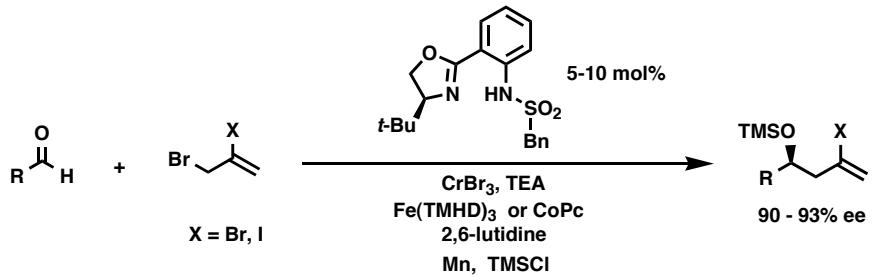
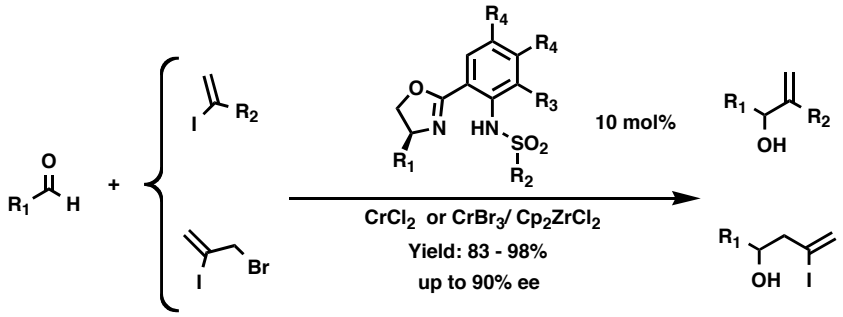
Fe/Cr- and Co/Cr- Mediated Catalytic Asymmetric 2-Haloallylations of Aldehydes



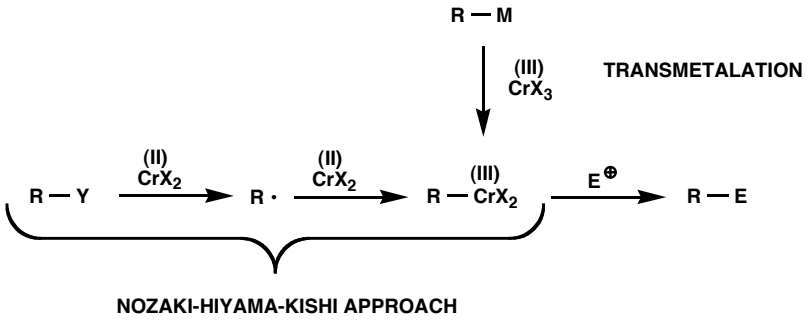
Kurosu, M.; Lin, M.-H.; Kishi*, Y.
Harvard University
J. Am. Chem. Soc. **2004**, *126*, 12248-12249.

New Catalytic Cycle for Couplings of Aldehydes with Organochromium Reagents



Namba, K.; Kishi*, Y.
Harvard University
Org. Lett. **2004**, *6*, 5031-5033.

Organochromium (III) Reagents in C-C Bond Formation



Unique Features of the Nozaki-Hiyama-Kishi (NHK) Reactions:

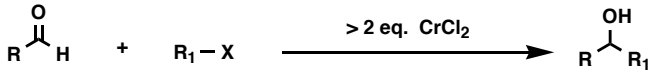
- ***High Chemoselectivity*** **favoring additions to aldehydes**
- ***Excellent Compatibility*** **with an array of other electrophilic groups**
- ***Low Basicity*** **(chiral centers α to the reacting aldehyde are not racemized, free hydroxy groups are in some cases compatible with the reaction conditions)**
- **The *High Stability* of the emerging O-Cr(III) bond constitutes a formidable driving force (synthetic tool for the formation of highly strained ring systems)**

For a Review on C-C Bond Formations Involving Organochromium (III) Reagents see:
Fürstner, A. *Chem. Rev.* **1999**, *99*, 991.

NHK Reactions: Background (I)

Stoichiometric NHK Reactions

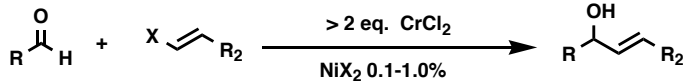
- Nozaki-Hiyama (1977-1983):

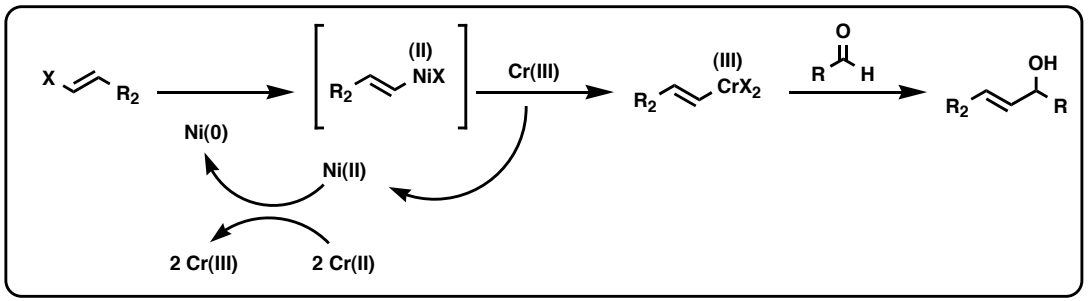


R_1 = allyl- , propargyl- , alkenyl- , alkynil-, aryl-

- Kishi and Nozaki-Takai (1986):

Traces of Nickel salts exert a catalytic effect on the formation of the C-Cr(III) bond:

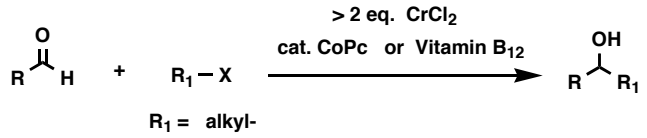


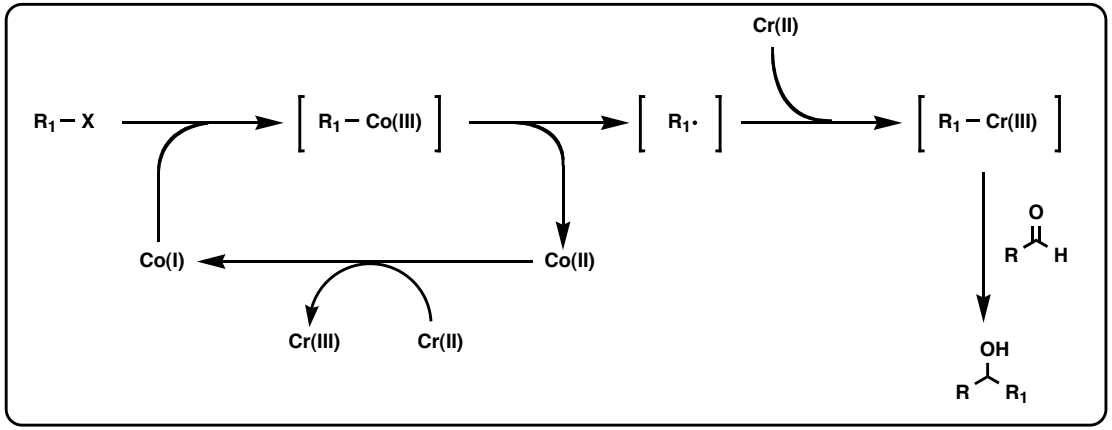


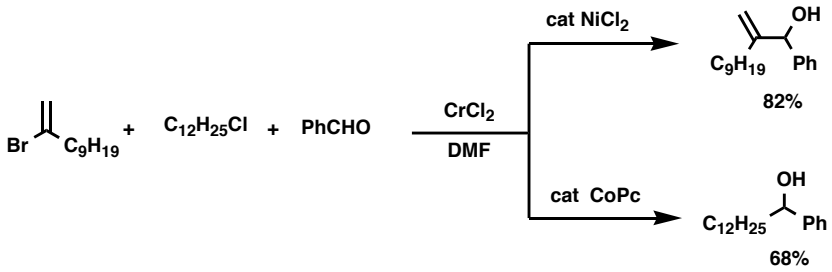
NHK Reactions: Background (II)

Addition of Alkylchromium (III) Reagents to Aldehydes

- Takai - Utimoto (1989):



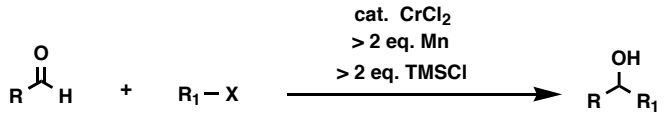




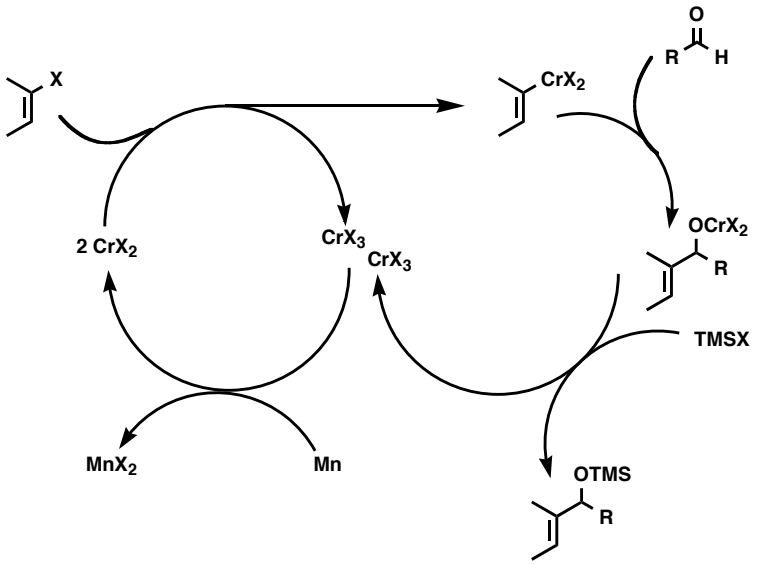
NHK Reactions: Background (III)

Catalytic NHK Reactions

- Fürstner-Shi (1996):



R = allyl- , propargyl- , alkenyl- , alkynil-, aryl-



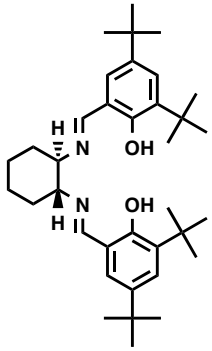
A Problem:

With low catalyst-loading, coupling reactions smoothly progress only to a certain degree but not to completion due to the formation of TMS-enol ethers of aldehydes

NHK Reactions: Background (IV)

Catalytic Asymmetric NHK Reaction

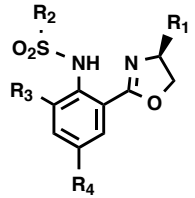
- Cozzi - Umani Ronchi (1999):



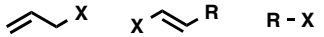
Nucleophiles Used:

Y = (40 - 67) %, ee = (65 - 89)%

- Kishi (2002):

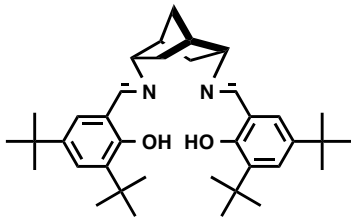


Nucleophiles Used:



Y = (70 - 90)%, de = (75 - 90)%

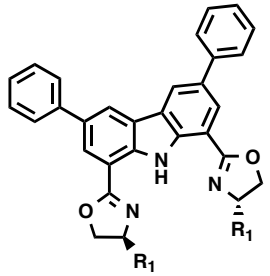
- Paterson - Berkessel (2003):



Nucleophiles Used:

Y = (54 - 78) %, ee = (54 - 90)%

- Nakada (2003):



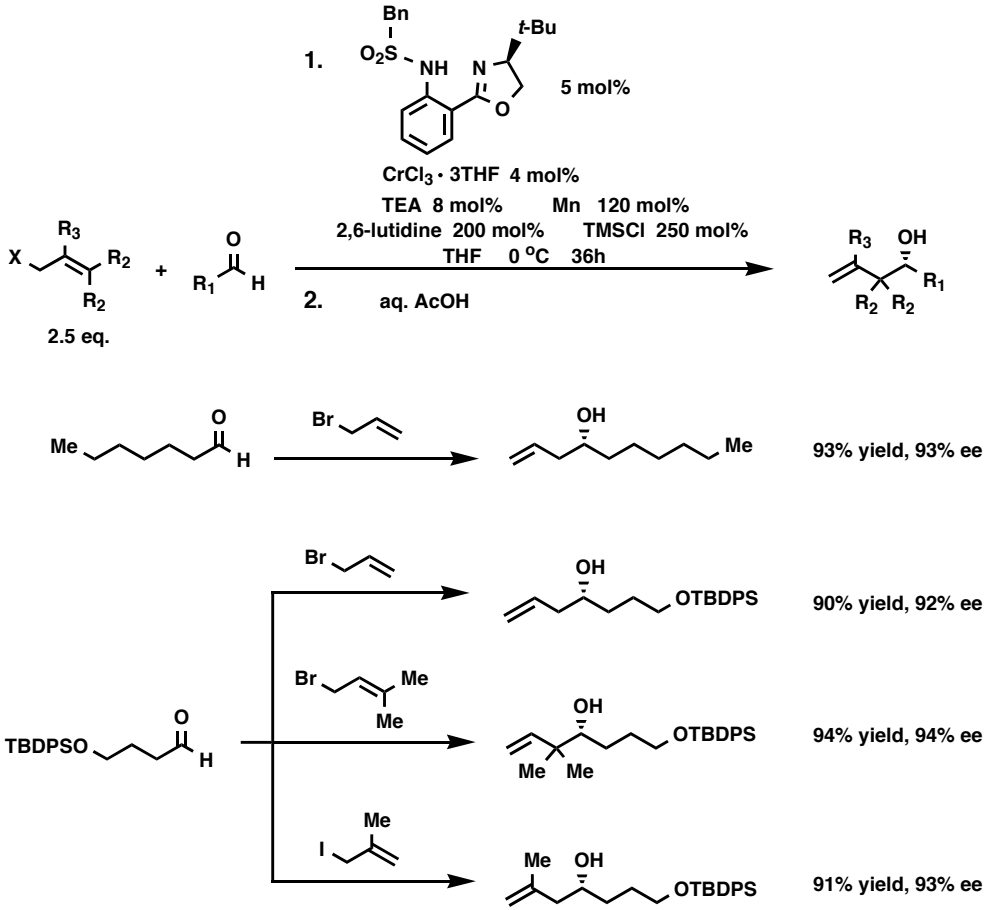
Nucleophiles Used:

Y = (77 - 98)%, ee = (89 - 96)%

Y = (20 - 93)%, ee = (51 - 98)%

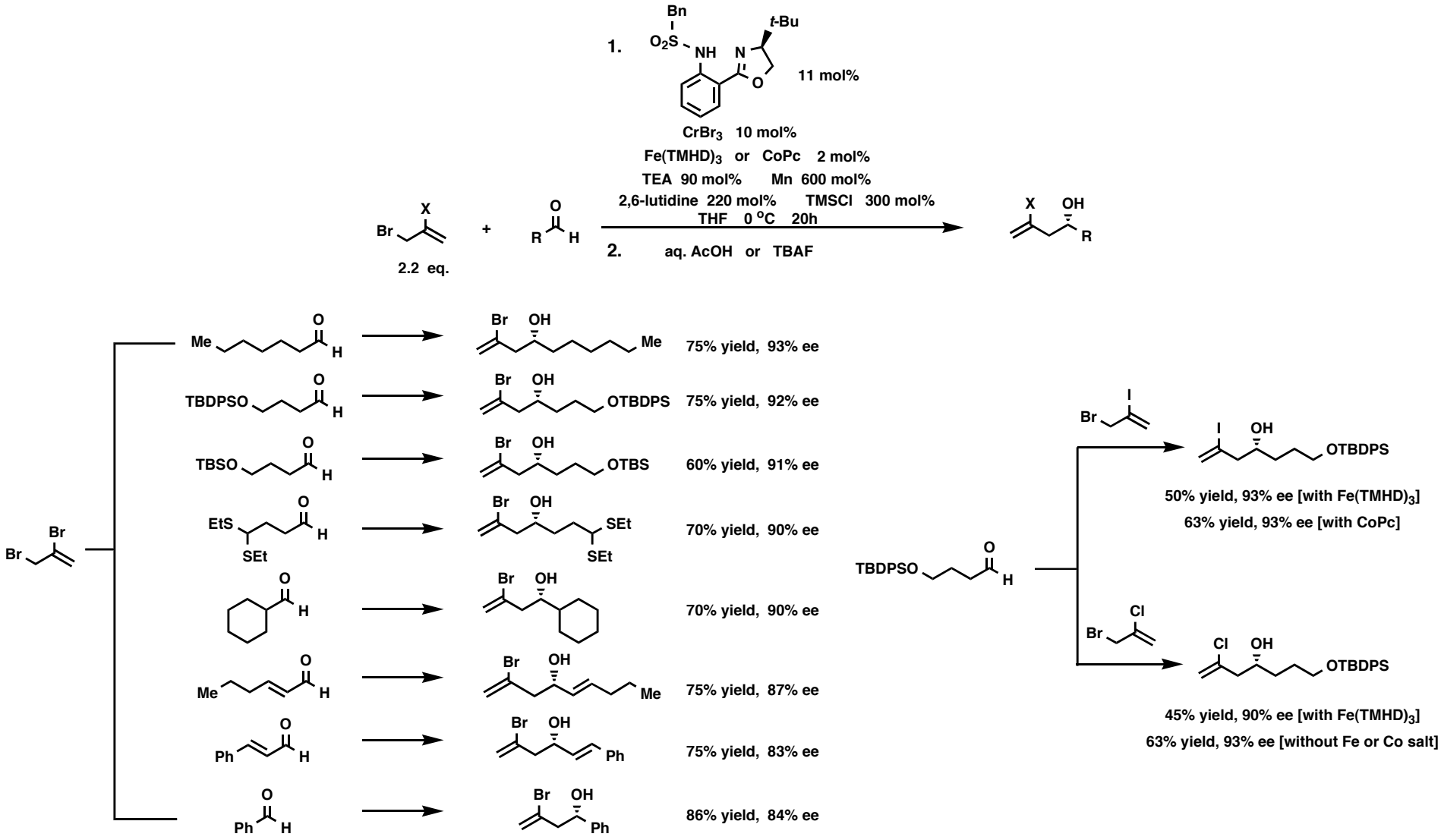
Fe/Cr- and Co/Cr- Mediated Catalytic Asymmetric 2-Haloallylations of Aldehydes (I)

Catalytic Asymmetric Allylations of Aldehydes



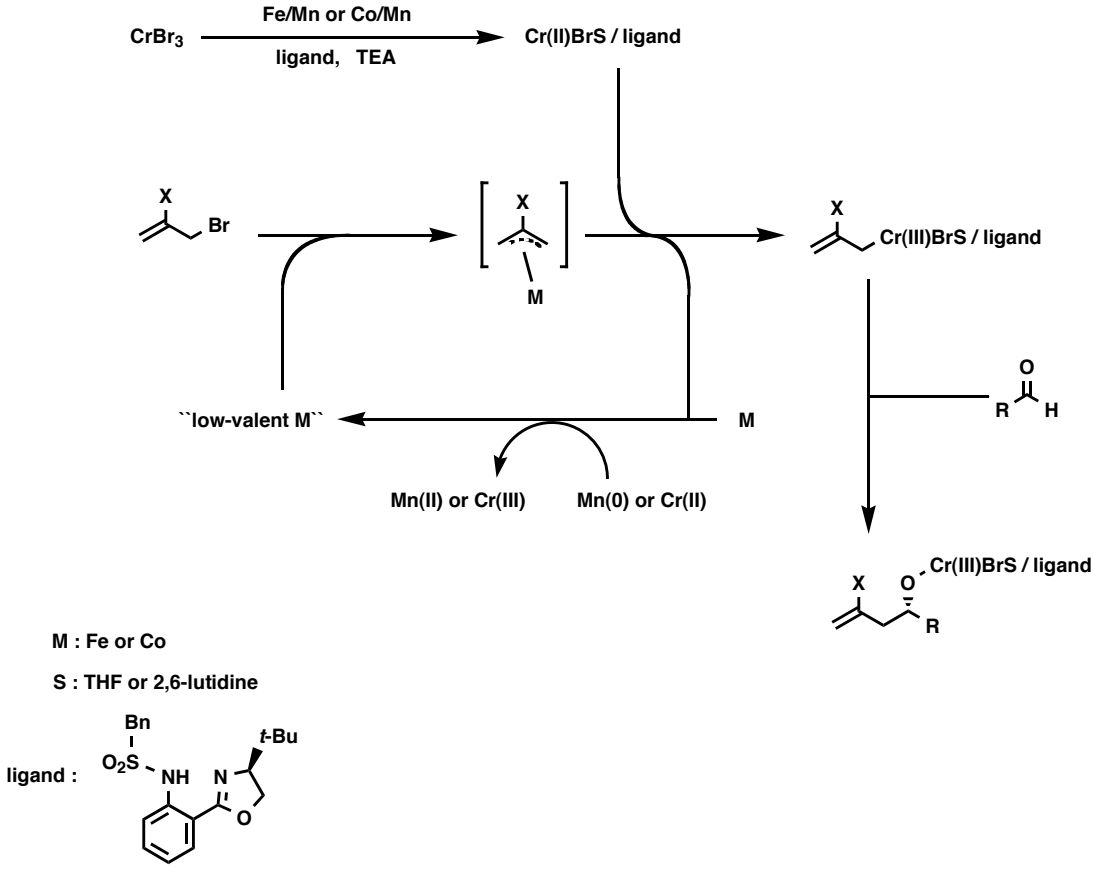
Fe/Cr- and Co/Cr- Mediated Catalytic Asymmetric 2-Haloallylations of Aldehydes (II)

Catalytic Asymmetric 2-Haloallylations of Aldehydes



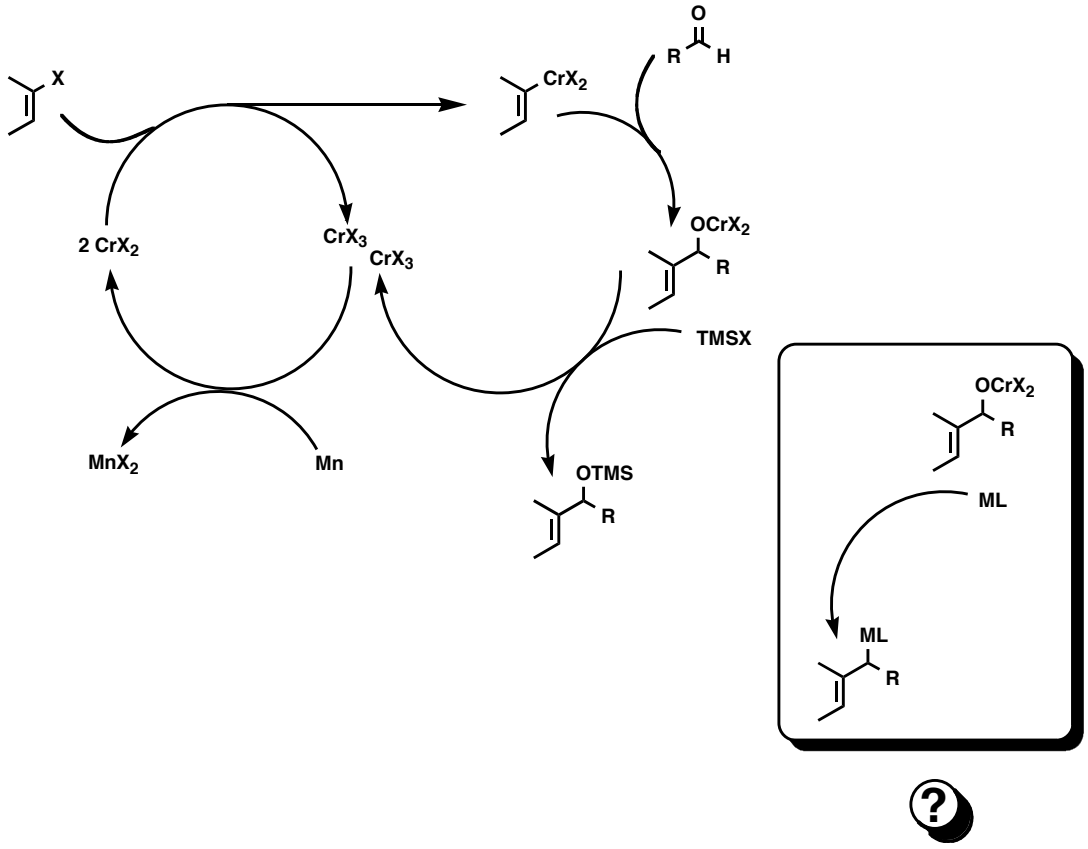
Fe/Cr- and Co/Cr- Mediated Catalytic Asymmetric 2-Haloallylations of Aldehydes (III)

Proposed Mechanism



New Catalytic Cycle for Couplings of Aldehydes with Organochromium Reagents (I)

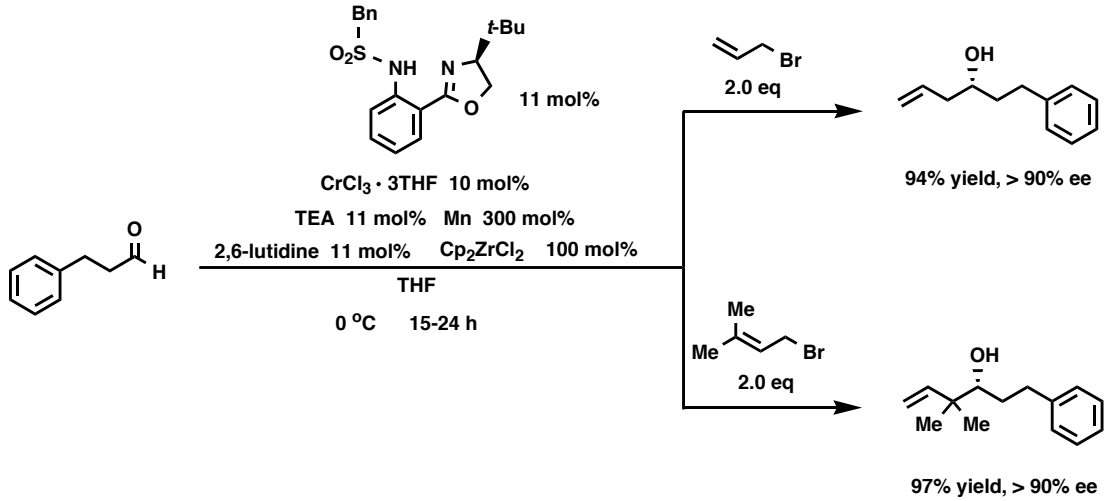
Is It Possible to Improve the Fürstner Catalytic Cycle?



Yes, Cp_2ZrCl_2 Can Replace TMSCl !

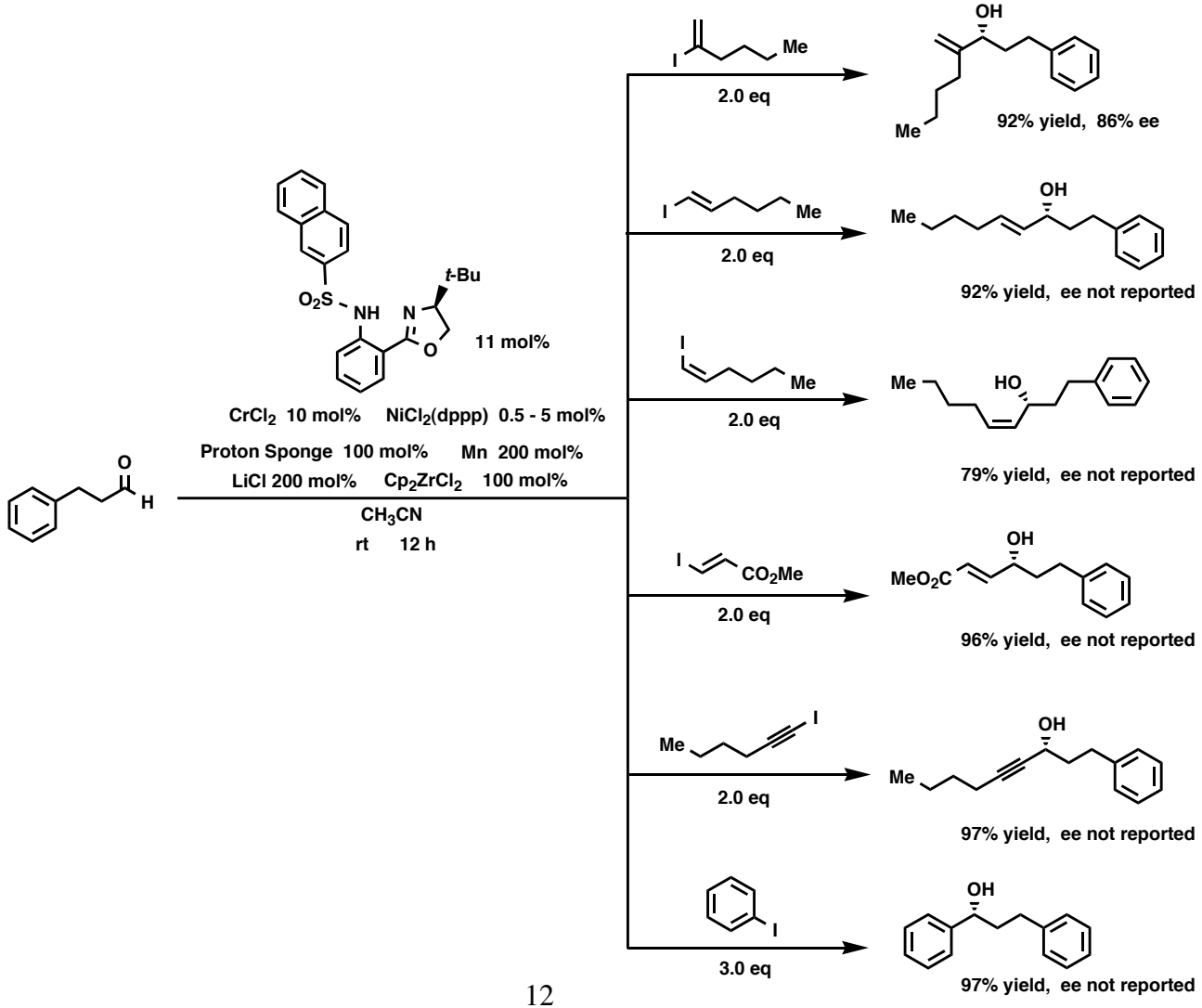
New Catalytic Cycle for Couplings of Aldehydes with Organochromium Reagents (II)

Cr Mediated Couplings



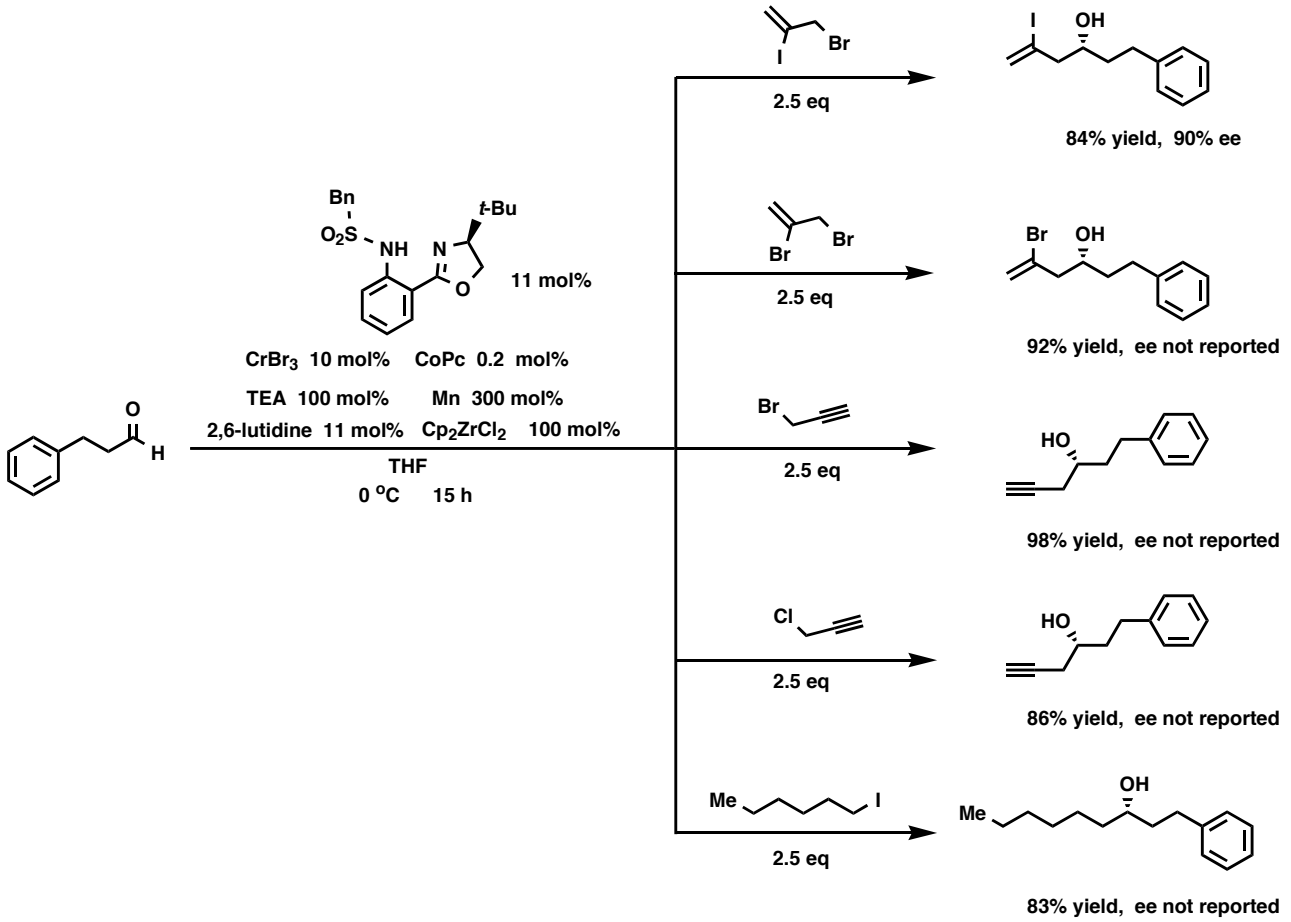
New Catalytic Cycle for Couplings of Aldehydes with Organochromium Reagents (III)

Ni/Cr Mediated Couplings



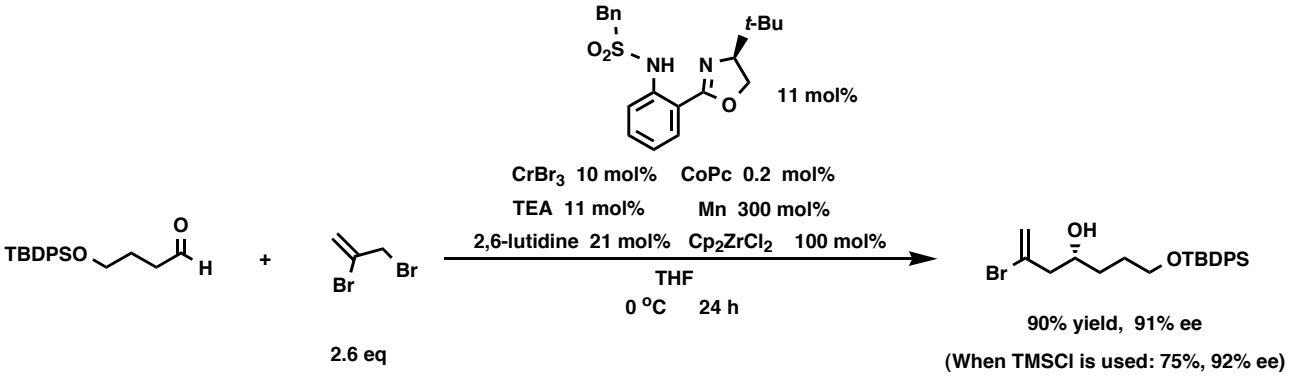
New Catalytic Cycle for Couplings of Aldehydes with Organochromium Reagents (IV)

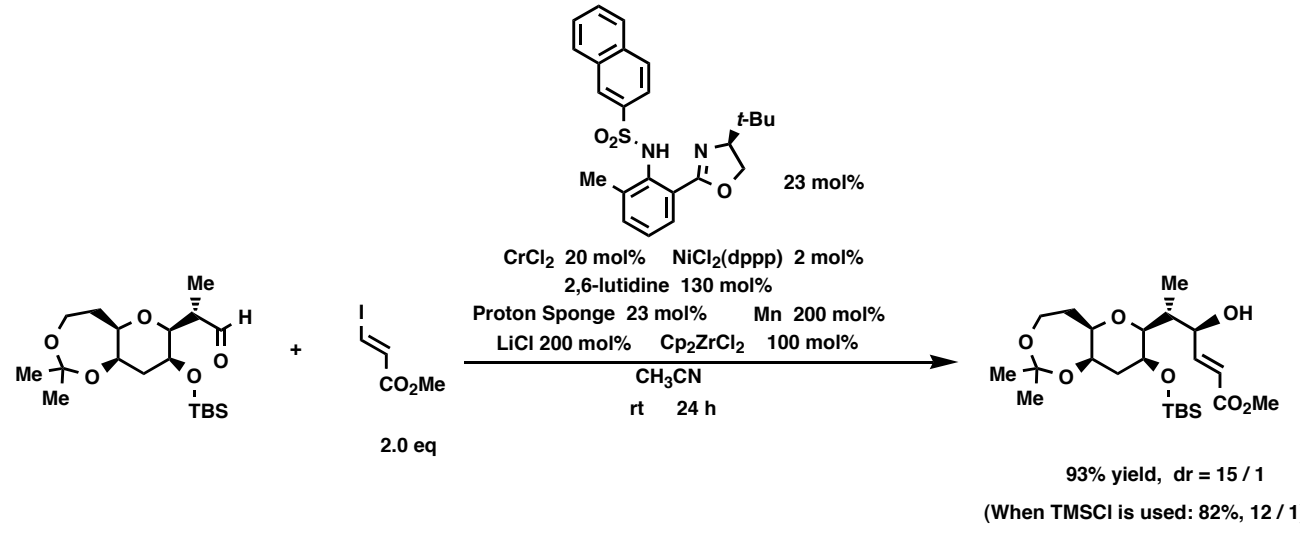
Fe/Cr- and Co-Cr- Mediated Couplings



New Catalytic Cycle for Couplings of Aldehydes with Organochromium Reagents (V)

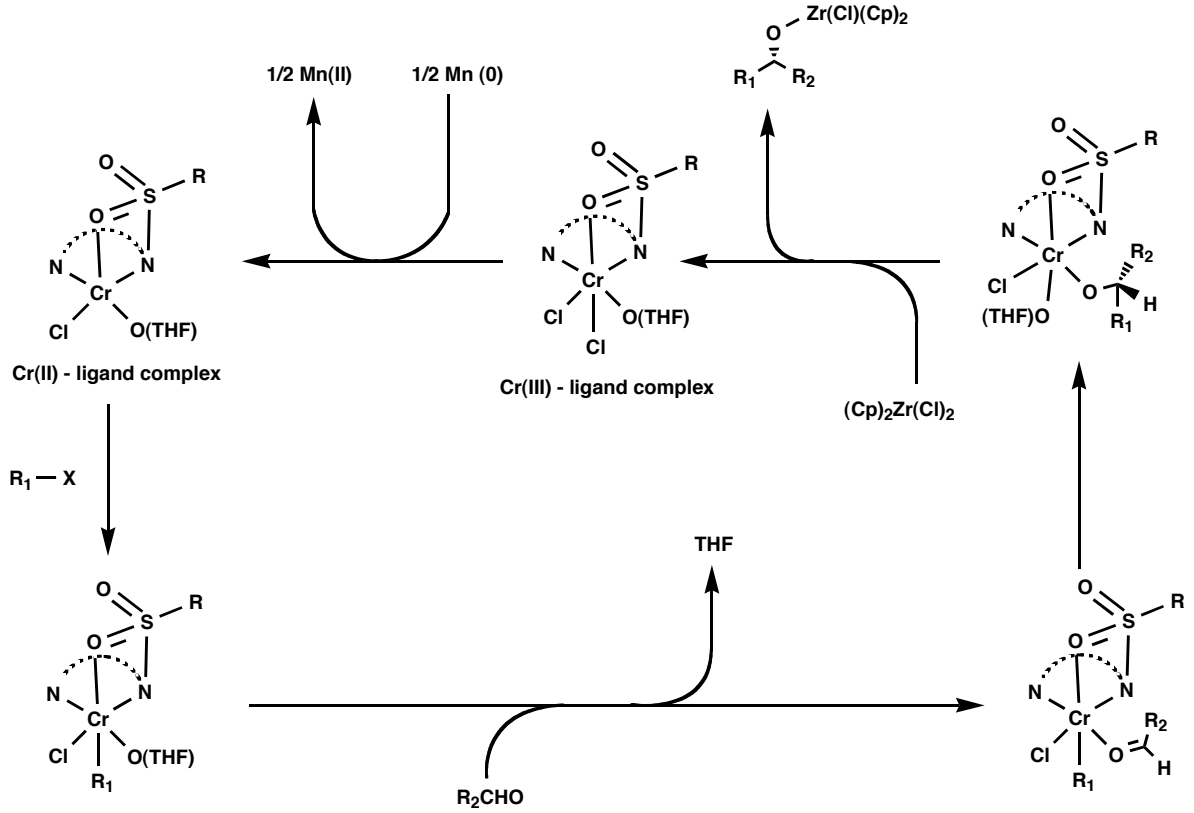
Examples Selected from the Ongoing Halichondrin Program: Usefulness of the New Catalytic Cycle





New Catalytic Cycle for Couplings of Aldehydes with Organochromium Reagents (VI)

Proposed Catalytic Cycle



Summary

Fe/Cr and Co/Cr Mediated Catalytic Asymmetric 2-Haloallylation of Aldehydes

- **A novel class of (transition metal)-Cr mediated process has been applied in a new kind of allylation reaction (2-haloallylation) of aldehydes**
- **The new 2-haloallylation process has been successfully realized in a catalytic and asymmetric fashion**
- **The coupling reactions furnish products that are valuable synthetic intermediates in organic synthesis**

New Catalytic Cycle for Couplings of Aldehydes with Organochromium Reagents

- **The use of Cp_2ZrCl_2 in place of TMSCl has resulted in the discovery of a new catalytic cycle for NHK reactions**
- **With the new catalytic cycle higher yields of the coupling products are obtained**
- **No additional desilylation step is required at the end of the coupling process**

Future Work

Fe/Cr and Co/Cr Mediated Catalytic Asymmetric 2-Haloallylation of Aldehydes

- **An investigation of the Scope and Limitations of this new class of reaction is required as well as a detailed Mechanistic Investigation.**
  (What is the role of 2,6-lutidine? Why the 2-chloroallylation reaction works better without Fe or Co salts? What is the exact role of Fe and Co?)

Catalytic Asymmetric NHK reactions

Ligand Optimization is still needed