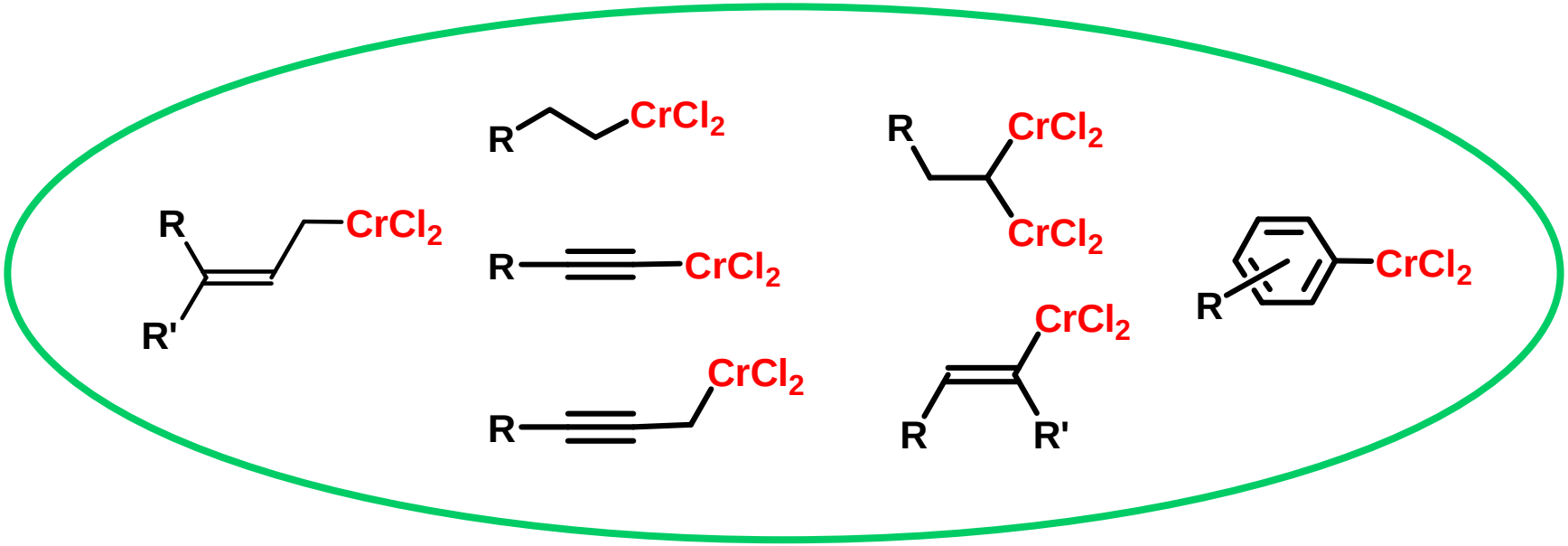
Dmitry VALYAEV

Organochromium Reagents for C–C bond formation: from Stoichiometric Reactions to Enantioselective Catalysis



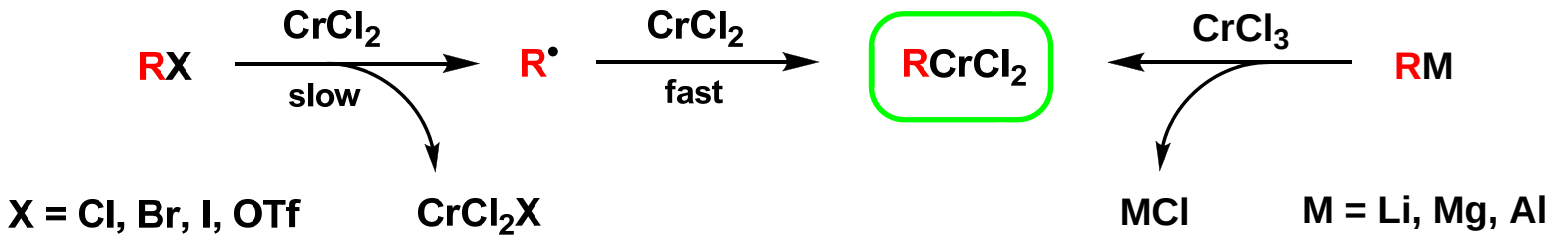
Séminaire Biblio, le 8 mars 2012

The most important milestones of organochromium chemistry

1977	**Stoichiometric activation of allylhalogenides by $CrCl_2$ Highly chemoselective addition of $RCrCl_2$ to aldehydes**	*Nozaki and Hiyama*
1986	**Doping of $CrCl_2$ with $NiCl_2$: broadening of the scope for less reactive vinyl- and aryl-substituted substates**	*Nozaki, Hiyama, Kishi*
1987	**$CrCl_2$-promoted aldehyde olefination with geminal dihaloalkanes**	*Utimoto, Takai*
1989	**Discovery of Co-cocatalysts for the $CrCl_2$ activation of alkylhalides**	*Utimoto, Takai*
1996	**First catalytic-in-chromium Nozaki-Hiyama-Kishi (NHK) reaction**	*Fürstner*
1999	**Development of the first enantioselective catalytic NHK reaction**	*Cozzi*
2004-	**Design of highly effective catalytic systems for enantioselective NHK reaction for the majority of applied halogenated substrates**	*Kishi, Sigman, Yamamoto*

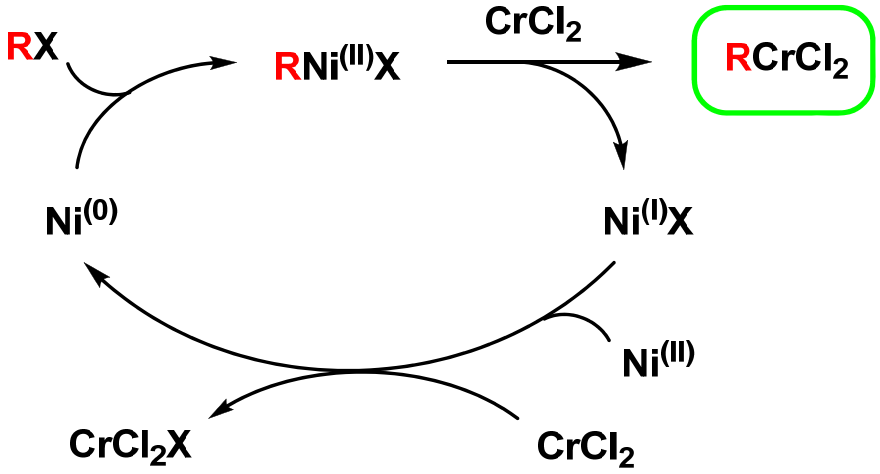
Reviews on NHK reactions: *Chem. Rev.* **1999**, *99,* 991; *Adv. Synth. Catal.* **2007**, *349*, 2407

Possible routes to the formation of organochromium species

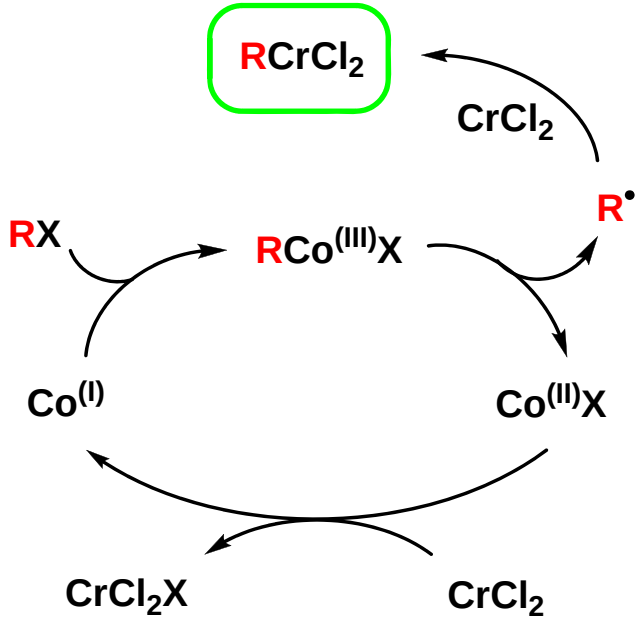


Reduction followed by radical trapping

Direct transmetallation

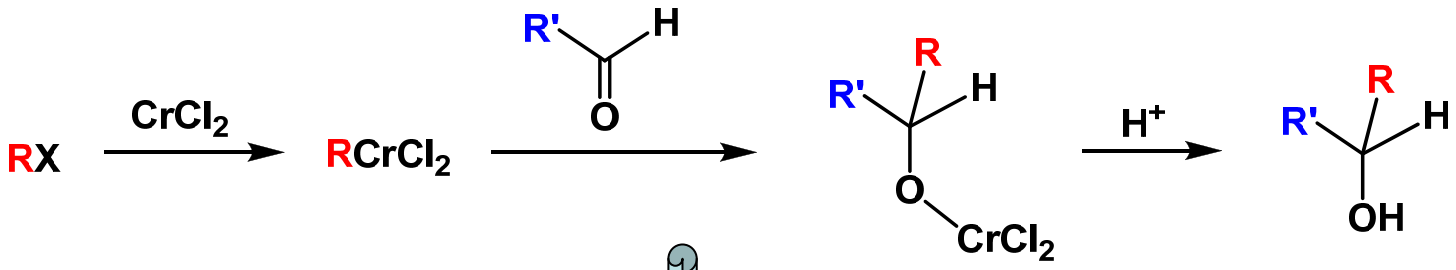


Activation of the substrate by the oxidative addition on Ni(0) followed by transmetallation



Cobalt-catalyzed free radical formation

Synthesis and reactivity of organochromium compounds: general remarks



Insertion of Cr(II) under mild conditions into wide variety of substrates

Exceptional chemoselectivity of organo-chromium compounds towards aldehydes

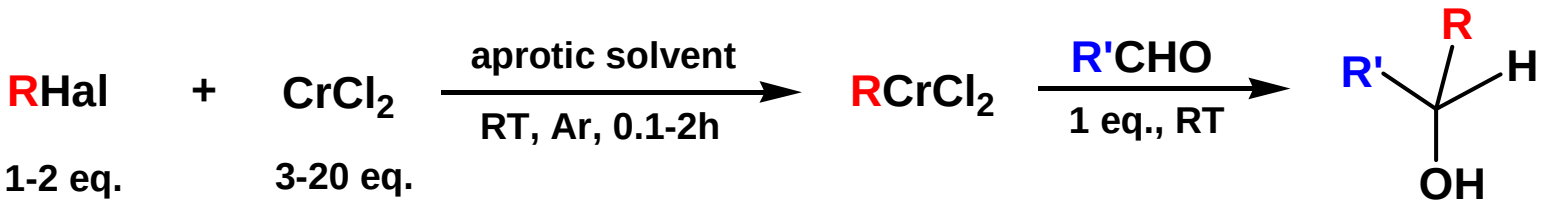
Strong driving force of $RCrCl_2$ addition due to the O–Cr(III) bond formation

Low basicity of organochromium reagents

High tolerance to various functional groups in both reaction partners

High and predictable stereochemical preferences

NHK reaction setup: choice of chromium source and nickel co-catalyst



\+ $NiCl_2$ 0.1-10%

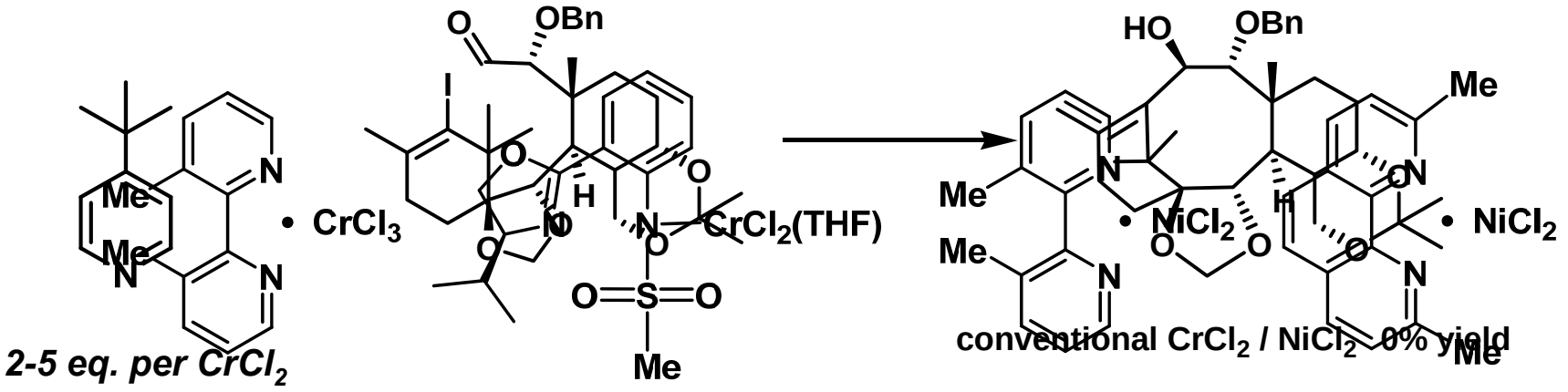
$CrCl_2$

Very air-sensitive
Highly hydroscopic

$CrCl_3$

Air and moisture stable
Much cheaper than $CrCl_2$

$LiAlH_4$, Zn, Na/Hg, Mn



Kishi, *TL* **1997**, *38*, 6355; Kishi, *Org. Lett.* **2005**, *7*, 5417; *Org. Lett.* **2005**, *7*, 5421

Influence of the solvent and work-up on the output of NHK reaction

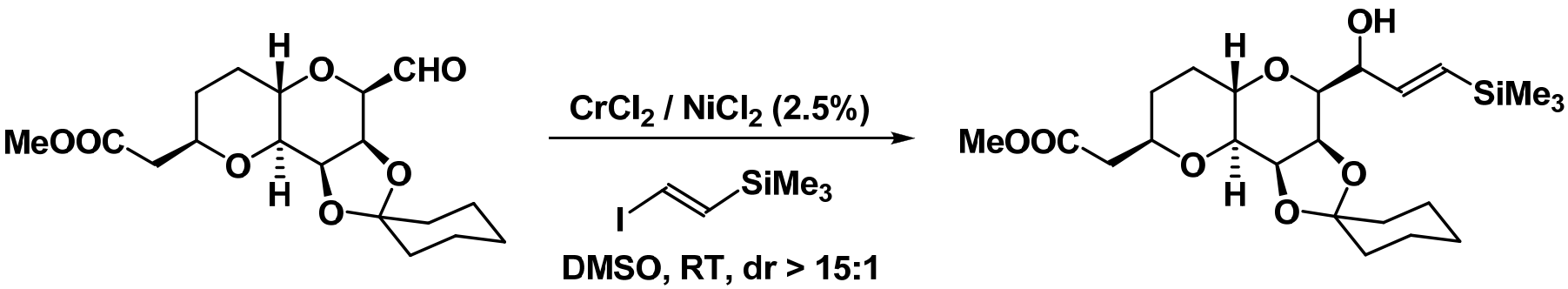
THF, DME, Dioxane, MeCN, DMF, DMSO

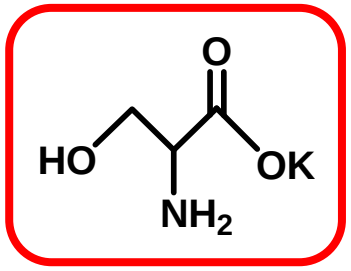
↓

DME/DMF 20:3 — **Solubility of the chromium salts** — **Dioxane/THF 6:1**

↓

DME/MeCN 3:1 — **Influence of the solvent on the reduction potential of Cr(II) species** — **THF/DMF 20:1**





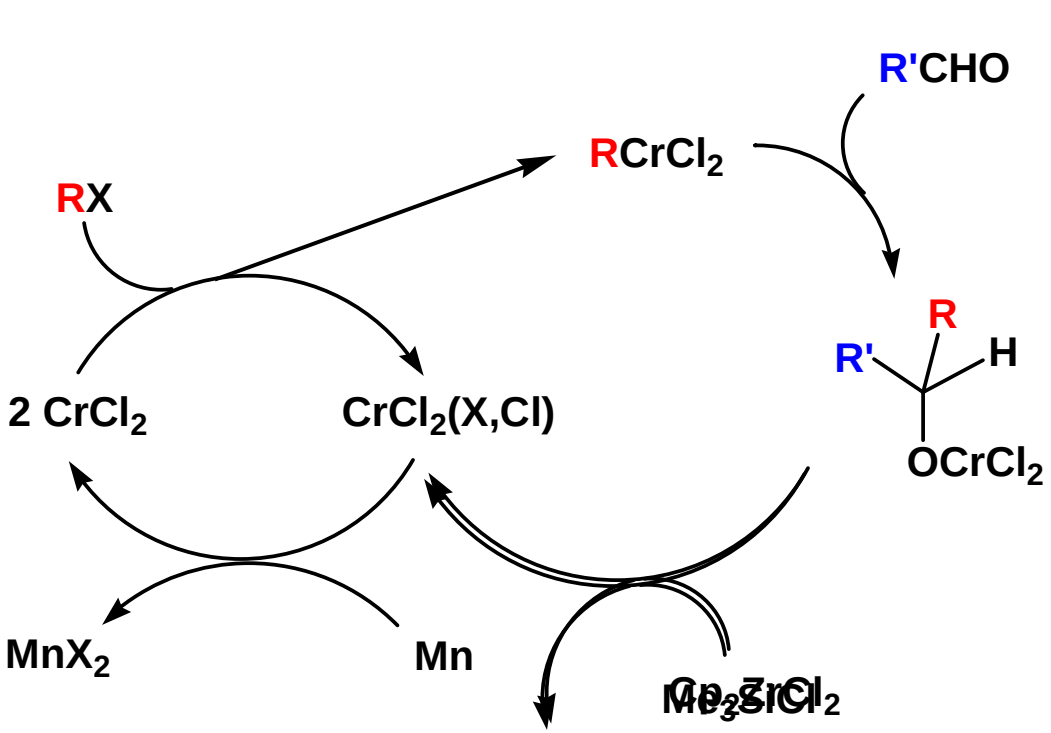
Aqueous potassium *d,l*-serinate

work-up with NH_4Cl_{aq} ***45% yield***

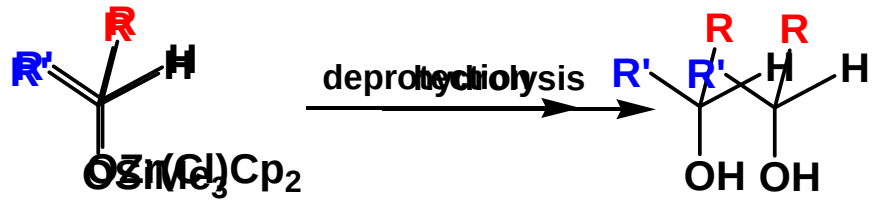
work-up with EDA /HCl_{aq} ***75% yield***

Kishi, *TL* **1997**, *38*, 6355

Catalytic-in-Cr NHK reaction: two strategies for Cr–O bond cleavage

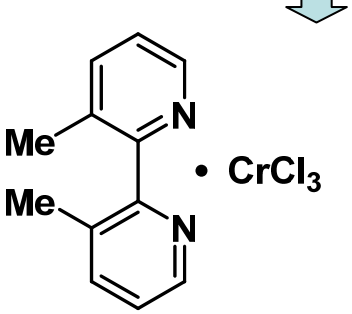


Fürstner
Kishi
JACS **1996**, *118*, 2533
Org. Lett. **2004**, *6*, 5031

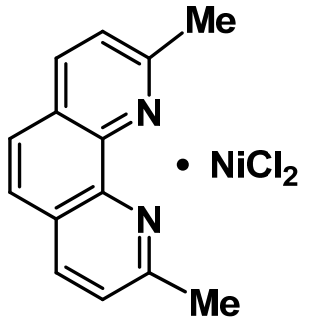


4-16 eq. $CrCl_2$ / 1-10% $NiCl_2$

10-20% $CrCl_3$ / 1-2% $NiCl_2$



1%

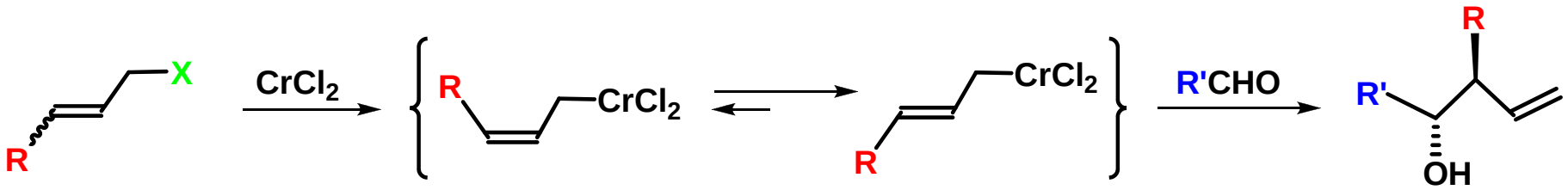


0.2%

Direct formation of unprotected alcohols

Better aldehyde conversion with low catalyst loadings

Allylchromium reagents: effective synthesis of anti-homoallylic alcohols



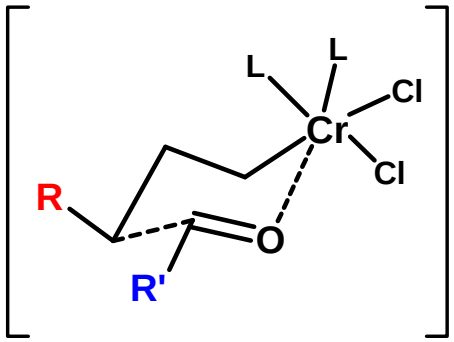
X = Cl, Br, I, OTs, OMs, OP(O)(OEt)$_2$

No additives required to $CrCl_2$

Possible application of di- and trihaloallyls

S_N2' allyl addition mechanism

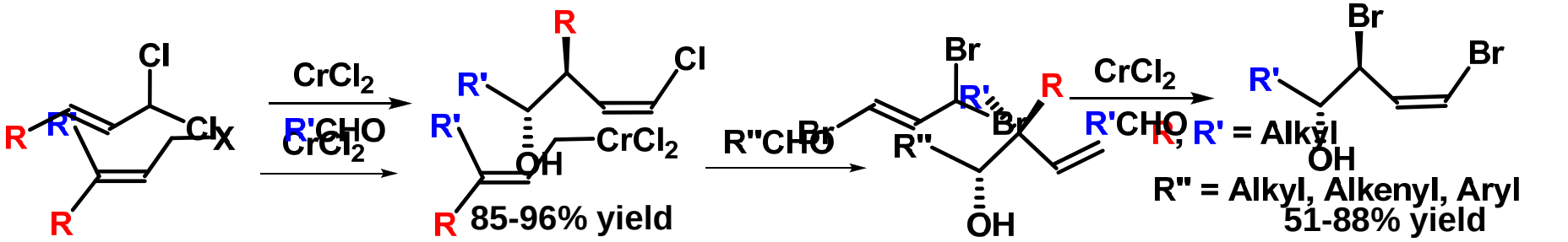
High anti-selectivity for crotyl derivatives



Zimmerman-Traxler transition state

60-100% yield

***anti*:*syn* > 95:5**



85-96% yield

***anti*:*syn* > 97:3**

***Z*:*E* > 95:5**

R, R' = Alkyl

R" = Alkyl, Alkenyl, Aryl

51-88% yield

66-90% selectivity

Takai, Utimoto

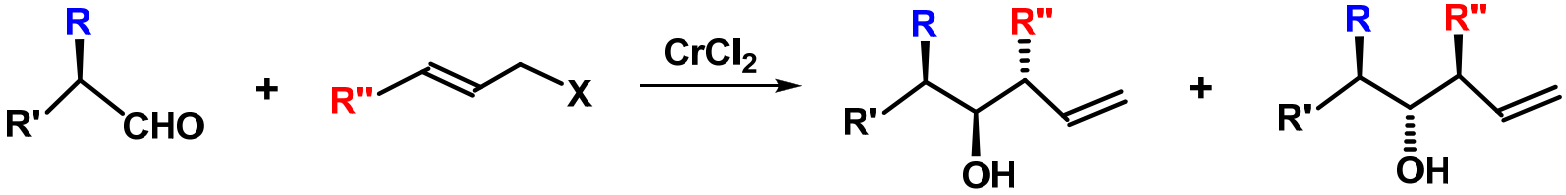
TL **1989**, *30*, 4389

Augé

TL **1988**, *29*, 6107

Translation of allyl configuration into the stereochemistry of final product

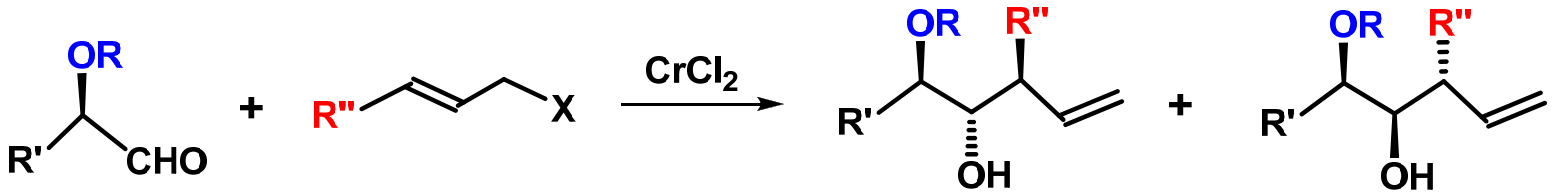
Stereochemical aspects of allylchromium addition to the aldehydes



The result controlled mainly by steric interactions

"Cram" "Anti-Cram"

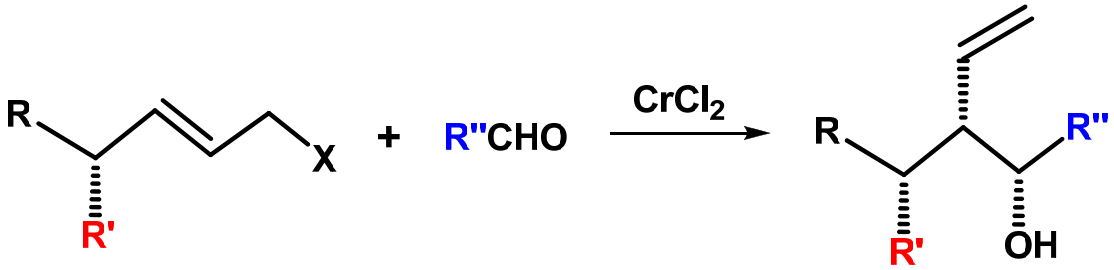
dr 1.2:1-10:1



"Felkin-Ahn" "Chelate-Cram"

Strong tendence to the non-chelated mechanism

dr 7:1-100:1

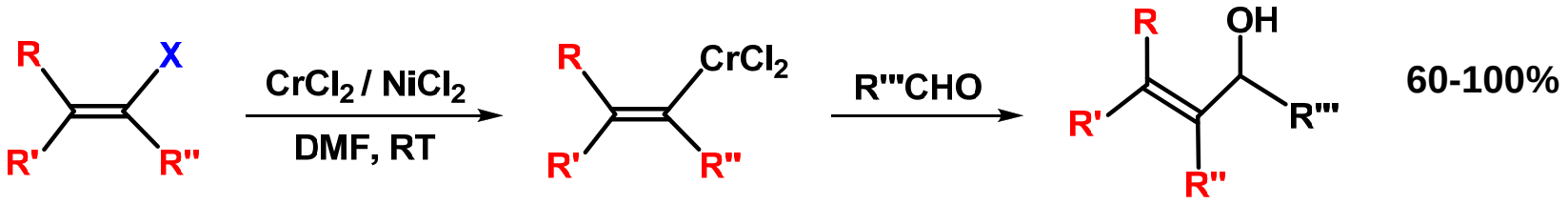


"Felkin-Ahn"

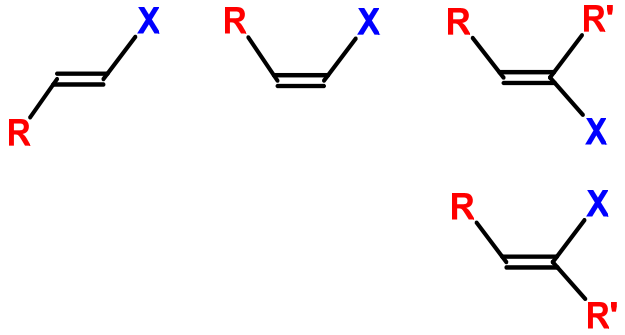
dr 5:1-20:1

Chiral center at the δ-position determines the assymmetric configuration of the product

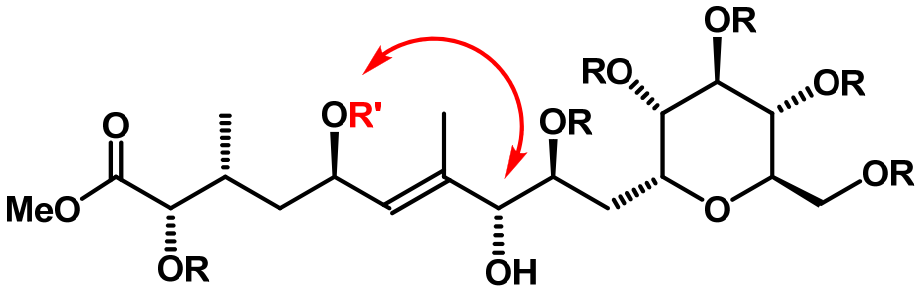
Stereoselectivity in the addition of vinylchromium species to the aldehydes



X = I, OTf, Br



- ***Usual complete retention of C=C bond configuration***
- ***Effective both in inter- and intramolecular fashions***
- ***No epimerization in α-position to the aldehyde***
- ***In some cases tolerance to the free OH groups***
- ***"Felkin-Ahn" addition to chiral substrates***
- ***Influence of the allyl group size on the reaction output***

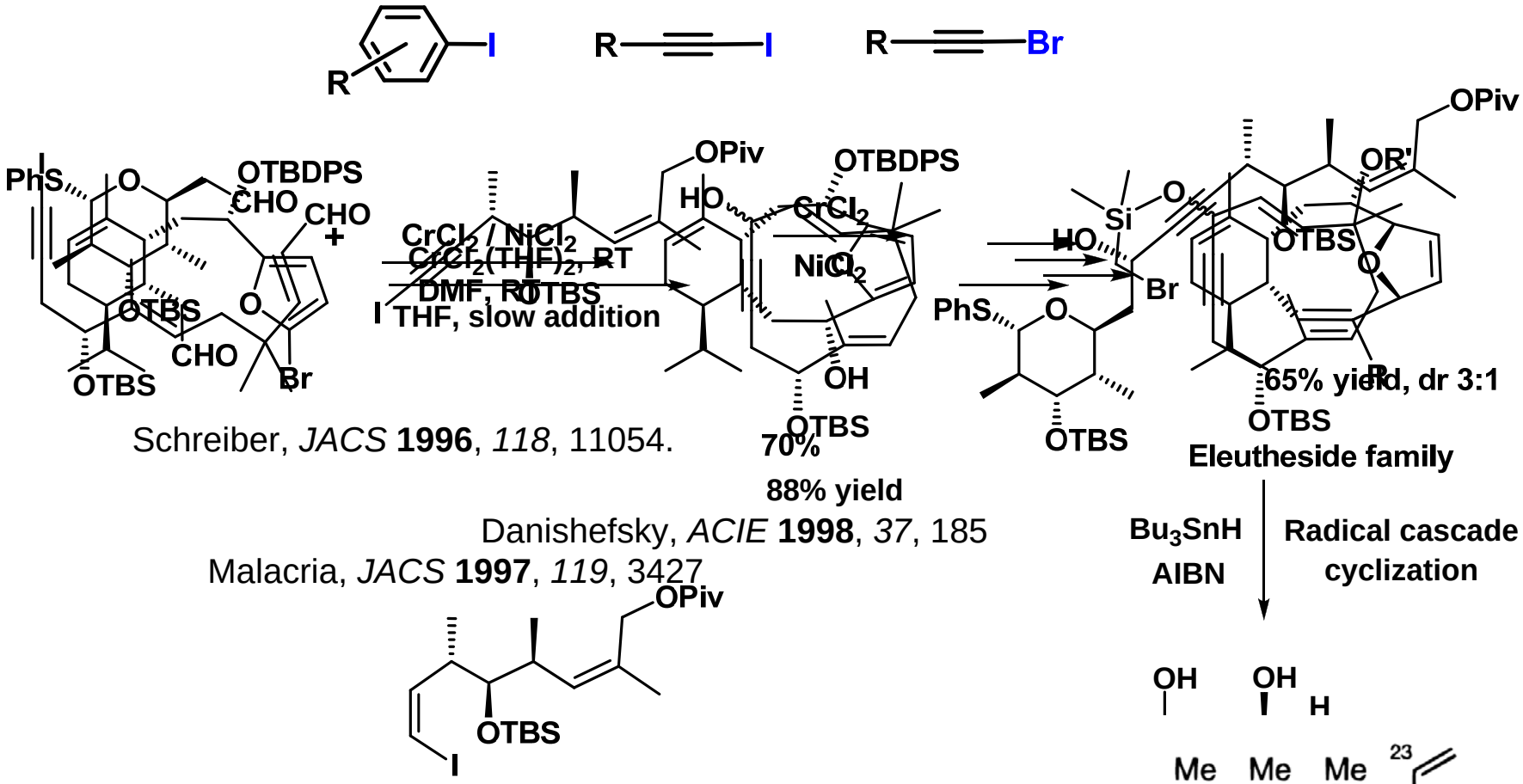


R = R' = Bn; 75% yield, dr 5:1

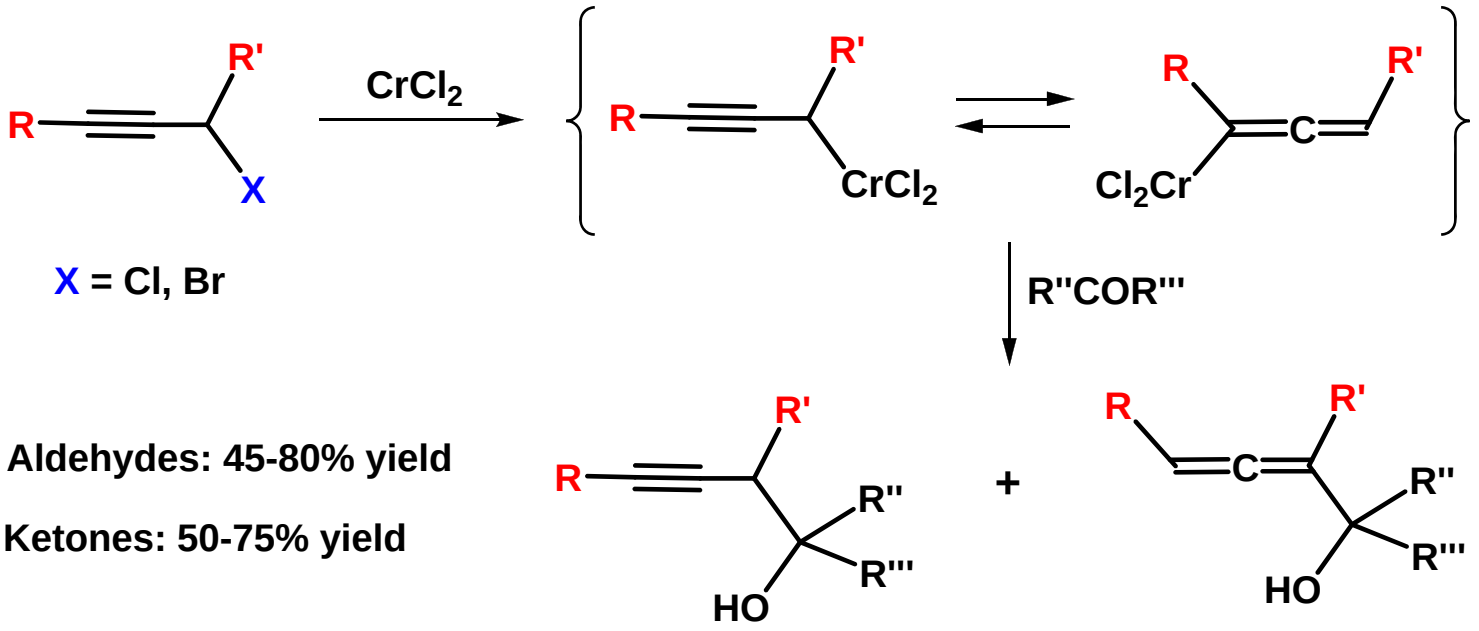
R = Bn, R' = TBS; 81% yield, dr 10:1

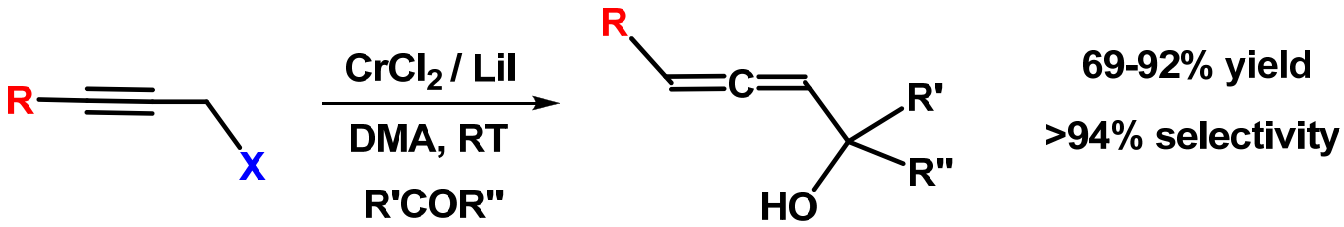
Kishi, *Pure Appl. Chem.* **1989**, *31*, 313

Synthesis and reactivity of aryl- and alkynylchromium compounds



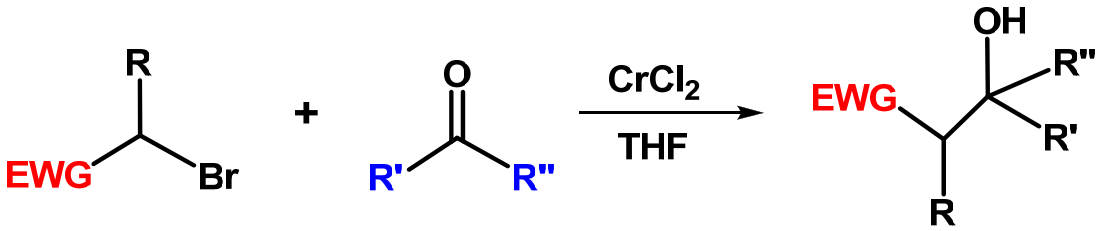
Chemoselectivity control in the reactions of propargylchromium derivatives





Knochel, *J. Org. Chem.* **1992**, *57*, 4070

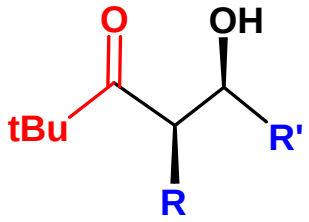
Chromium-mediated Reformatsky reaction



EWG = ketone, ester, lactone, amide, nitrile

40-90% yield

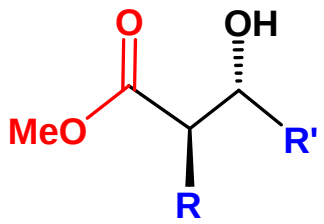
- ***No retroaldolization observed***
- ***Effective on microscale experiments***
- ***High chemoselectivity to aldehydes***



50-87% yield

100% *syn*-selectivity

TL **1985**, *26*, 4371

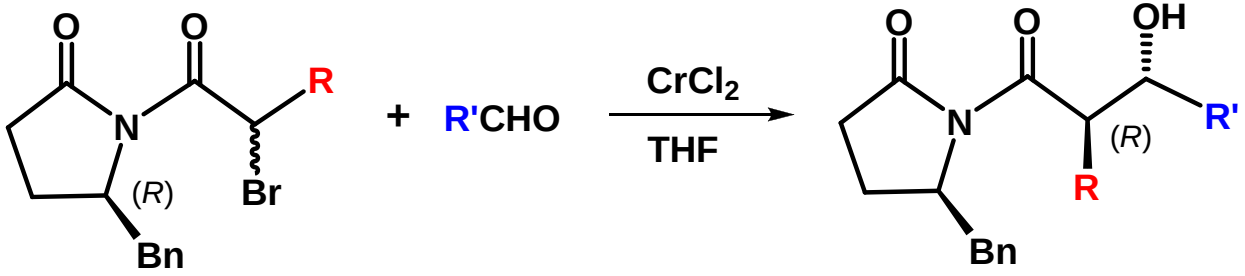


R, R' = Alkyl, Aryl

63-95% yield

***anti*:*syn* 70:30-95:5**

Synlett **1997**, 731



81-96% yield

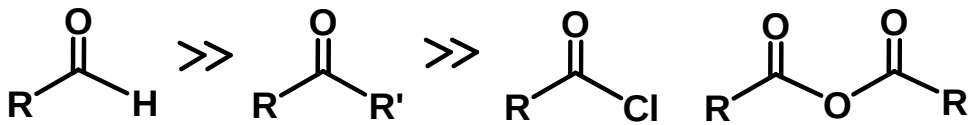
***anti*:*syn* 77:23-95:5**

***ee* > 97%**

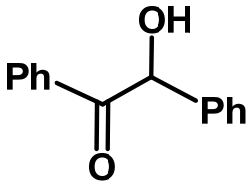
TL **1997**, *38*, 4387

Alkylchromium reagents: preference for functionalized substrates

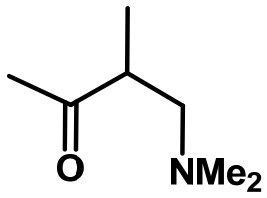
$MeCrCl_2(THF)_3$



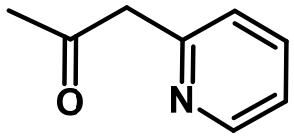
Kaufmann, TL **1986**, *27*, 5355



50% yield

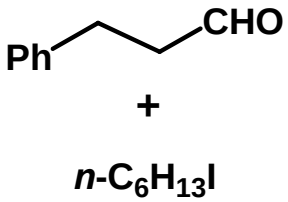


60% yield



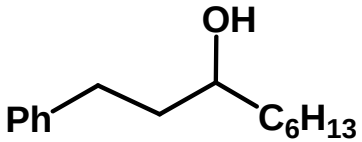
52% yield

Kaufmann, TL **1986**, *27*, 5351



[Cr]/[Co] 4:1, DME, RT

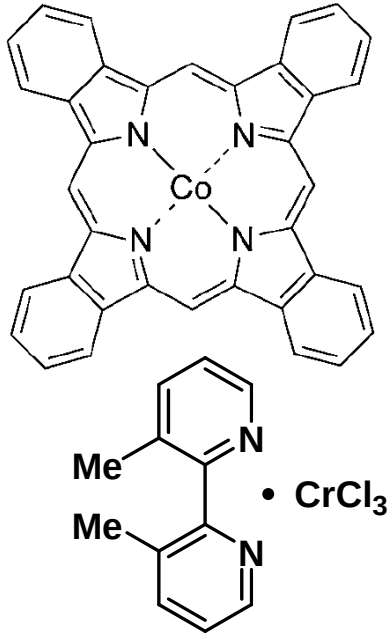
Mn (2 eq), Cp_2ZrCl_2 (2 eq)



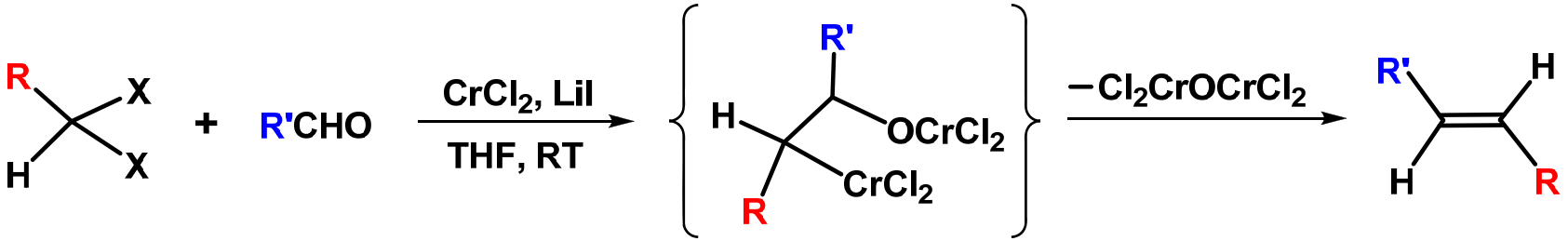
5% [Cr] 88% yield

1% [Cr] 89% yield

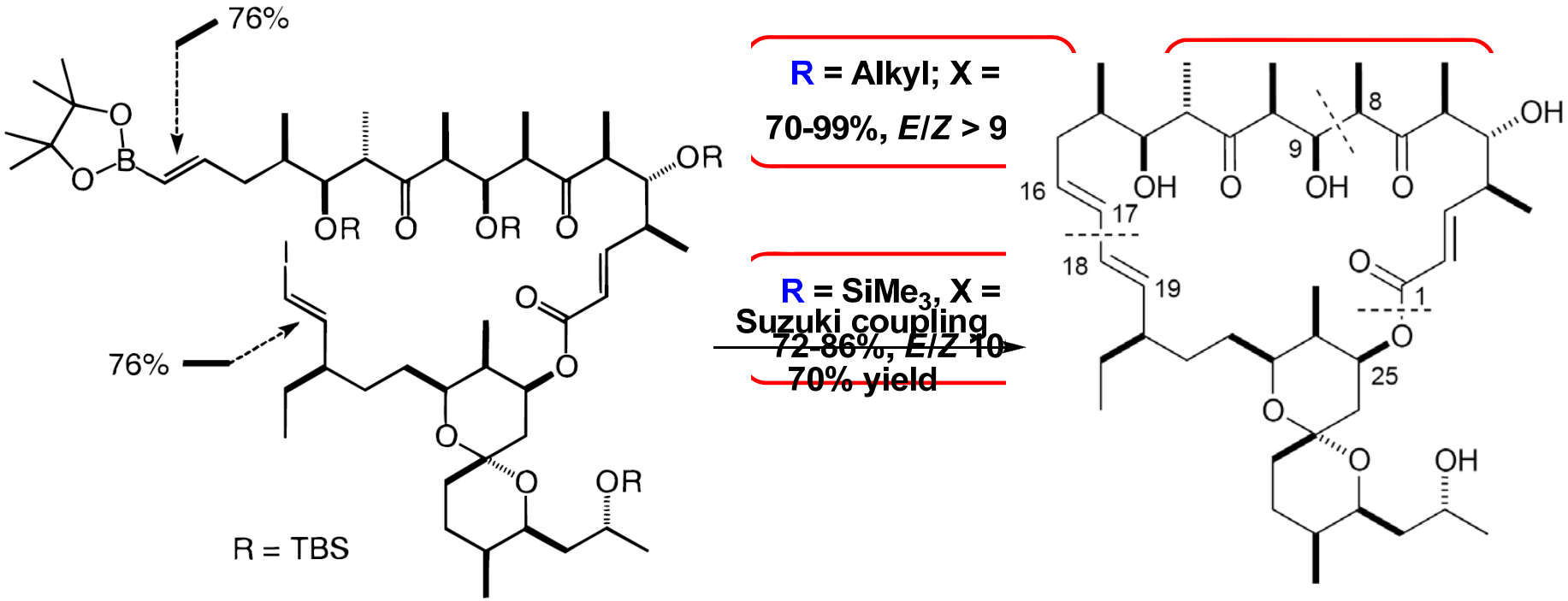
Kishi, Org. Lett. **2005**, *7*, 5421



Utimoto-Takai aldehyde olefination with deminal dihaloalkanes



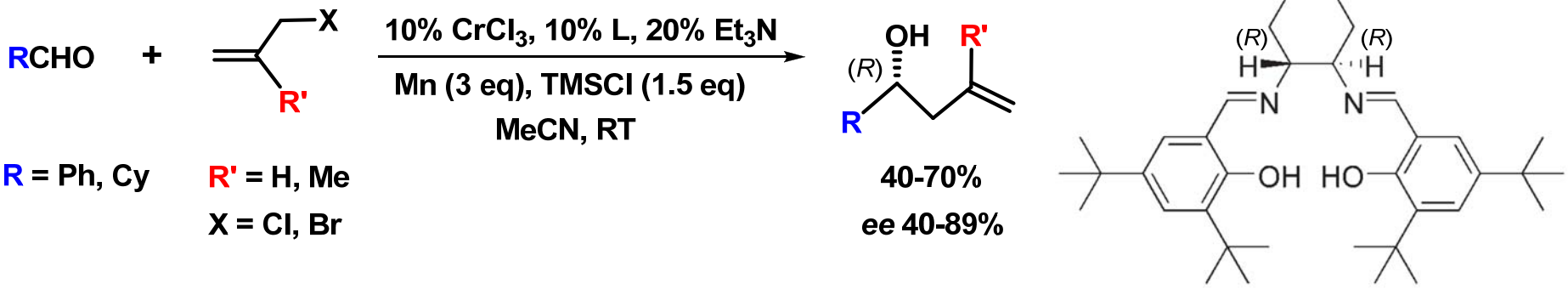
Takai, Utimoto, JACS **1987**, *109*, 951



White, *Chem. Commun.* **1998**, 79

Rutamycin B

Enantioselective catalytic NHK reactions: early state

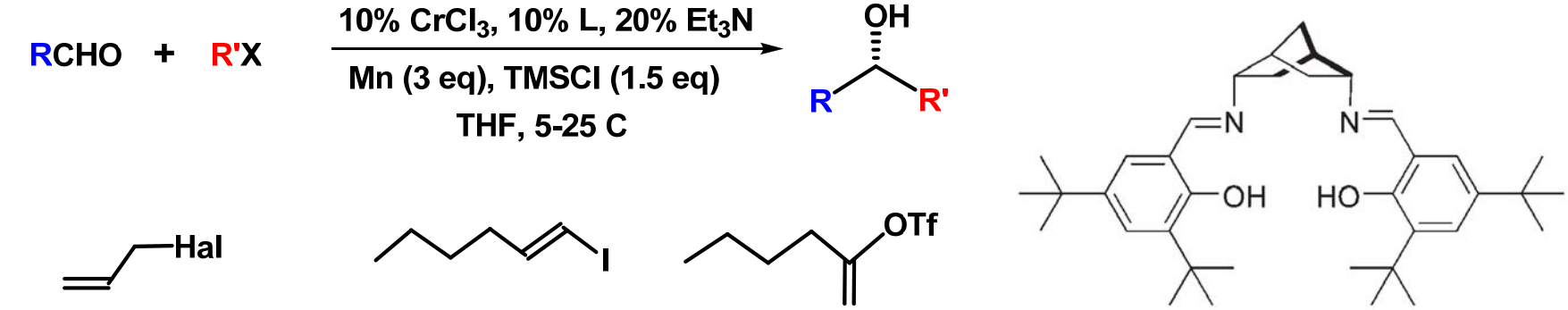


R = Ph, Cy **R' = H, Me** **X = Cl, Br**

40-70%

***ee* 40-89%**

Cozzi, *ACIE* **1999**, *38*, 3357



69-76%, *ee* 79-92%

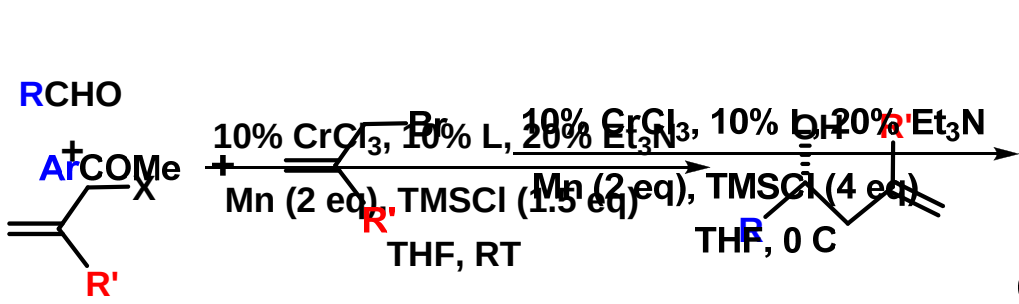
59%, *ee* 75%

54%, *ee* 61%

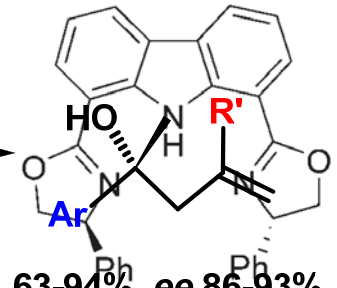
R = Ph, CH_2CH_2OPMB

Berkessel, *ACIE* **2003**, *42*, 1032

Application of oxazoline and sulfonamide ligands



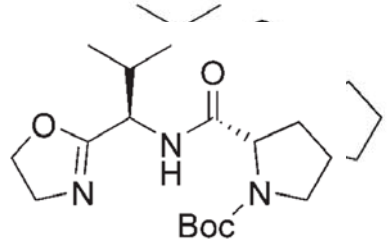
R = Aryl, Alkyl R' = H, Me X = Cl, Br



63-94%, *ee* 86-93%

83-93%, *ee* 90-95%

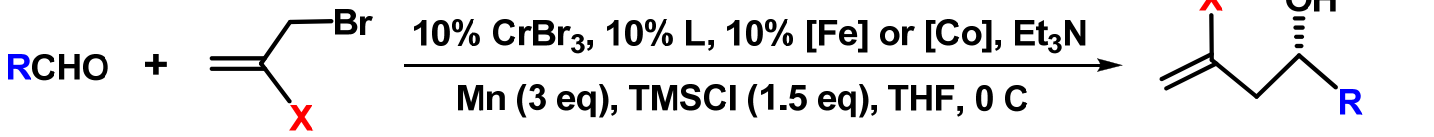
Nakada, *JACS* **2003**, *125*, 1140



81-98%, *ee* 87-94%

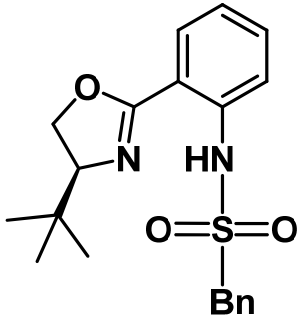
Sigman, *JACS* **2007**, *129*, 2752

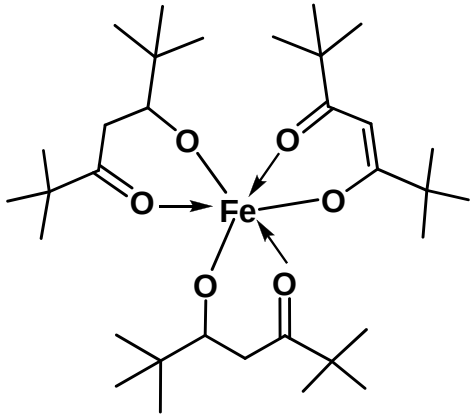
Sigman, *Org. Lett.* **2005**, *7*, 1837

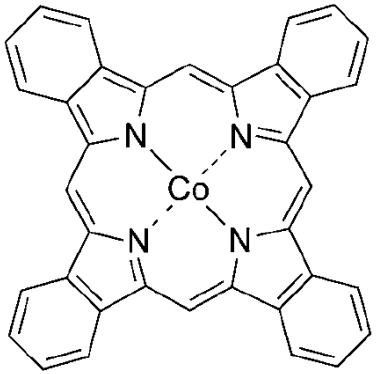


50-86%, *ee* 87-93%

X = Cl, Br, I

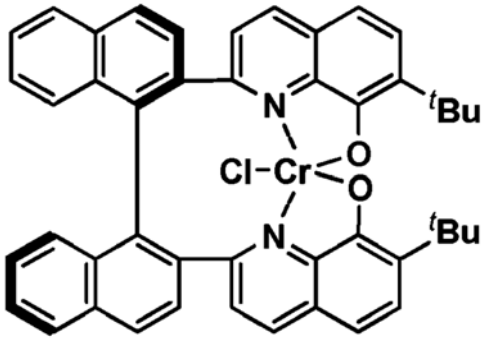






Kishi, *JACS* **2004**, *126*, 12248

Axially chiral TBOx chromium complex: highly efficient and universal tool for the assymetric NHK reactions



Yamamoto

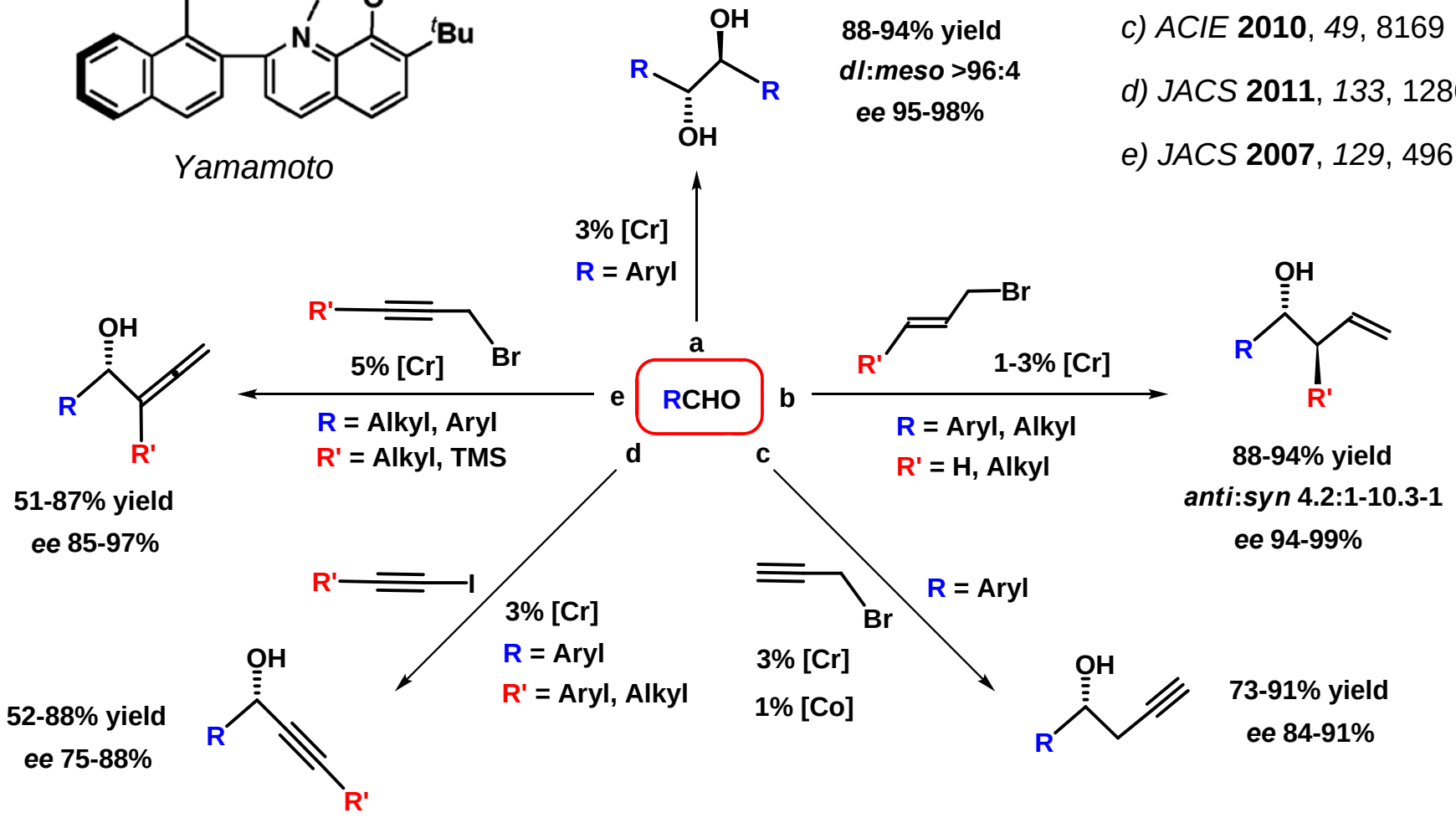
a) JACS **2004**, *126*, 13198

b) JACS **2006**, *128*, 2554

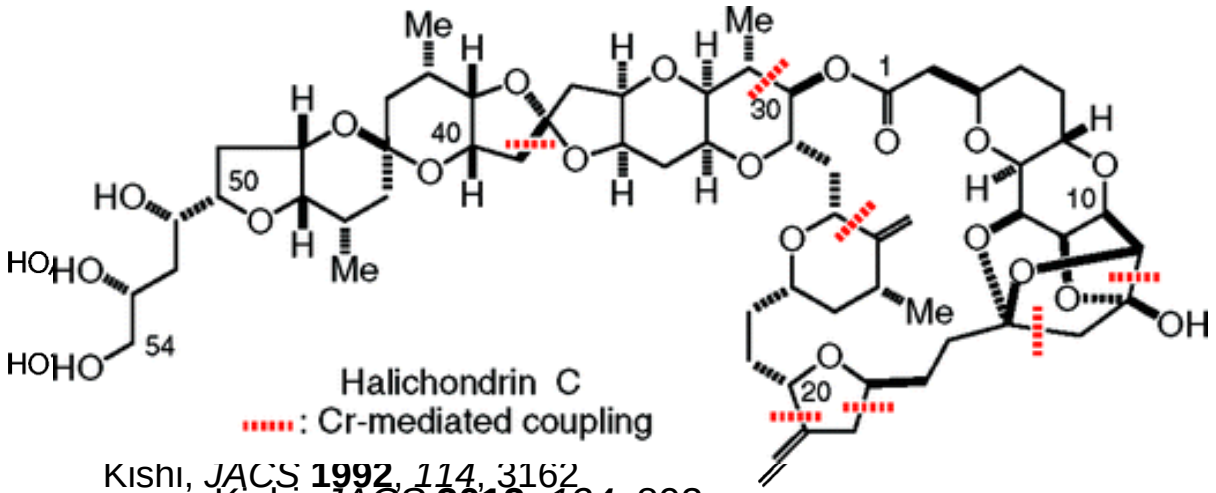
c) ACIE **2010**, *49*, 8169

d) JACS **2011**, *133*, 1286

e) JACS **2007**, *129*, 496



Application of NHK methodology in total synthesis of Halihondrins

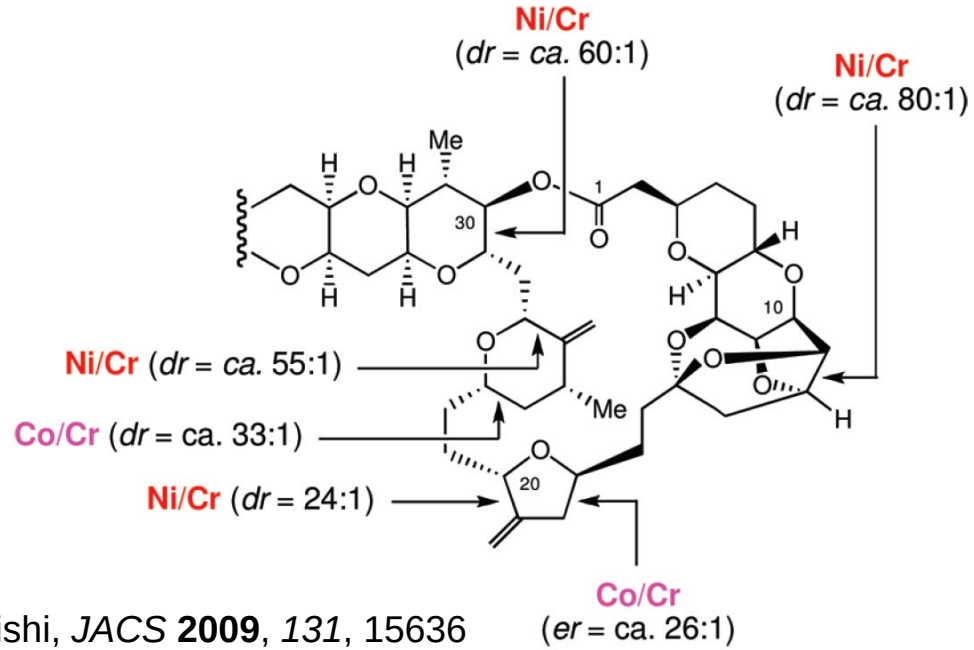


Kishi, *JACS* **1992**, *114*, 3162
Kishi, *JACS* **2012**, *134*, 893.

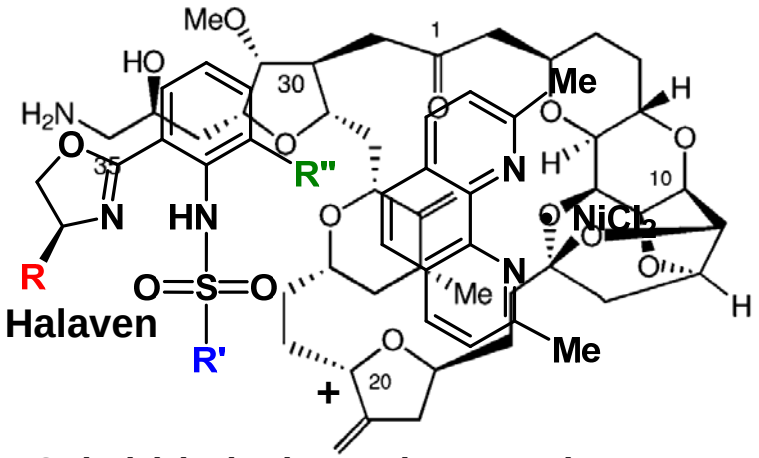
Halichondria okadai

Isolated in 1985 (12.5 mg / 600 kg of sponge)

Average GI_{50} *ca.* 0.7nM/L



Kishi, *JACS* **2009**, *131*, 15636



Cobalt(II) phtalocyanine complex