

Massachusetts Institute of Technology
Organic Chemistry 5.512

April 6, 2007
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Unit 4

Stereocontrolled 1,2-Addition to Carbonyl Groups

★ General Principles

- ★ Substrate Control: 1,2-Induction by Molecular Framework
- ★ Substrate Control: 1,3-Induction by Molecular Framework
- ★ Reagent Control: Organozinc and Related Addition Reactions

Addition of Alkyl, Aryl, Alkenyl, and Alkynyl Metal Compounds

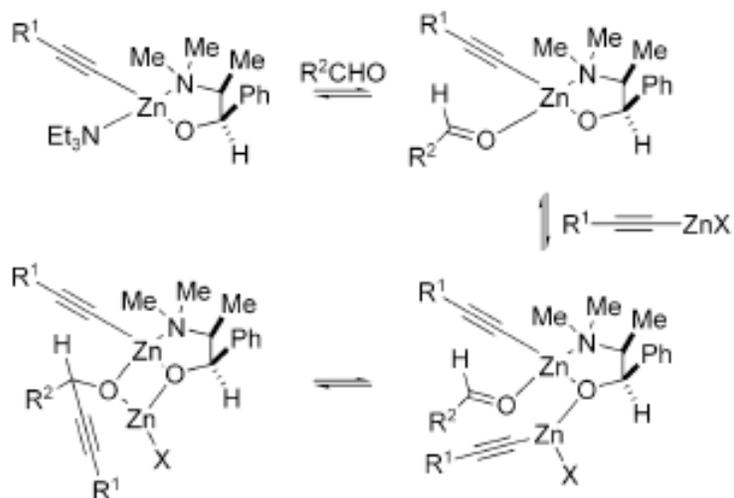
★ Asymmetric Addition of Alkynylzinc Compounds to Aldehydes

Reviews:

- (1) "Asymmetric Alkynylzinc Additions to Aldehydes and Ketones", Pu, L. *Tetrahedron* **2003**, 59, 9873
- (2) "Acetylenes in Catalysis: Enantioselective Additions to Carbonyl Groups and Imines and Applications Beyond", Cozzi, P. G.; Hilgraf, R.; Zimmermann, N. *Eur. J. Org. Chem.* **2004**, 4095



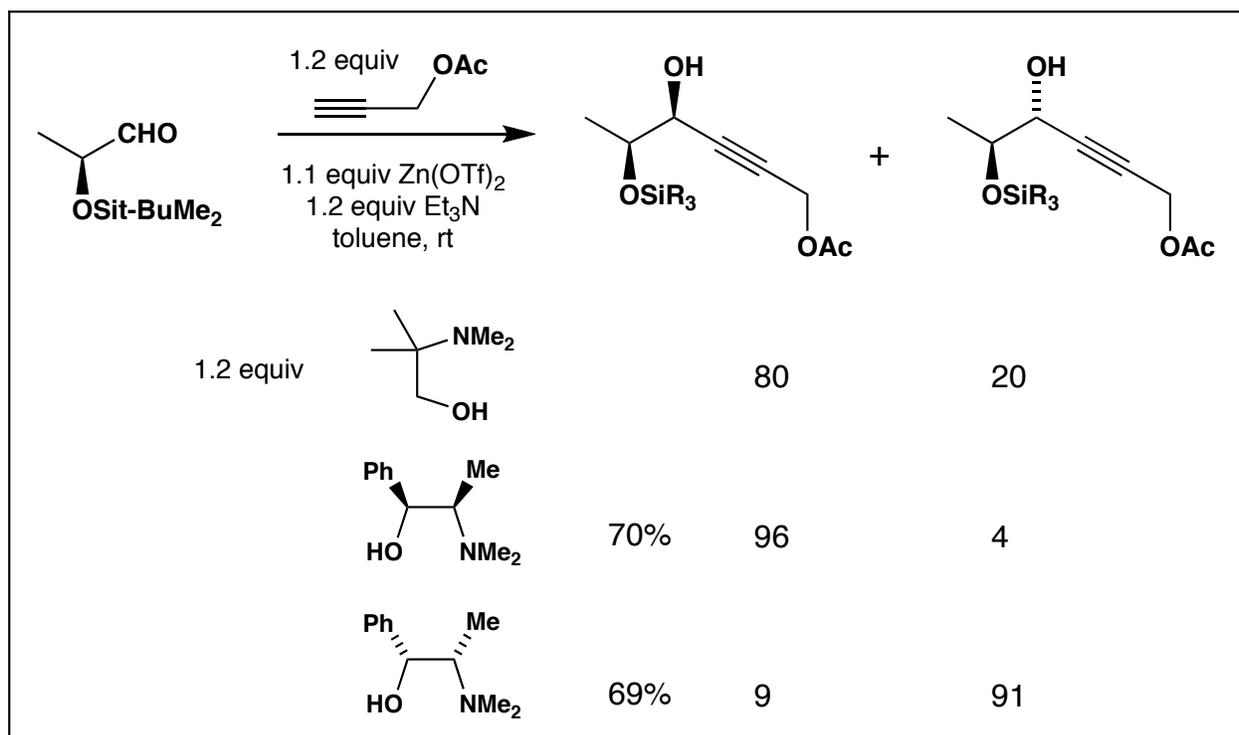
Erick M. Carreira



★ Asymmetric Addition of Alkynylzinc Compounds to Aldehydes

Double Asymmetric Synthesis: Carreira Alkynylation

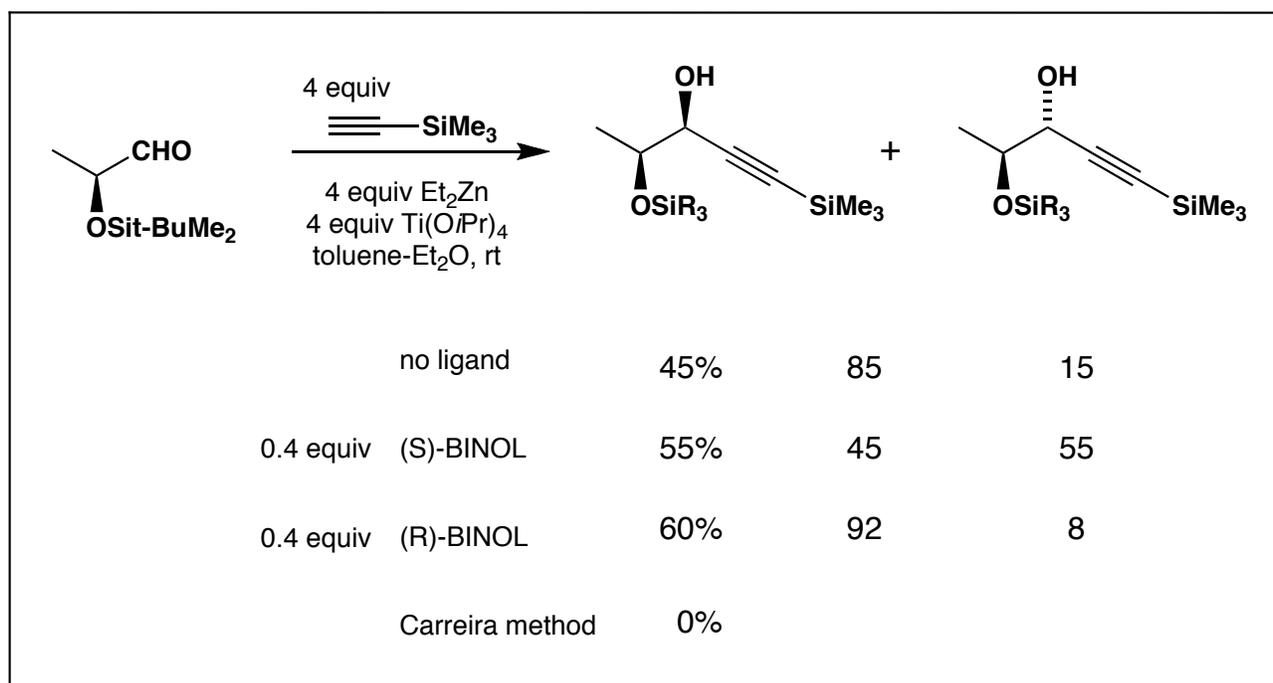
E. M. Carreira et al. *J. Am. Chem. Soc.* **2001**, *123*, 9687; *Org. Lett.* **2001**, *3*, 3017



Double Asymmetric Synthesis: Chan-Pu Alkynylation

L. Pu et al. *PNAS* **2004**, *101*, 5417; J. A. Marshall et al. *Org. Lett.* **2003**, *5*, 3197

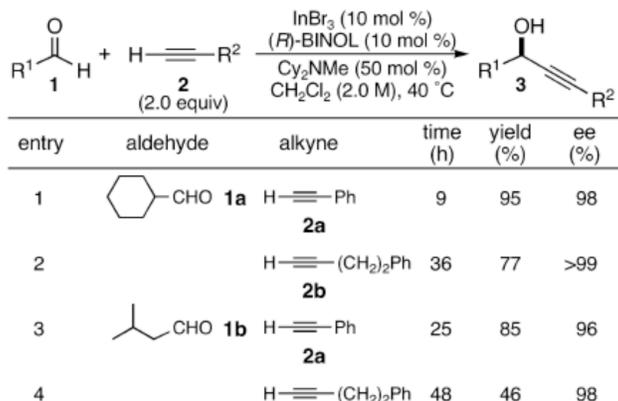
Also see J. A. Baldwin et al. *Tetrahedron* **2005**, *61*, 7219



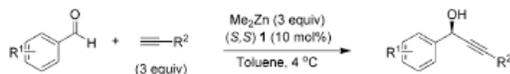
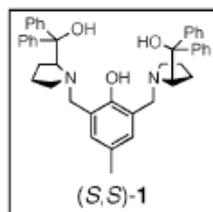
Review: "Alkynylation of Chiral Aldehydes: Alkoxy-, Amino-, and Thio-Substituted Aldehydes", Guillarme, S.; Pie, K.; Banchet, A.; Liard, A.; Haudrechy, A. *Chem. Rev.* **2006**, *106*, 2355

★ Frontiers in Asymmetric Alkynylation

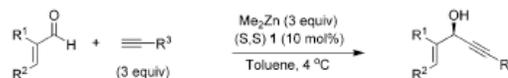
★ M. Shibasaki et al. *J. Am. Chem. Soc.* **2005**, *127*, 13760



★ B. M. Trost et al. *J. Am. Chem. Soc.* **2006**, *128*, 8;
Org. Lett. **2006**, *8*, 4461



entry	R ¹	R ²	yield (%) ^a	ee (%) ^b
1	2-NO ₂	Ph	84	92
2	3-NO ₂	Ph	91	68
3	4-NO ₂	Ph	78	83
4	H	Ph	95	81
5	C ₄ H ₄ (2-naphthyl)	Ph	89	75
6	2,4-(OCH ₃) ₂ -3-CH ₃	Ph	87	92
7	2,6-(OCH ₃) ₂	Ph	87	99
8	4-OCH ₃	TMS	74	85
9	2,6-(OCH ₃) ₂	TMS	79	97
10	2-furyl	TMS	81	84
11	2-OCH ₃	-CH ₂ OCH ₃	86	84
12	2-OCH ₃	-CO ₂ Et	95	82

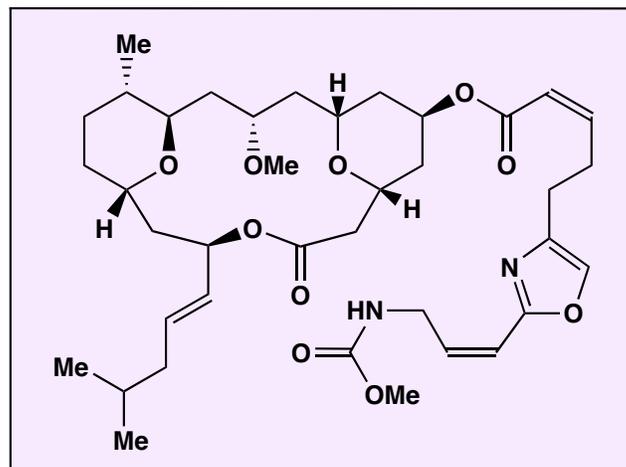


entry	R ¹	R ²	R ³	yield (%) ^a	ee (%) ^b
1	CH ₃	H	-CO ₂ CH ₃	94	90
2	H	-C ₆ H ₁₃	-CO ₂ CH ₃	86	97 ^c
3	H	-CH(CH ₃) ₂	-CO ₂ CH ₃	97	97
4	H	Ph	-CO ₂ CH ₃	92	95
5	H	Ph	-SiMe ₂ Bn	100	73
6	H	Ph	-C ₆ H ₁₃	100	77
7	H	-CH(CH ₃) ₂	-CH(OEt) ₂	85	87 ^d
8	H	Ph	-CH(OEt) ₂	85	82

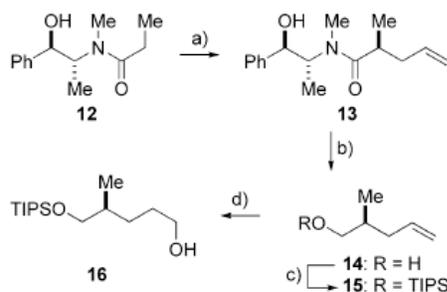
Case Study

Fettes, A.; Carreira, E. M.
J. Org. Chem. **2003**, *68*, 9274

leucascandrolide A

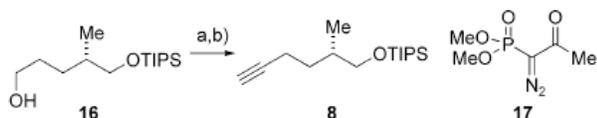


SCHEME 1^a



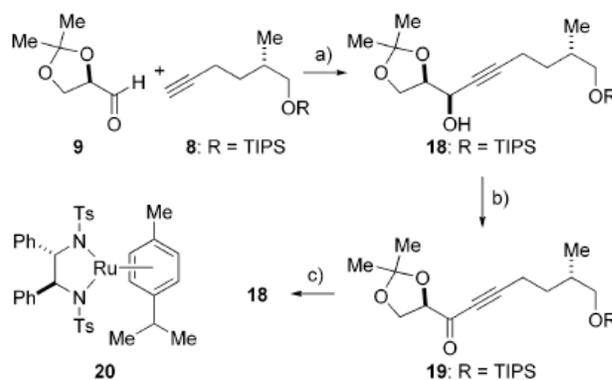
^a Reaction conditions: (a) LDA, LiCl, allyl iodide, THF, $-78\text{ }^{\circ}\text{C} \rightarrow 0\text{ }^{\circ}\text{C}$, 2 h (dr > 95:5); (b) LDA, $\text{NH}_3\text{-BH}_3$, THF, rt, 2 h; (c) TIPSCl, imidazole, DMAP, rt, 1 h; (d) 9-BBN, THF, rt, 6 h, 75% over four steps.

SCHEME 2^a



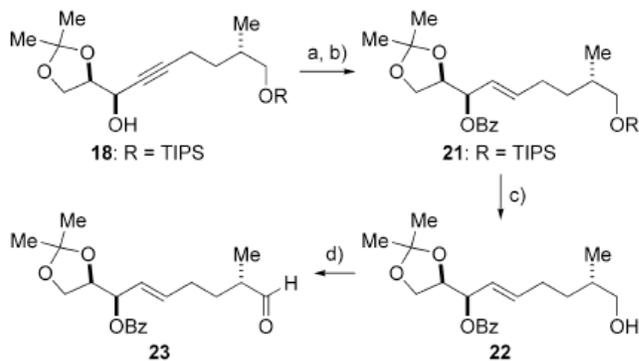
^a Reaction conditions: (a) aq NaClO, TEMPO (2.0 mol %), KBr (10 mol %), CH_2Cl_2 , pH 8.6 carbonate buffer, $0\text{ }^{\circ}\text{C}$, 15 min; (b) $(\text{MeO})_2\text{P}(\text{O})\text{CN}_2\text{CO}_2\text{CH}_3$, K_2CO_3 , MeOH, 16 h, rt, 87% (over two steps).

SCHEME 4^a



^a Reaction conditions: (a) **8**, $\text{Zn}(\text{OTf})_2$, (-)-*N*-methyl ephedrine, Et_3N , toluene, then **9**, rt, 48 h, 75% (dr = 94:6); (b) 4 Å MS, NMO, CH_2Cl_2 , then TPAP, rt, 30 min, 75%; (c) **20**, *i*PrOH, rt.

SCHEME 6^a



^a Reaction conditions: (a) LiAlH_4 , THF, rt, 5 h; (b) BzCl, Et_3N , DMAP, CH_2Cl_2 , rt, 15 h, 90% (over two steps); (c) $n\text{Bu}_4\text{NF}$, THF, $0\text{ }^{\circ}\text{C} \rightarrow \text{rt}$, 24 h, 96%; (d) 4 Å MS, NMO, CH_2Cl_2 , then TPAP, rt, 30 min, 87%.