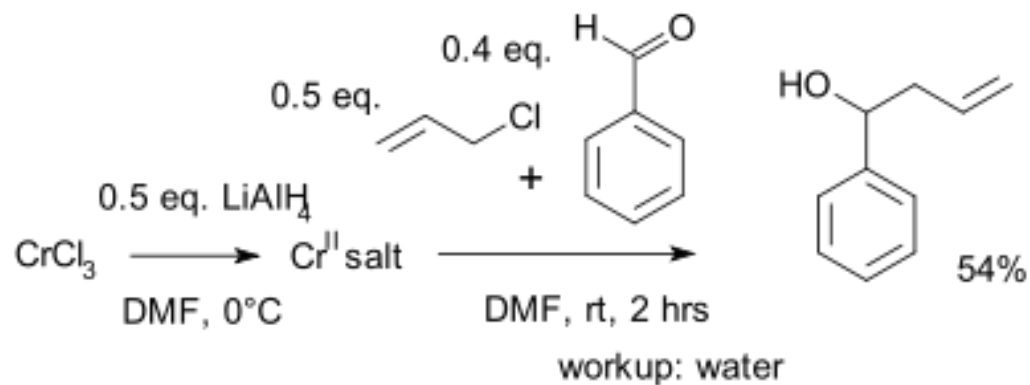


NOZAKI-HIYAMA-KISHI REACTION



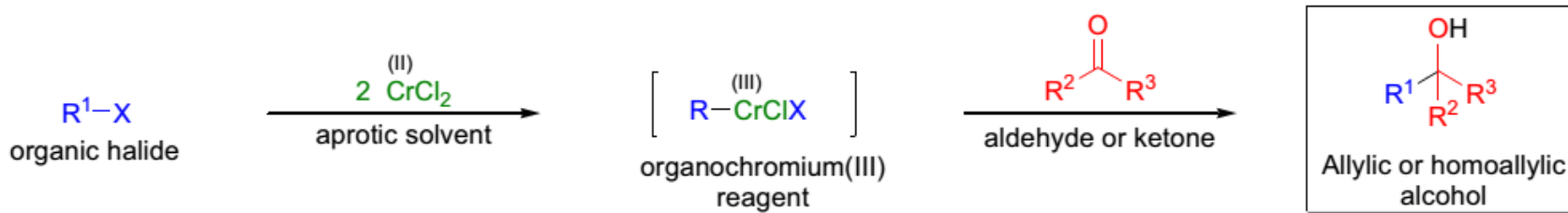
Origin

- In 1977, H. Nozaki and T. Hiyama et al. reacted aldehydes and ketones with organochromium(III) reagents, which were generated in situ from allyl and vinyl halides upon treatment with CrCl_2 under aprotic and oxygen-free conditions, and obtained the corresponding allylic and homoallylic alcohols with high chemospecificity and stereoselectivity.
- In 1986, Y. Kishi and H. Nozaki independently discovered that traces of nickel salts catalyzed the formation of carbon-chromium(III) bonds, even from otherwise less reactive substrates (e.g., vinyl and aryl halides). This modification helped to make the process more reliable.
- The one-pot addition of alkenyl, alkynyl, aryl, allyl, or vinylchromium compounds to aldehydes or ketones is known as the **Nozaki-Hiyama-Kishi (NHK) reaction**.



R^1 = alkenyl, aryl, allyl, vinyl, propargyl, alkynyl, allenyl; X = Cl, Br, I, OTf, etc.; R^2, R^3 = alkyl, aryl, alkenyl, H;
solvent: DMF, DMSO, THF

Features&Drawbacks



R^1 = alkenyl, aryl, allyl, vinyl, propargyl, alkynyl, allenyl; X = Cl, Br, I, OTf, etc.; R^2, R^3 = alkyl, aryl, alkenyl, H;
solvent: DMF, DMSO, THF

Features:

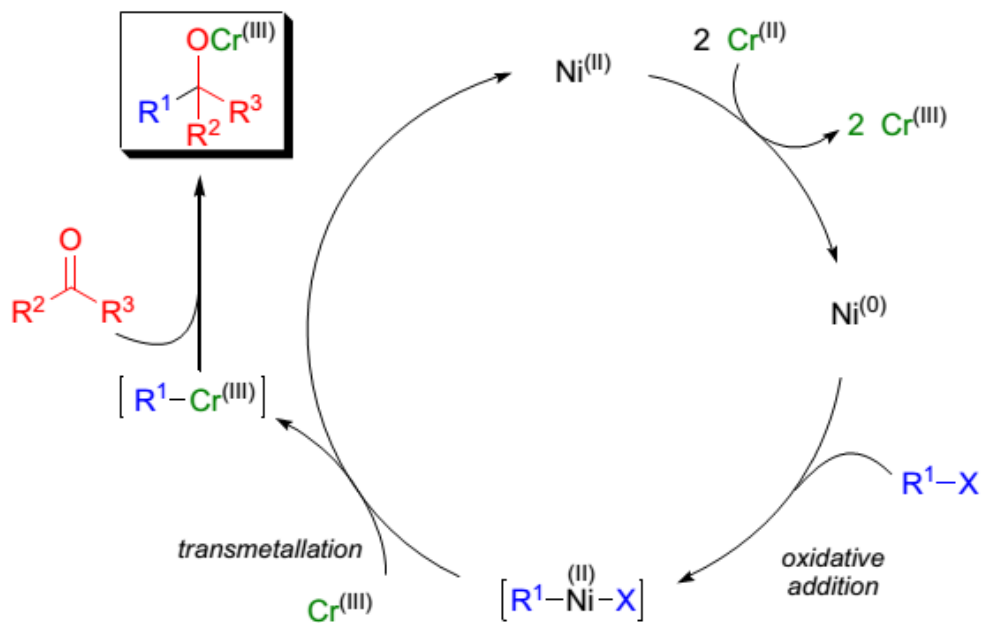
- The CrCl_2 is either purchased commercially or prepared by the reduction of CrCl_3 prior to the reaction.
- Cr(II) is a one-electron donor, and therefore two moles of the chromium(II) salt are required to reduce one mol of organic halide to the corresponding organochromium(III) reagent.
- aldehydes react markedly faster than ketones.
- because of their low basicity, organochromium reagents are compatible with a wide range of sensitive functional groups.

Drawbacks:

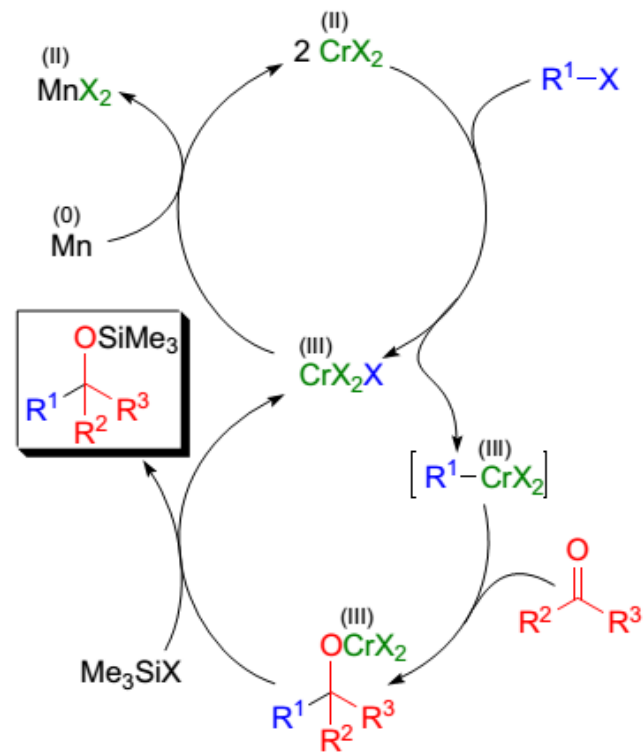
- The nickel and chromium salts are very toxic.
- Usually a large excess of CrCl_2 is required.
- The Lewis acidic salts formed during the preparation of CrCl_2 may alter the stereochemical outcome of the reaction for polyfunctional substrates where chelation control determines the stereochemical course.

Mechanism

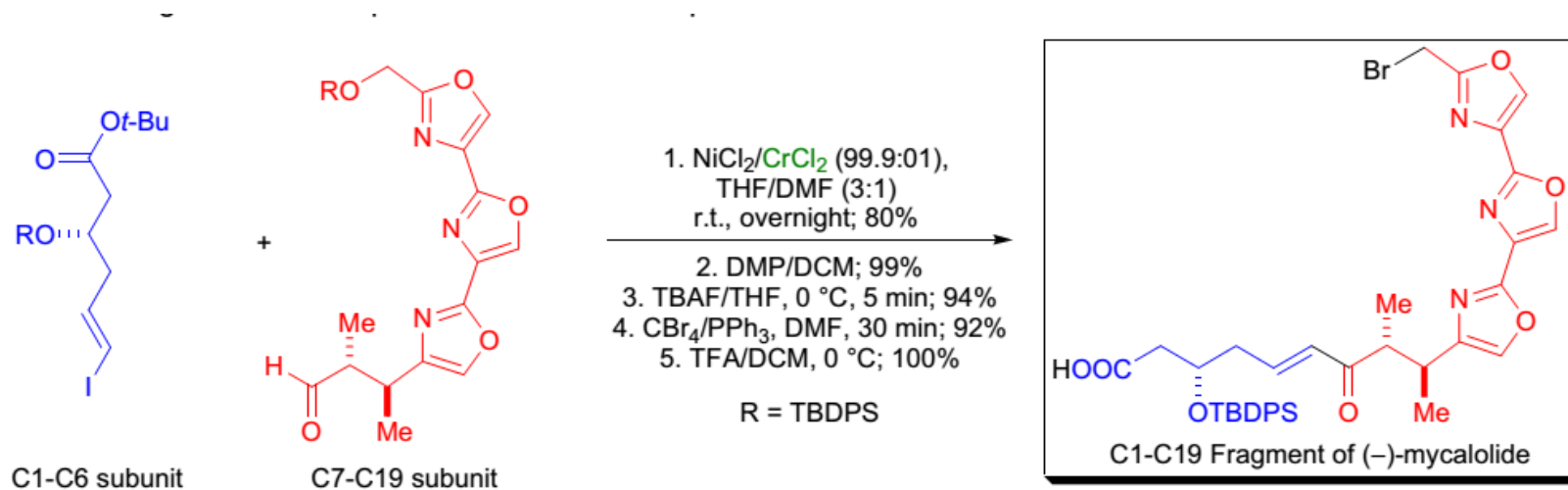
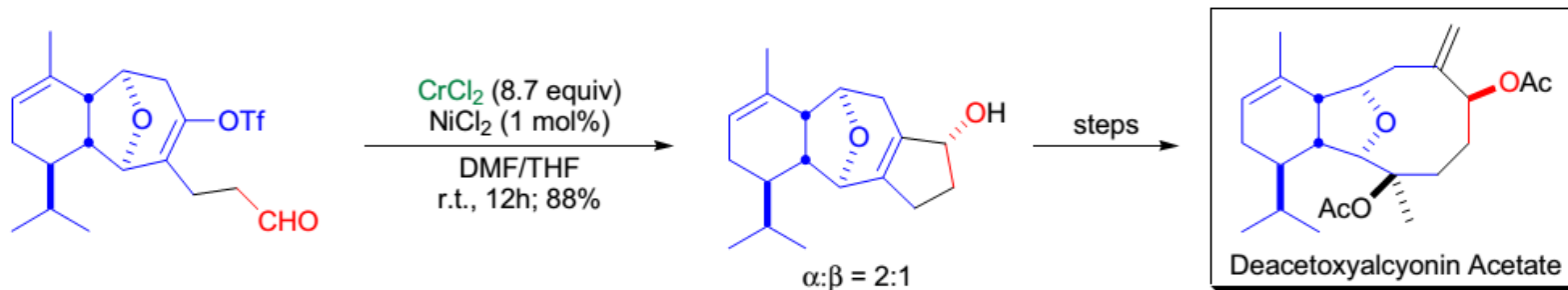
Ni^(II)-catalyzed process:

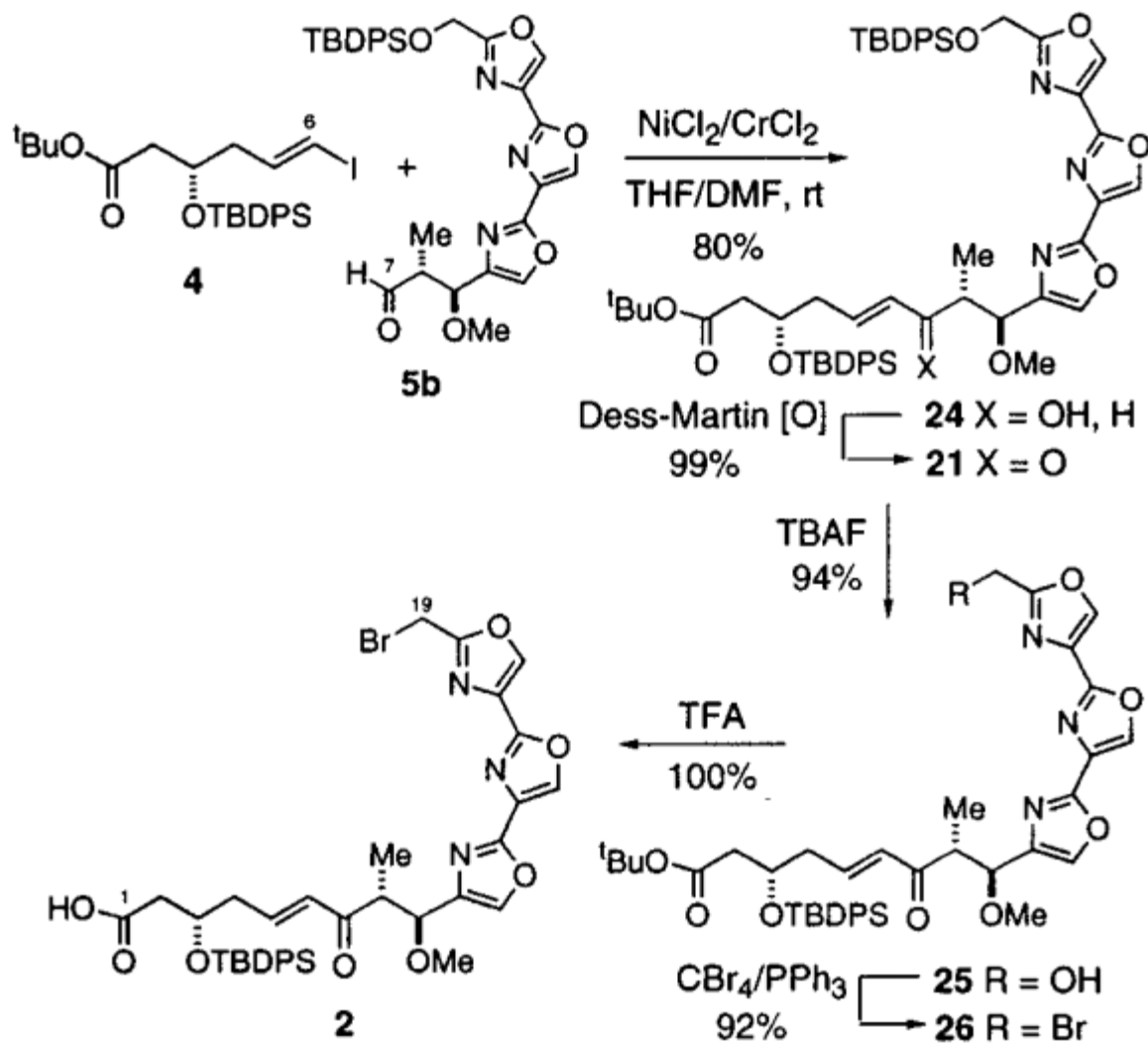


Chromium-catalyzed process:



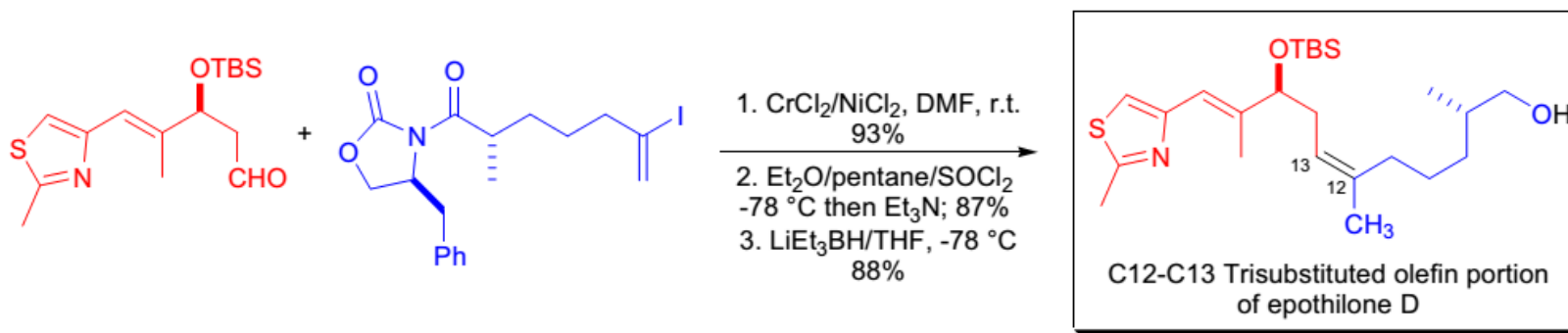
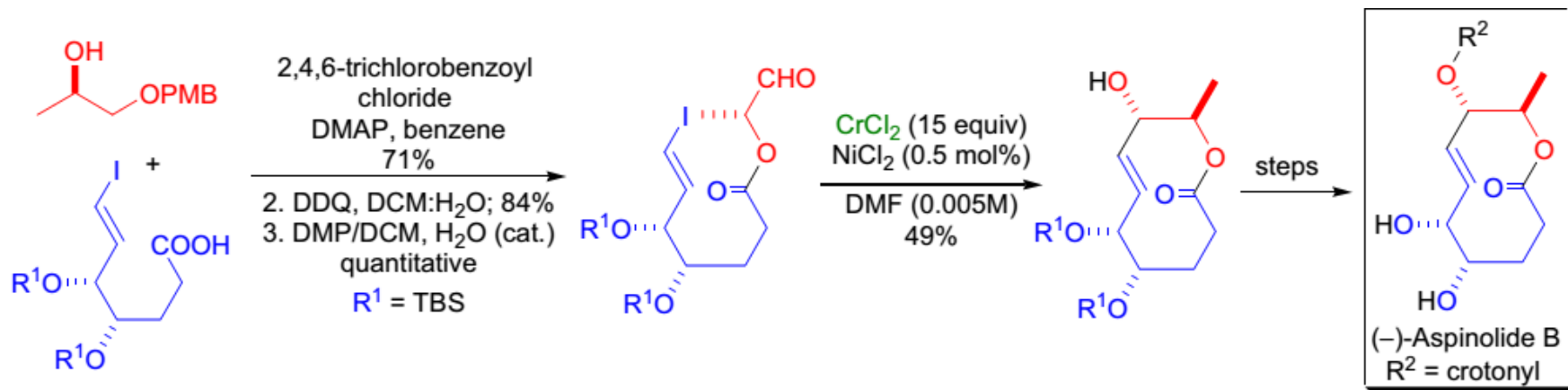
Synthetic Applications

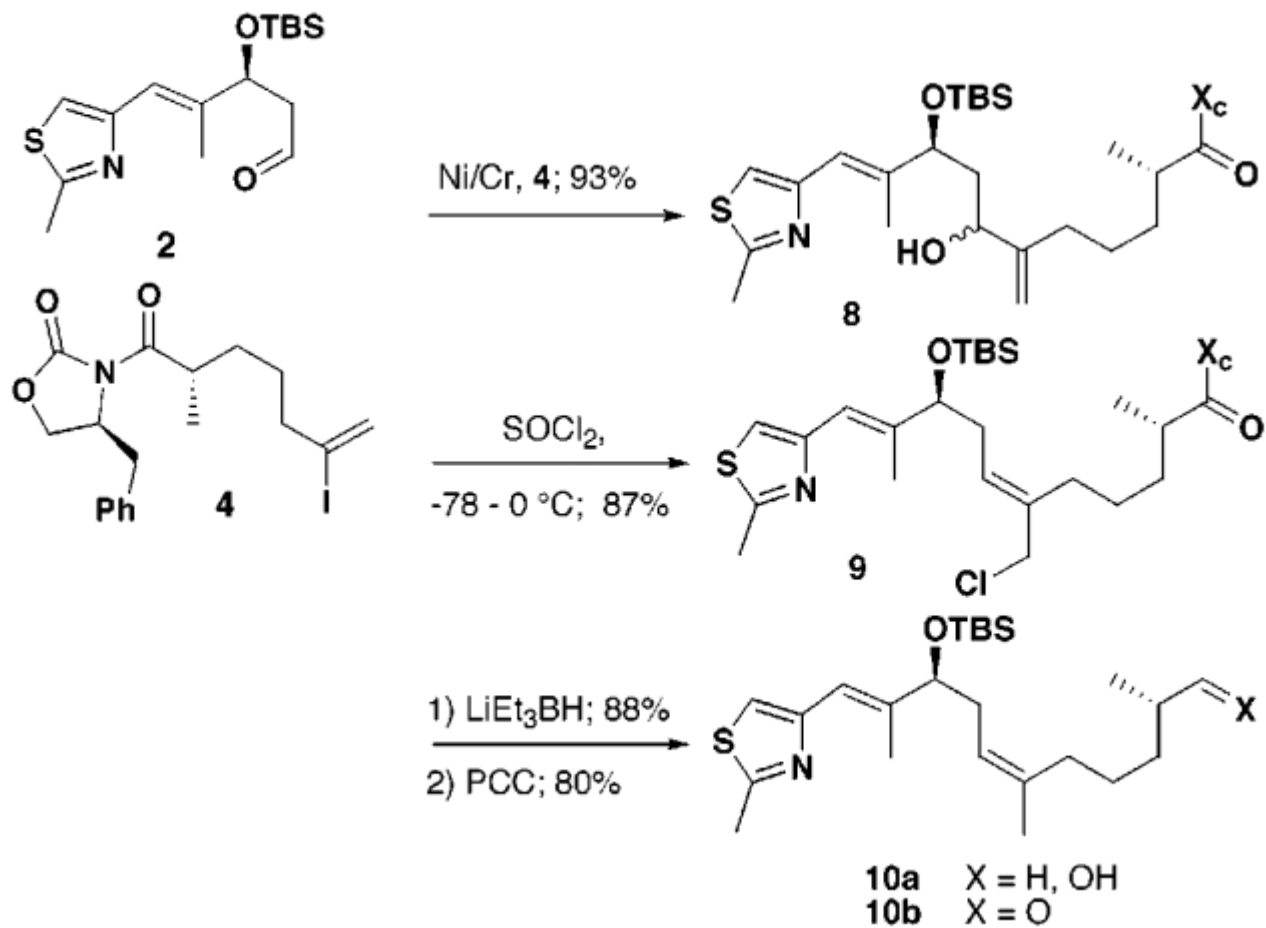




Panek, J. S., Liu, P. Total Synthesis of the Actin-Depolymerizing Agent (-)-Mycalolide A. *J. Am. Chem. Soc.* **2000**, 122, 11090-11097.

Synthetic Applications





Taylor, R. E., Chen, Y. Total Synthesis of Epothilones B and D. *Org. Lett.* **2001**, 3, 2221-2224.

Thanks