

Nozaki-Hiyama-Kishi Coupling

Useful Papers:

Furstner, A. *Chem. Rev.* **1999**, 99, 991-1045.

Wessjohann, L. A. et al, *Synthesis*, **1999**, 1-36.

Takai, K. et al, *Proc. Jpn. Acad. Ser. B* **2000**, 123-131.

Feng

Columbia Synthesis Literature Group

August, 1, 2008

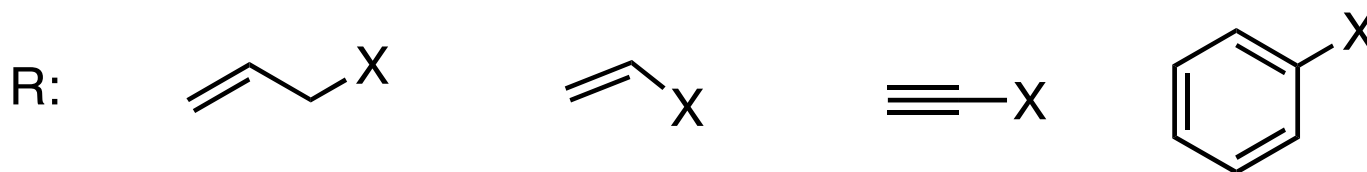
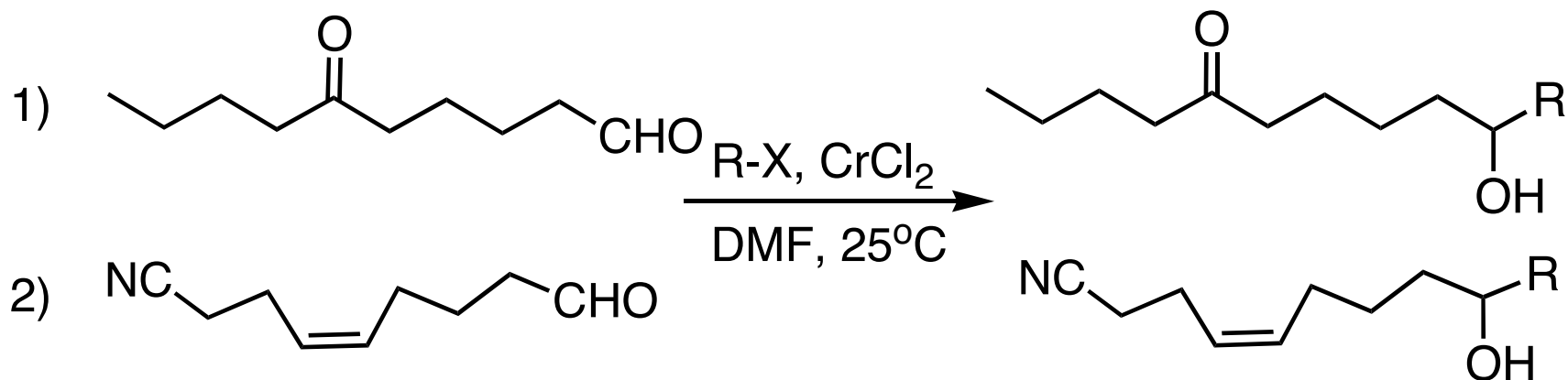
Presentation Plan

- Discovery, Early Developments
- Synthesis Applications
- Recent Developments

Introduction: Chromium

- Name after Greek word "Chroma", which means color.
- $3d^54s^1$, Cr(II), Cr(III), Cr(VI)
- Ph_2Cr , PDC, PCC, Takai Reaction
- very toxic(chromium salt)

Nozaki-Hiyama Coupling: Early Examples

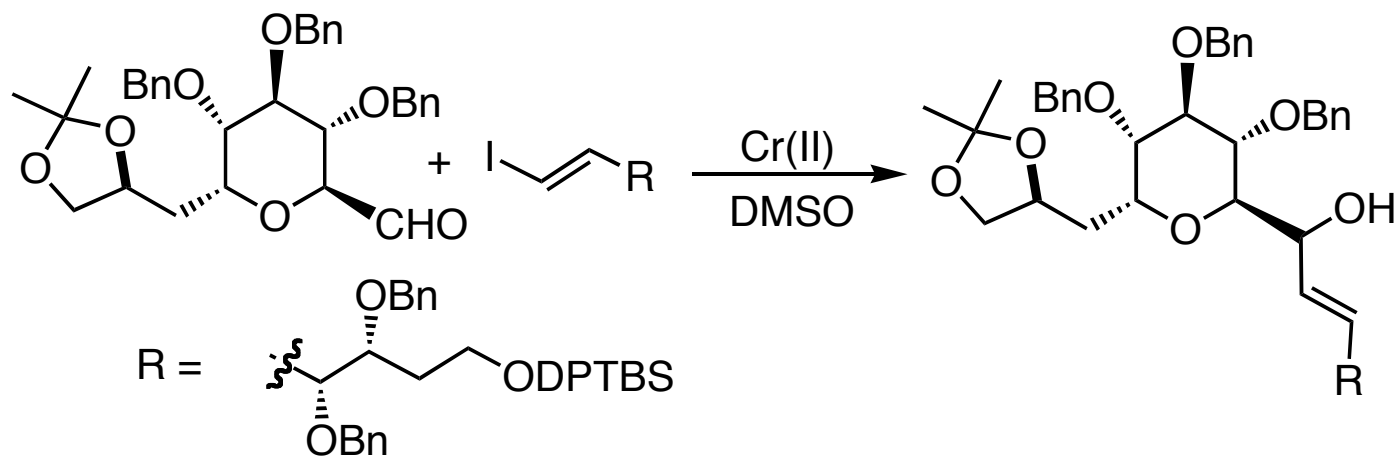


X: Cl, Br, I, OTs, OTf

Hiyama & Nozaki, *JACS*, **1976**, 3179-3181.

Hiyama & Nozaki, *TL*, **1983**, 5281-5284.

Kishi's Contribution: NHK



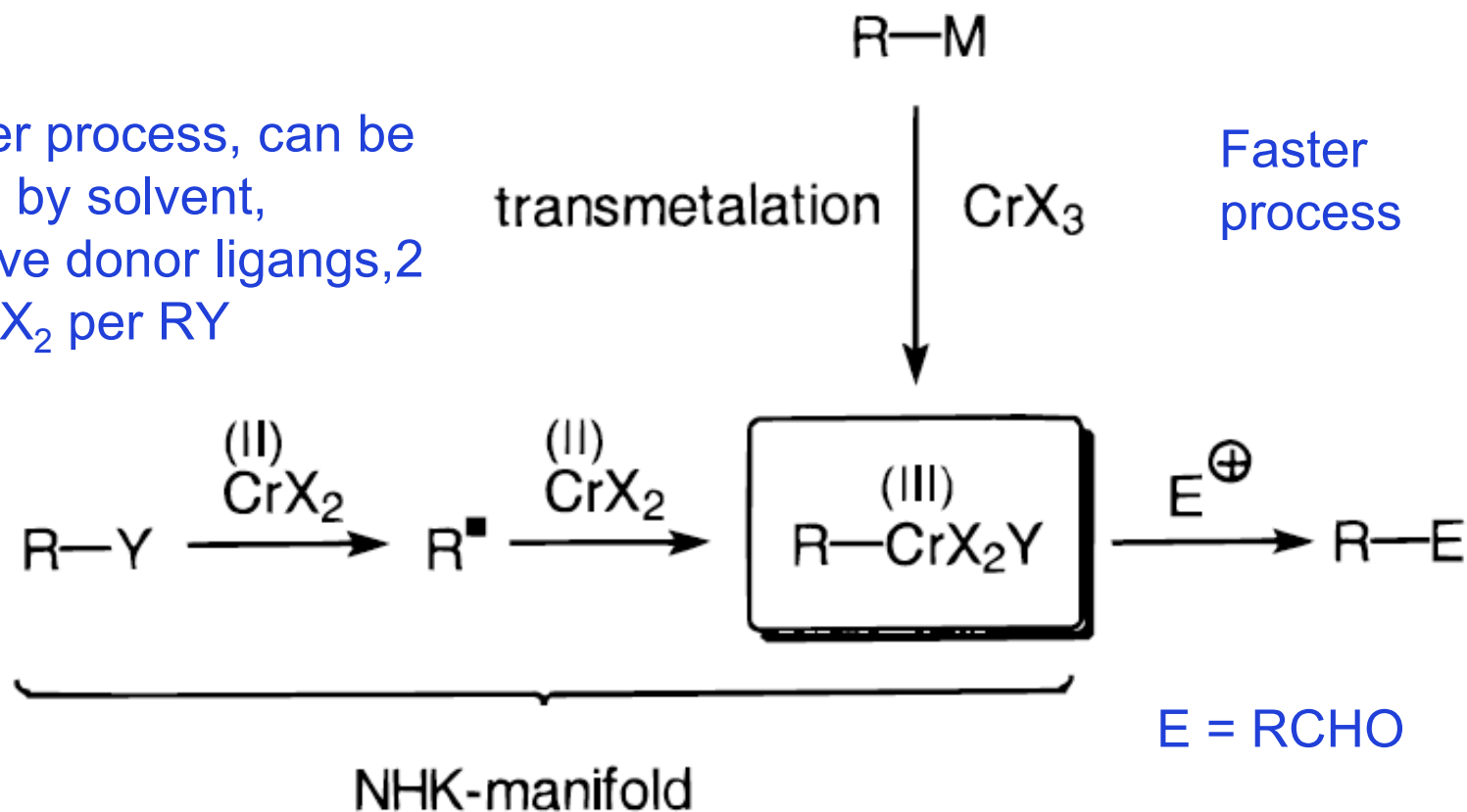
Aldehyde(eq)	Halide(eq)	Reagent	Yield(%)
1	3	CrCl ₂ /NiCl ₂ (0.1%) (6eq)	71
1	1.5	CrCl ₂ /Pd(OAc) ₂ (3eq)	54
1	10	CrCl ₂ /NiCl ₂ (0.1%) (10eq)	80
1	3	undoped CrCl ₂	0-80

Kishi, Y. et al, *JACS*, **1986**, *108*, 5644-5646.

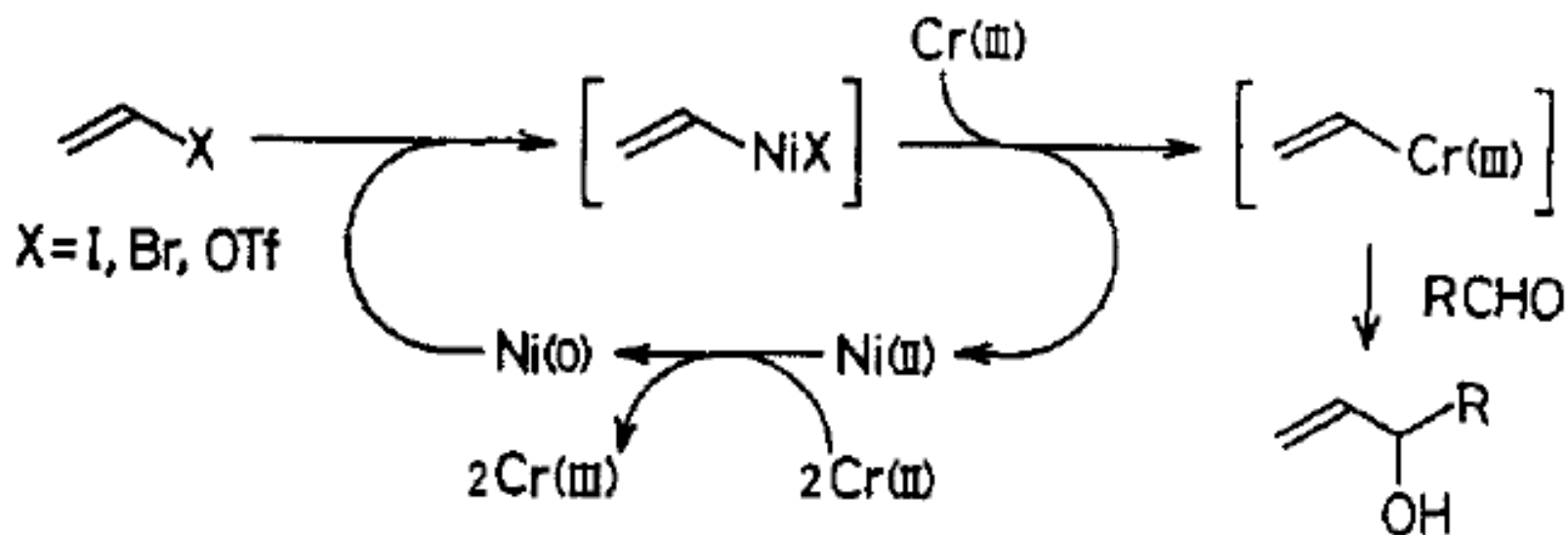
Nozaki & Takai, *JACS*, **1986**, *108*, 6048-6050.

Tentative Mechanism

Slower process, can be tuned by solvent, additive donor ligands, 2 eq CrX_2 per R-Y

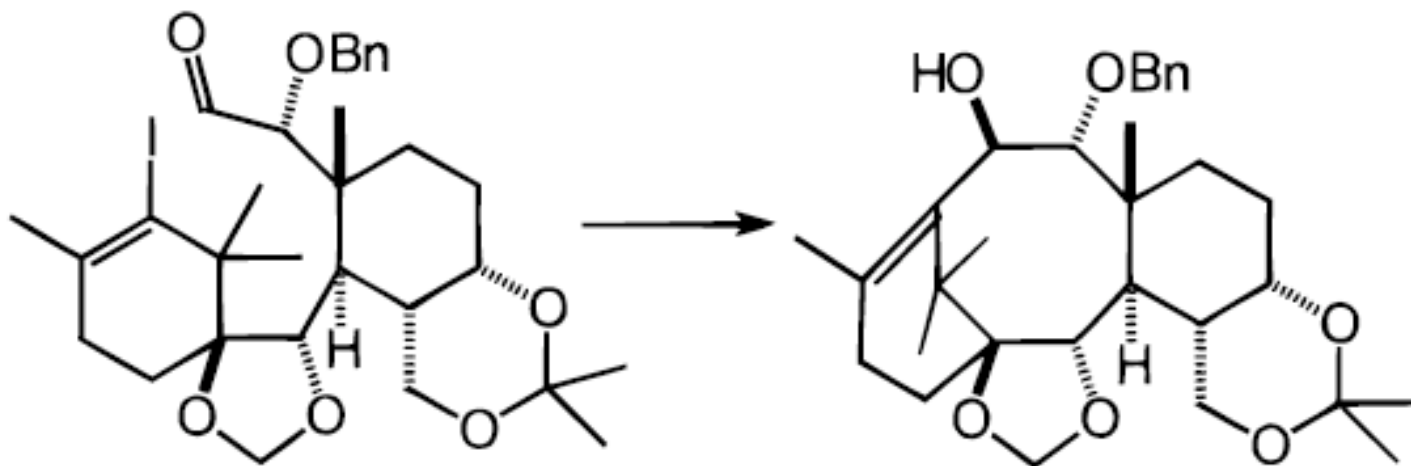


Tentative Mechanism



Nozaki & Takai, JACS, 1986, 108, 6048-6050.

Synthesis Application: Ring Formation Reaction



conventional $\text{CrCl}_2/\text{NiCl}_2$ cat., 0%

$\text{CrCl}_2/\text{NiCl}_2$ (10%), THF:DMF:4-t-BuPy (6:3:1),

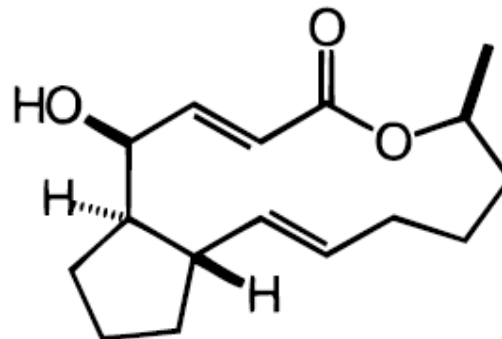
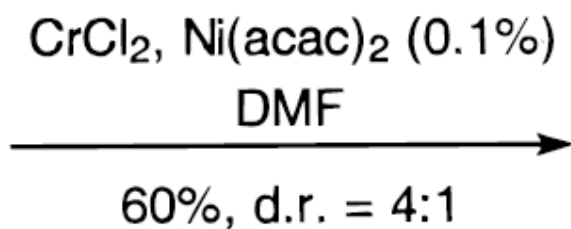
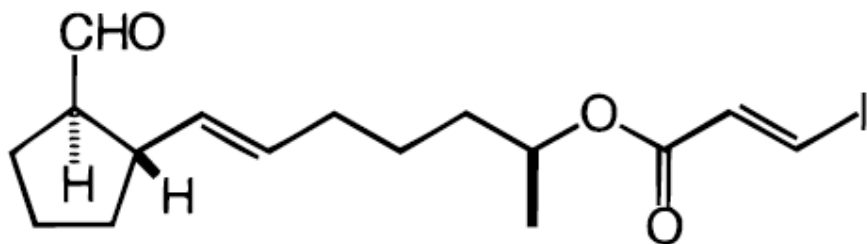
65%

Py!!!

Kishi, et al, *TL*, **1993**, 34, 5999-6002.

Kishi, et al, *TL*, **1993**, 34, 6003-6006.

Ring Formation Reaction: Brefeldin



RCM

Suzuki

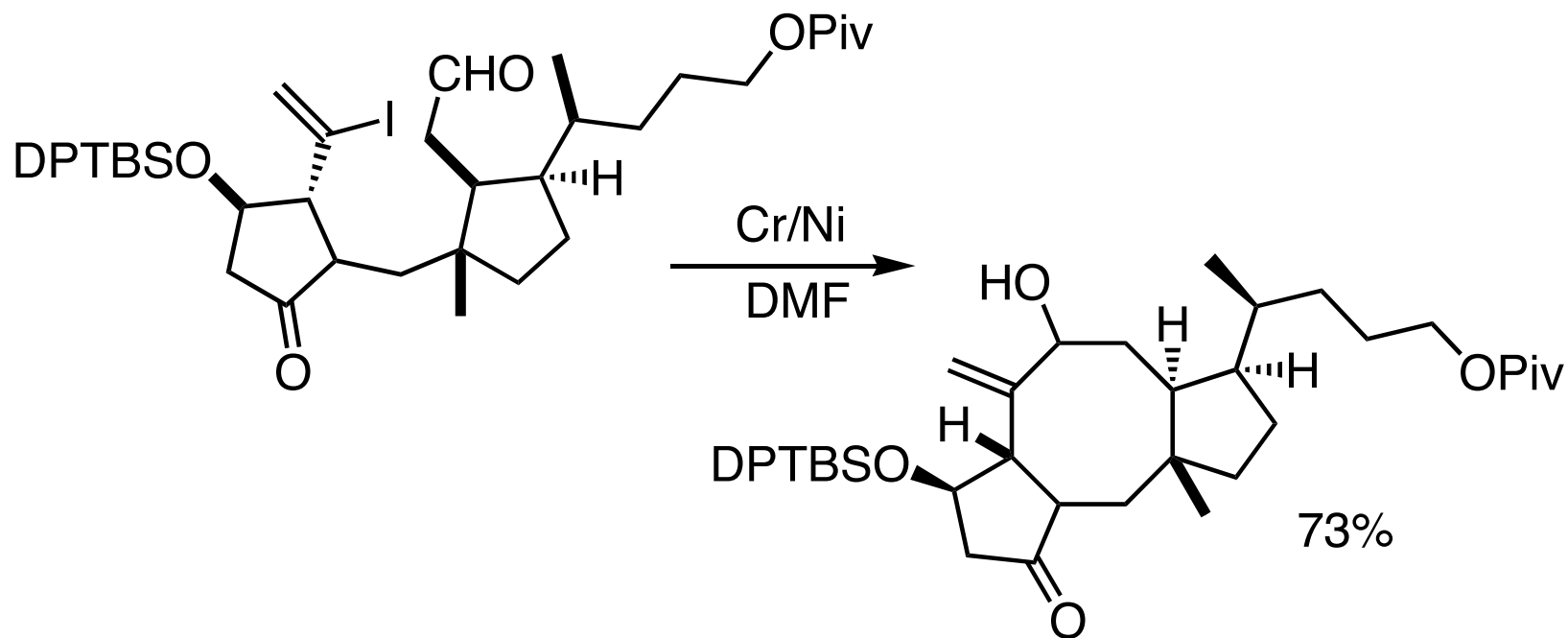
Wittig

Yamaguchi

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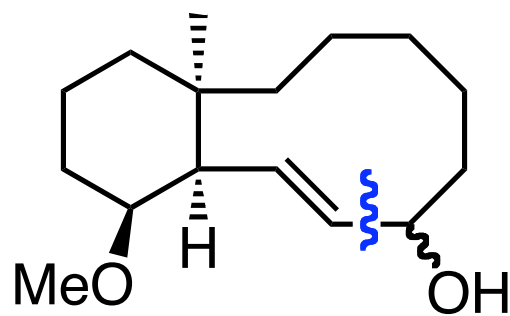
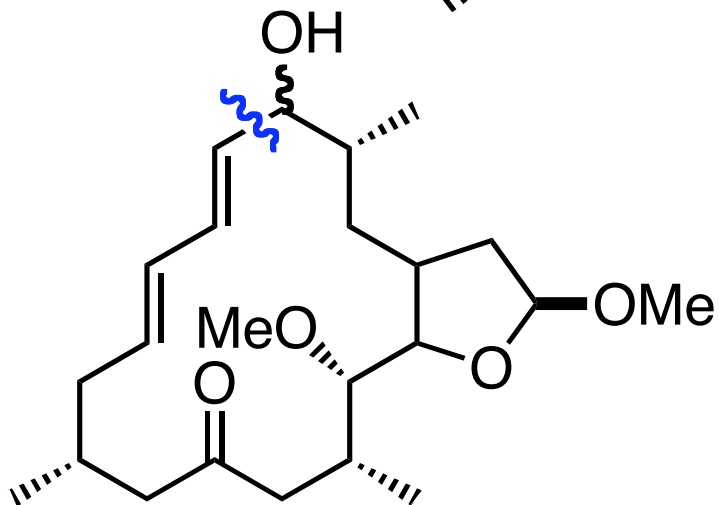
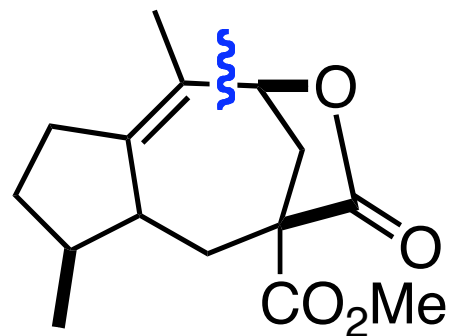
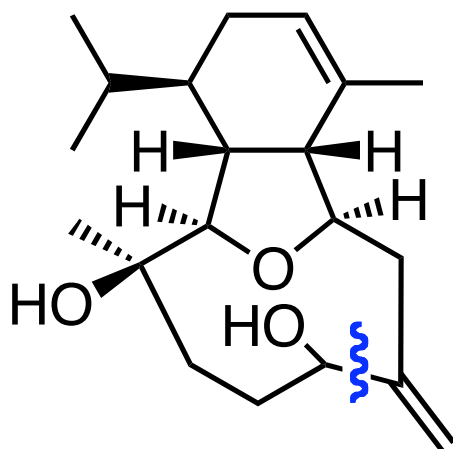
Schreiber, S. L. et al, *JACS*, **1988**, *110*, 5198-5200.

Ring Formation Reaction: OphiobolinC

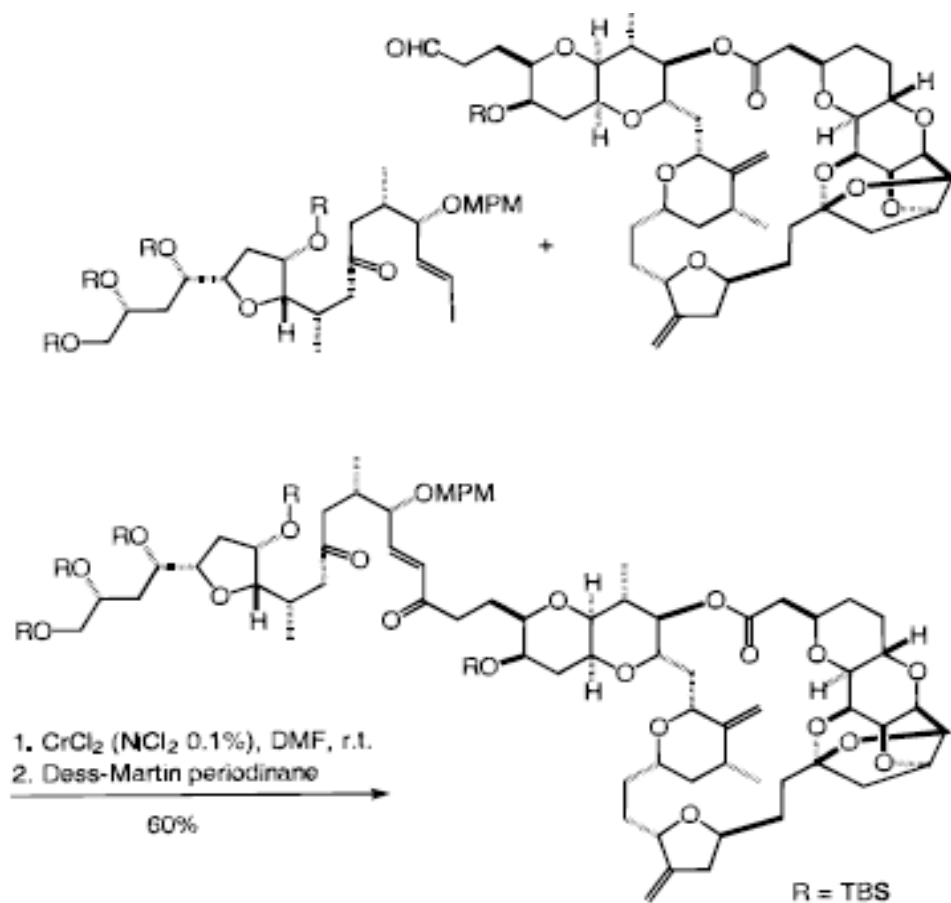


Kishi, Y. et al, *JACS*, **1989**, *111*, 2735-2737.

More Examples

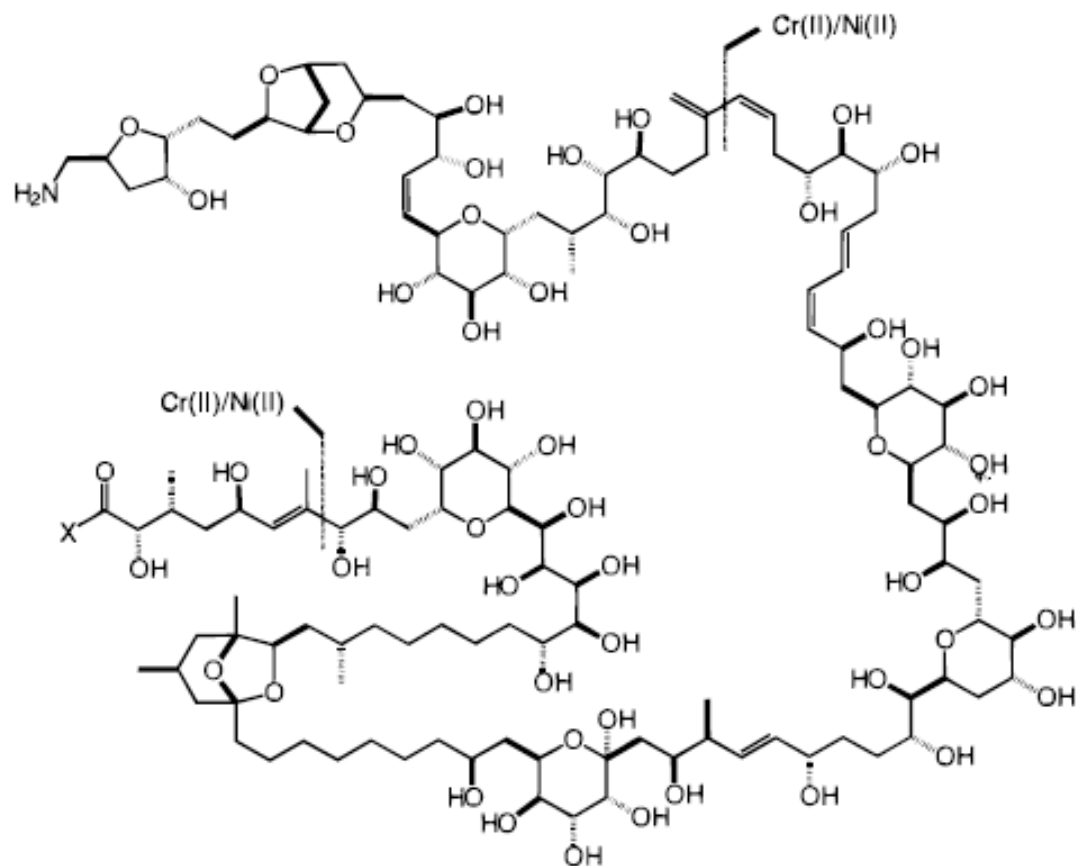


Synthesis Application: Cross Coupling, Halichondrin B



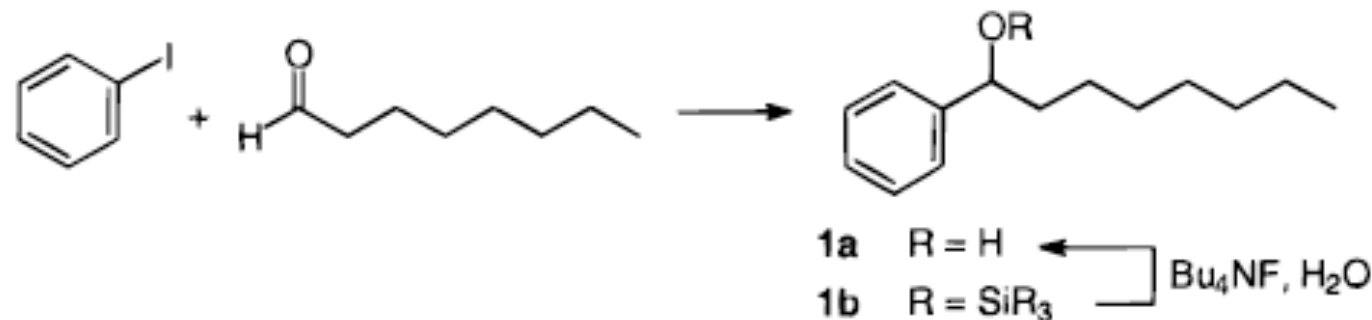
Kishi, Y. *Pure Appl. Chem.* **1992**, 64, 343.

Synthesis Application: Cross Coupling, Palytoxin



Kishi, Y. et al, *JACS*, **1989**, *111*, 7525.

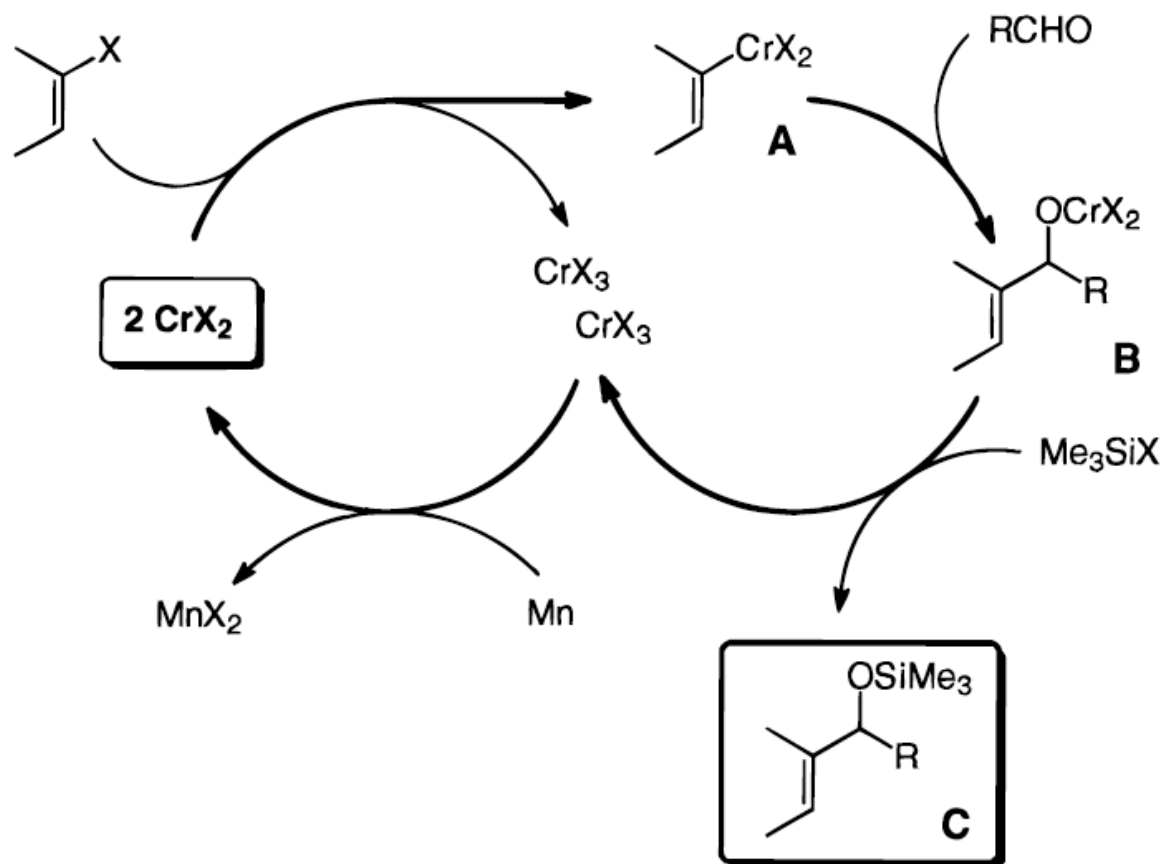
Recent Development: Catalytic Amount Cr(II)



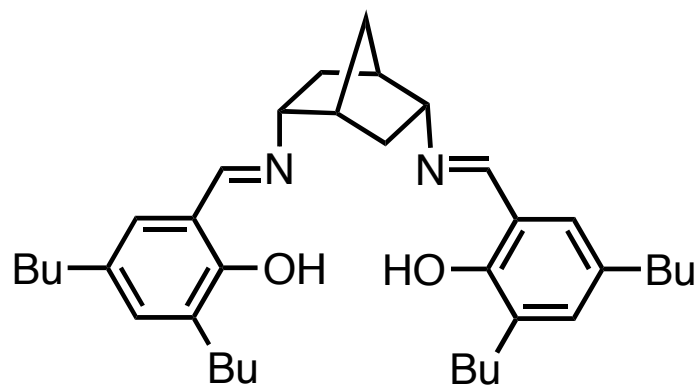
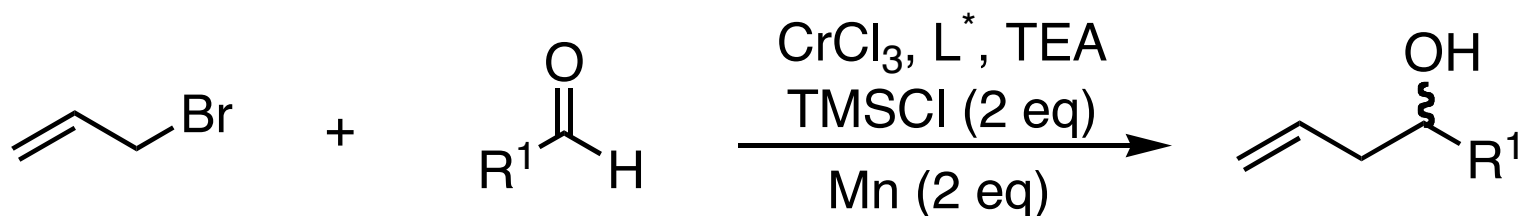
entry	CrCl ₂ (mol %) ^a	additives	T (°C)	isolated yield (%) ^b
1	400		20	78 ^c
2	400		50	65
3	30	Zn, TMSCl	70	30–40 ^d
4	15	Mn, TMSCl	50	67
5	15	Mn, ClMe ₂ Si(CH ₂) ₃ CN	50	72
6	9	Mn, ClMe ₂ Si(CH ₂) ₃ CN	50	58
7	0	Mn, ClMe ₂ Si(CH ₂) ₃ CN	50	0 ^e
8	0	Mn, ClMe ₂ Si(CH ₂) ₃ CN, NiCl ₂ (cat.)	50	0 ^e

Furstner, A.; Shi, N. *JACS*, **1996**, *118*, 2533-2534.

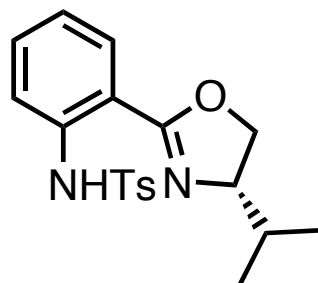
Tentative Mechanism



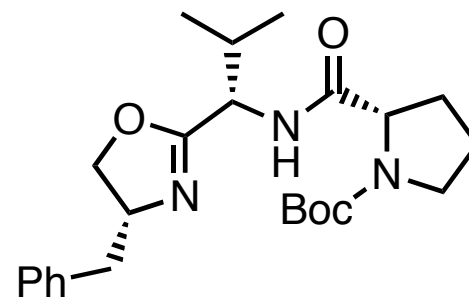
Catalytic Enantioselective NHK Reaction



Berkessel, ACIE, 2003
ee 30%-90%



Kishi, JACS, 2004
ee 83%-94%



Sigman, OL, 2005
ee 51%-94%

Outlook

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