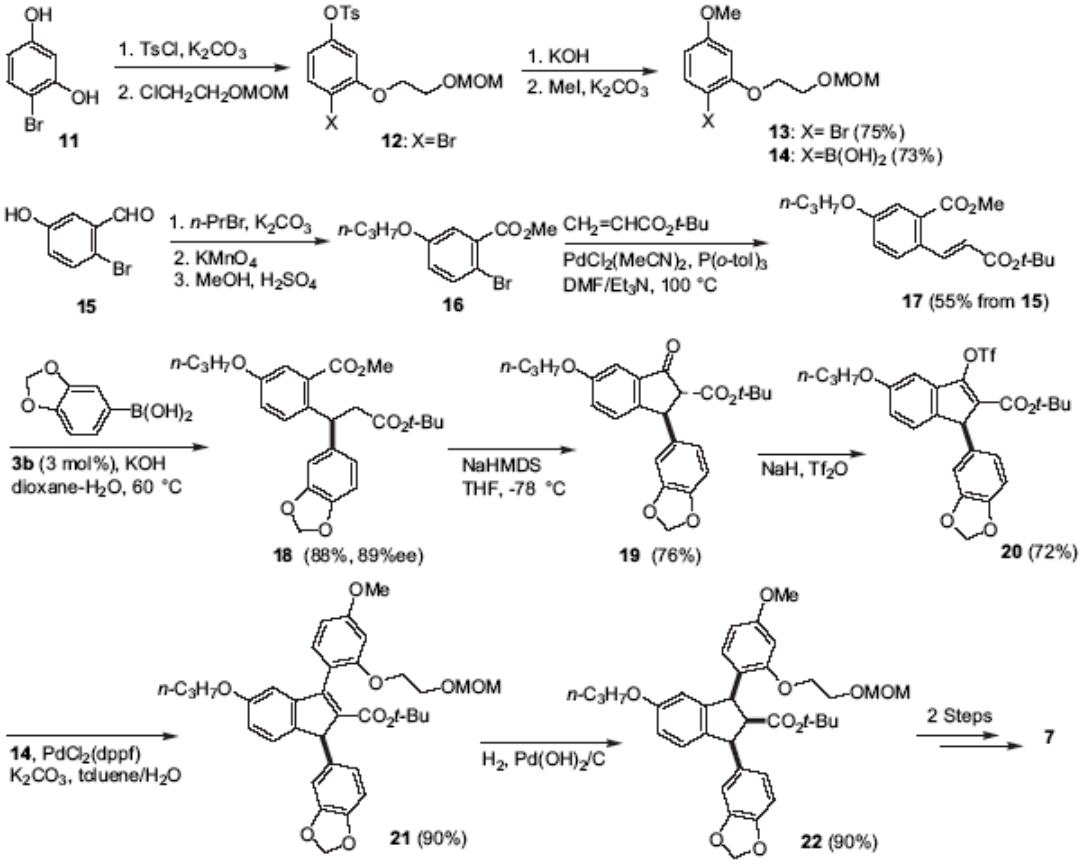
Hayashi-Miyaura Rh-Catalyzed Conjugate Addition Reactions

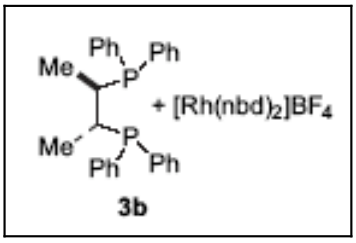


Case Study

SmithKline Beecham
Endothelin A receptor antagonist

N. Miyaura et al. *Tetrahedron* **2006**, *62,* 9610





(R,R)-chiraphos/$[Rh(nbd)_2]BF_4$