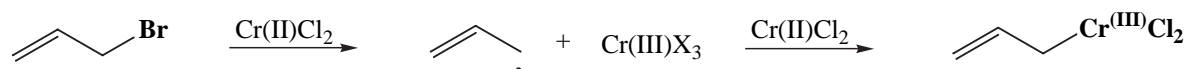
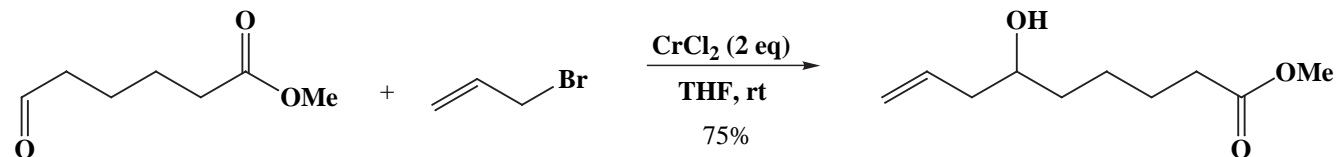


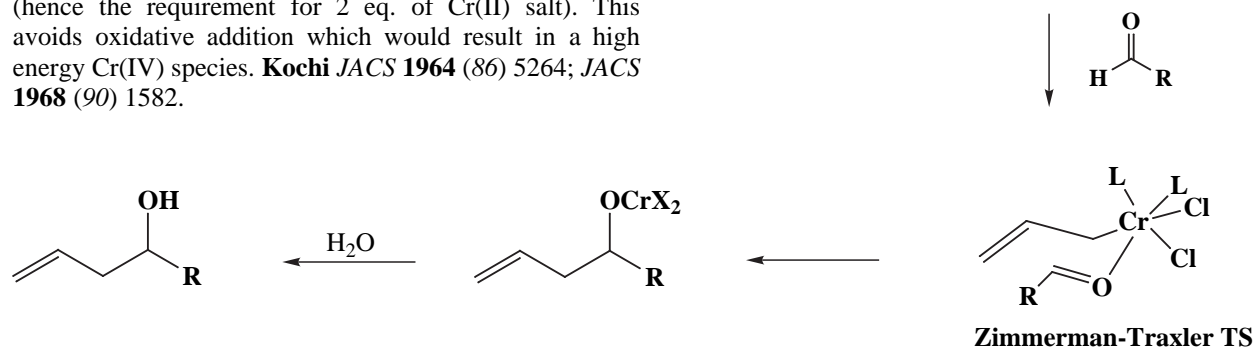
Nozaki-Hiyama Reaction

In 1977, Nozaki and Hiyama reported a remarkably chemoselective Cr(II)-mediated "Barbier-type" coupling of allyl halides with aldehydes. Unlike a Mg(0)-mediated Barbier coupling, aldehydes may be coupled in the presence of ketones and esters.

Nozaki, Hiyama. *JACS* 1977 (99) 3179.

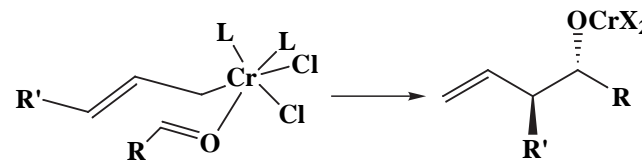


Insertion of Cr occurs *via* 2 single electron transfer events (hence the requirement for 2 eq. of Cr(II) salt). This avoids oxidative addition which would result in a high energy Cr(IV) species. **Kochi** *JACS* 1964 (86) 5264; *JACS* 1968 (90) 1582.



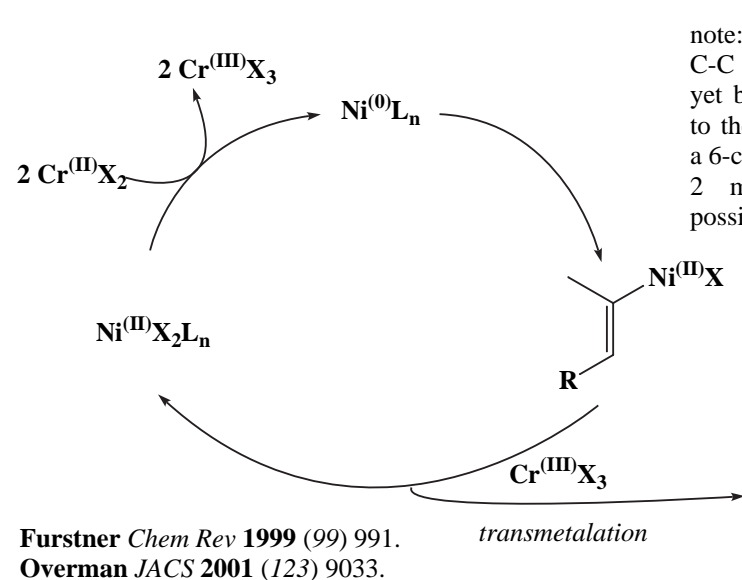
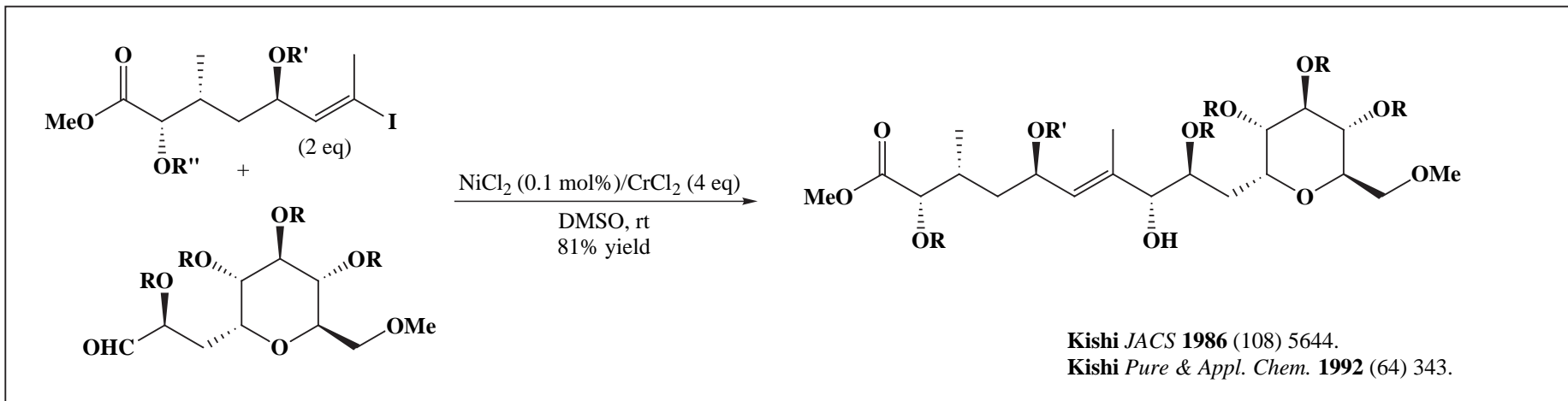
M-C bonding in early main group metals (*e.g.* Li, Mg) is strongly ionic in character. The C retains a great deal of negative charge which renders it highly nucleophilic and competent to attack such weak electrophiles as ester carbonyls. Cr-C bonds are significantly more covalent in character and thus are competent nucleophiles only towards strong electrophiles such as activated aldehyde carbonyls. The aldehyde is approximated and activated towards attack *via* coordination to the electrophilic Cr(III) center.

Rxns with γ -substituted allyl-chromium reagents afford homoallylic alcohols with a high degree of *anti* selectivity.



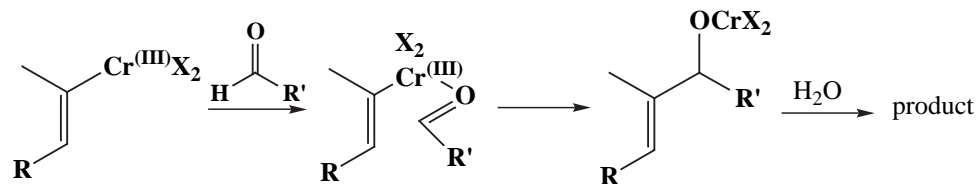
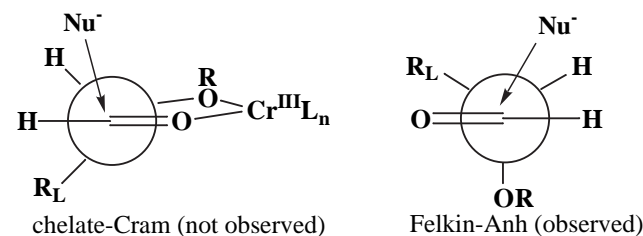
Nozaki-Hiyama-Kishi Reaction

In 1983, Nozaki and Hiyama reported that alkenyl iodides could be used in their Cr(II)-mediated "Barbier-type" coupling reaction to stereospecifically generate allylic alcohols. During model studies aimed at using this remarkably functional group tolerant reaction to couple two highly oxygenated alkenyl iodide and aldehyde fragments in the synthesis of palytoxin, Kishi found that the success of the coupling was highly dependent on the Cr(II)Cl₂ batch used. This reproducibility problem was solved by the addition of catalytic quantities of Ni(II)Cl₂. Nozaki subsequently reported that batches of Cr(II)Cl₂ effective in promoting the alkenyl iodide/aldehyde coupling contained *ca.* 0.5 mol% Ni on the basis of Cr. The Nozaki-Hiyama-Kishi reaction has since become one of the most widely used synthetic methods for forming allylic alcohols in the context of highly functionalized substrates.



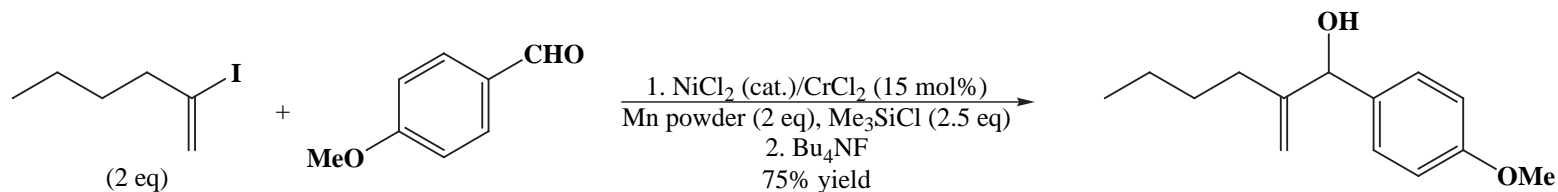
note: The exact nature of this C-C bond forming step has not yet been determined. In addition to the 4-centered process shown, a 6-centered process that involves 2 molecules of Cr is also possible.

The NHK reaction generally affords the Felkin-Anh rather than the chelate-Cram product with α -alkoxy aldehydes:



Nozaki-Hiyama-Kishi Reaction

The requirement for 2 mol of Cr(II) salts/mol of halide in the Nozaki-Hiyama-Kishi reaction has limited its use in industry and in large scale applications. In 1996, Furstner reported the first example of a Nozaki-Hiyama-Kishi reaction that was catalytic in chromium.



Furstner *JACS* 1996 (118) 2533.

