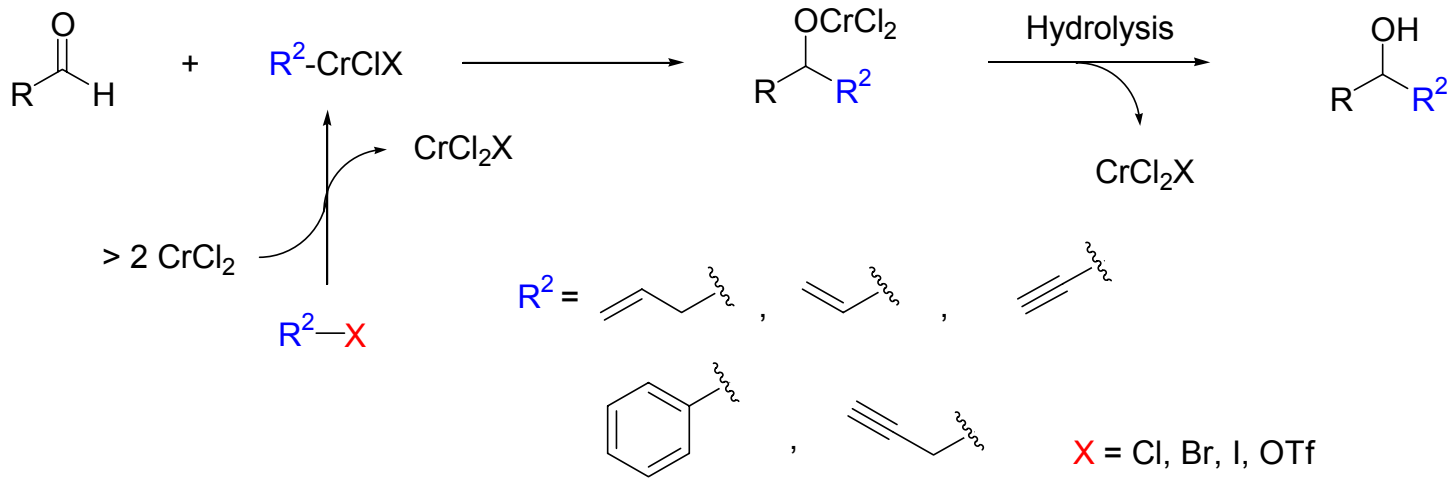


Die Nozaki-Hiyama-Kishi Reaktion

Dr. Dirk Menche

Hannover, 2.5.2005

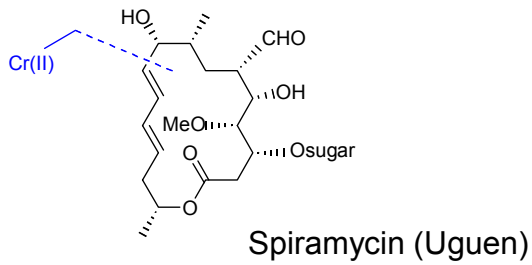
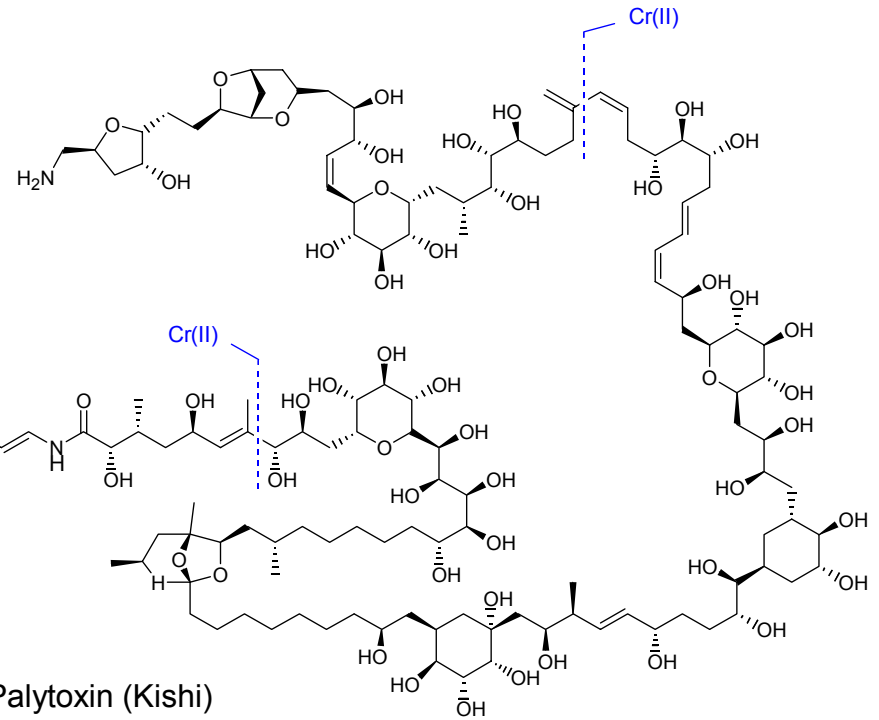
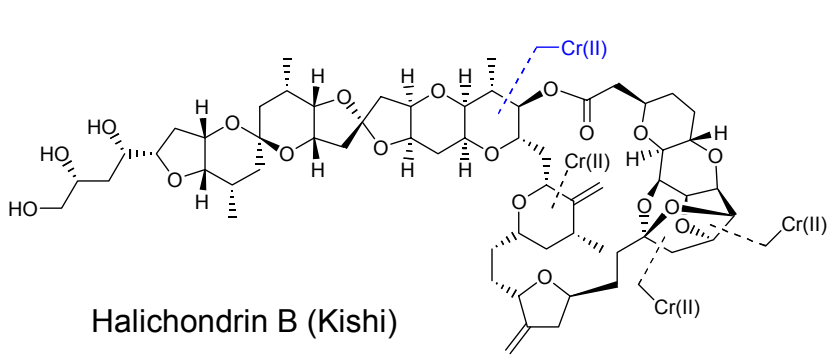
Die Nozaki-Hiyama-Kishi Reaktion



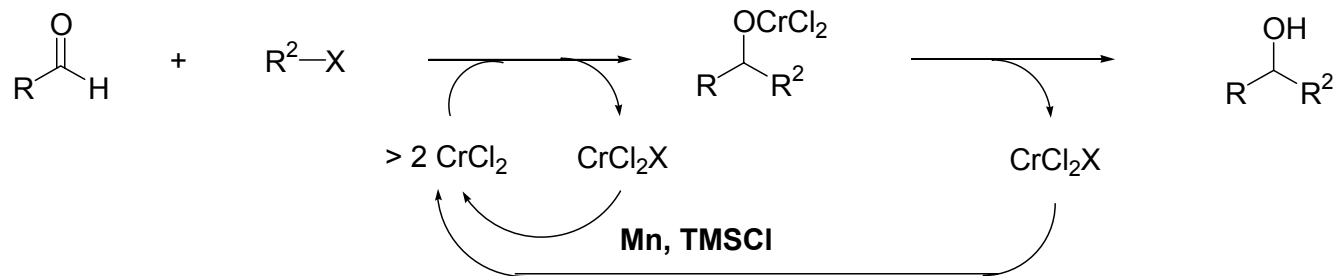
- C-C Verknüpfungsreaktion (vgl. Grignard-Reaktion)
- katalytische Mengen Ni(II)-Salz zur Aktivierung von Vinyl-, Phenyl-, Alkynylhaliden
- Addition hochselektiv an Aldehyde, Vielzahl verschiedenster Funktionalitäten werden toleriert
- vielfach in Naturstofftotalsynthesen angewendet
- Felkin-Anh Selektivität

Übersicht: A. Fürstner, *Chem. Rev.* **1999**, 991-1045.

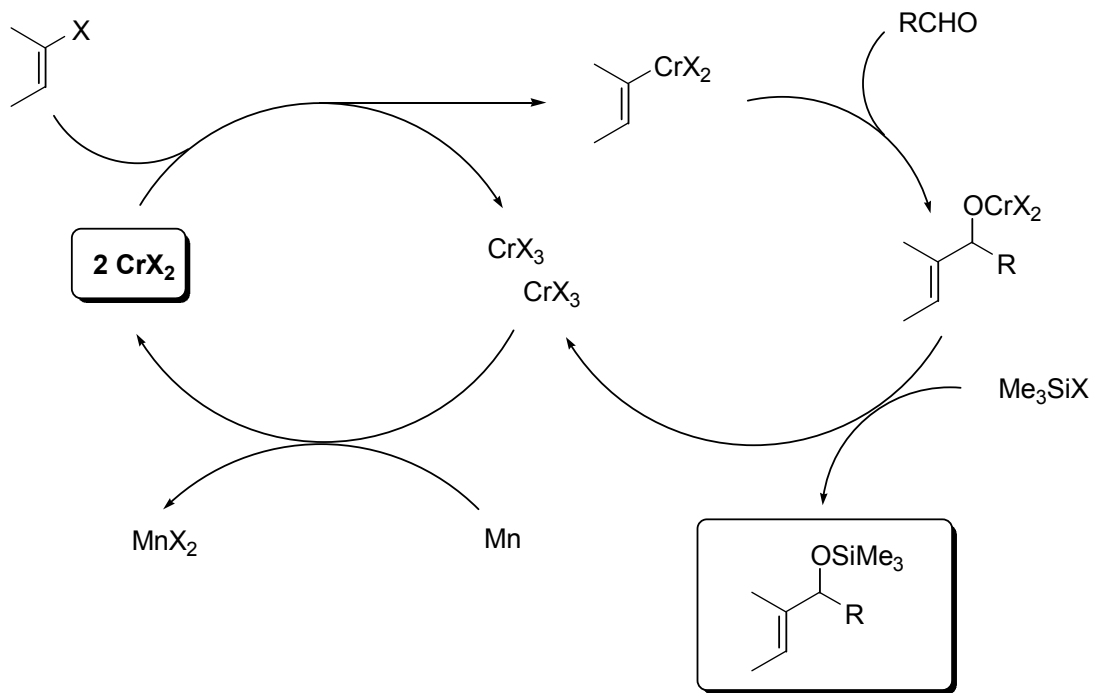
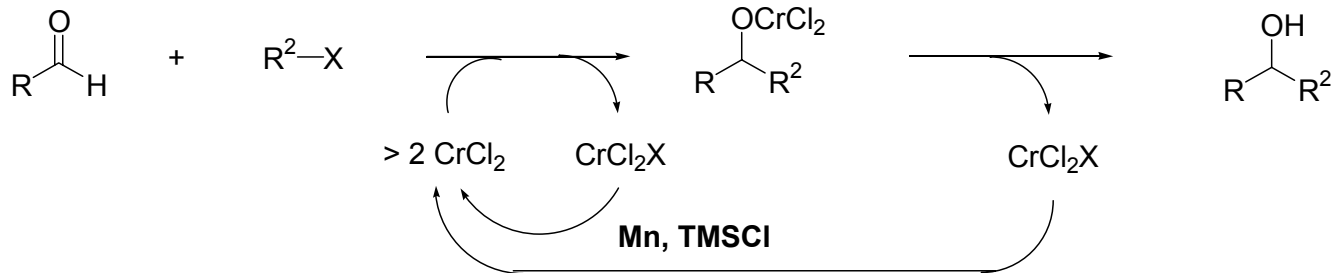
Vielfältigste Anwendungen in der Naturstofftotalsynthese



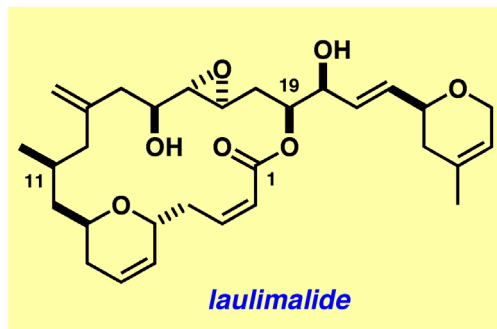
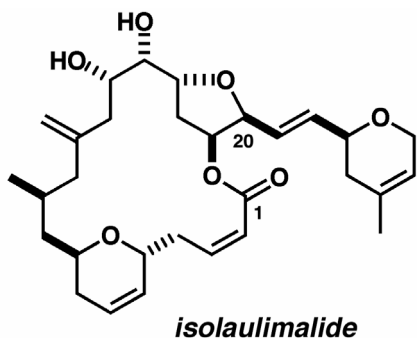
Die Nozaki-Hiyama-Kishi Reaktion: Katalytische Mengen Chrom (II)



Mechanismus

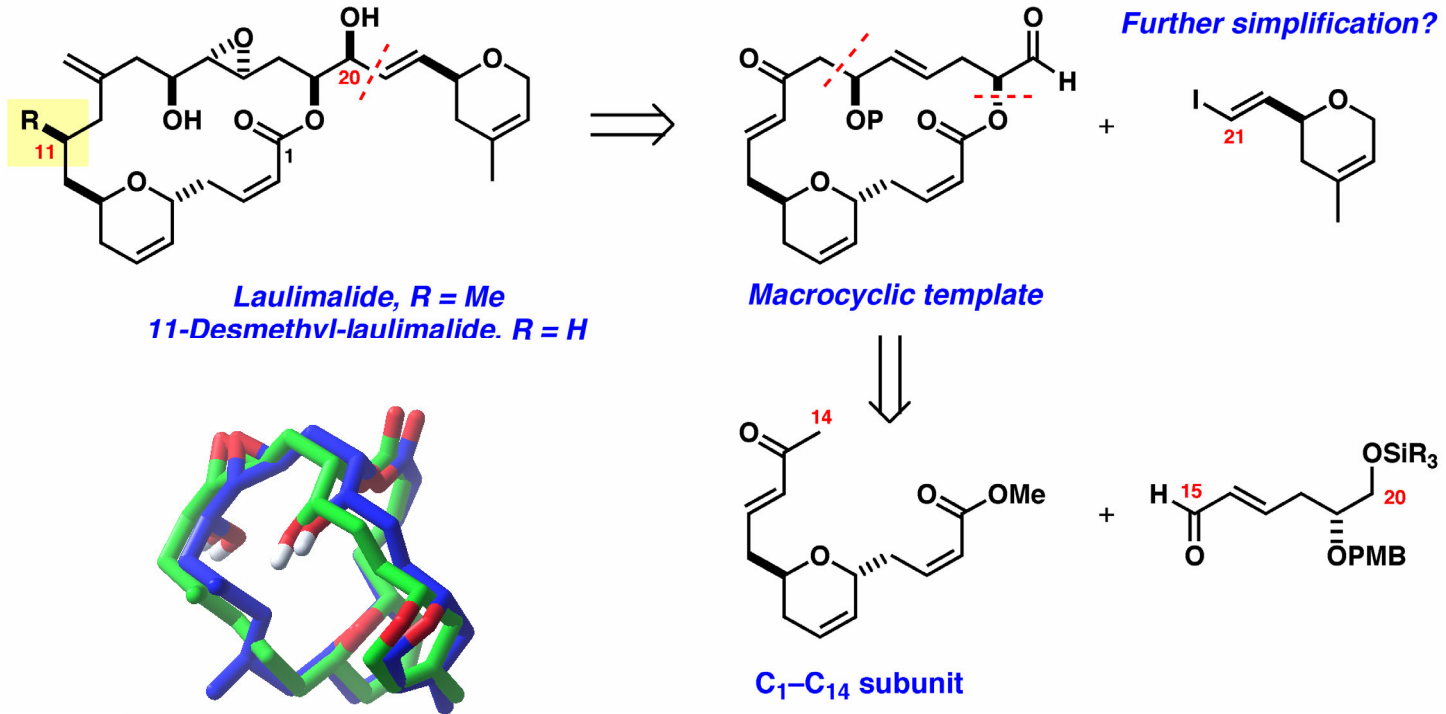


Anwendungsbeispiel: Laulimalide



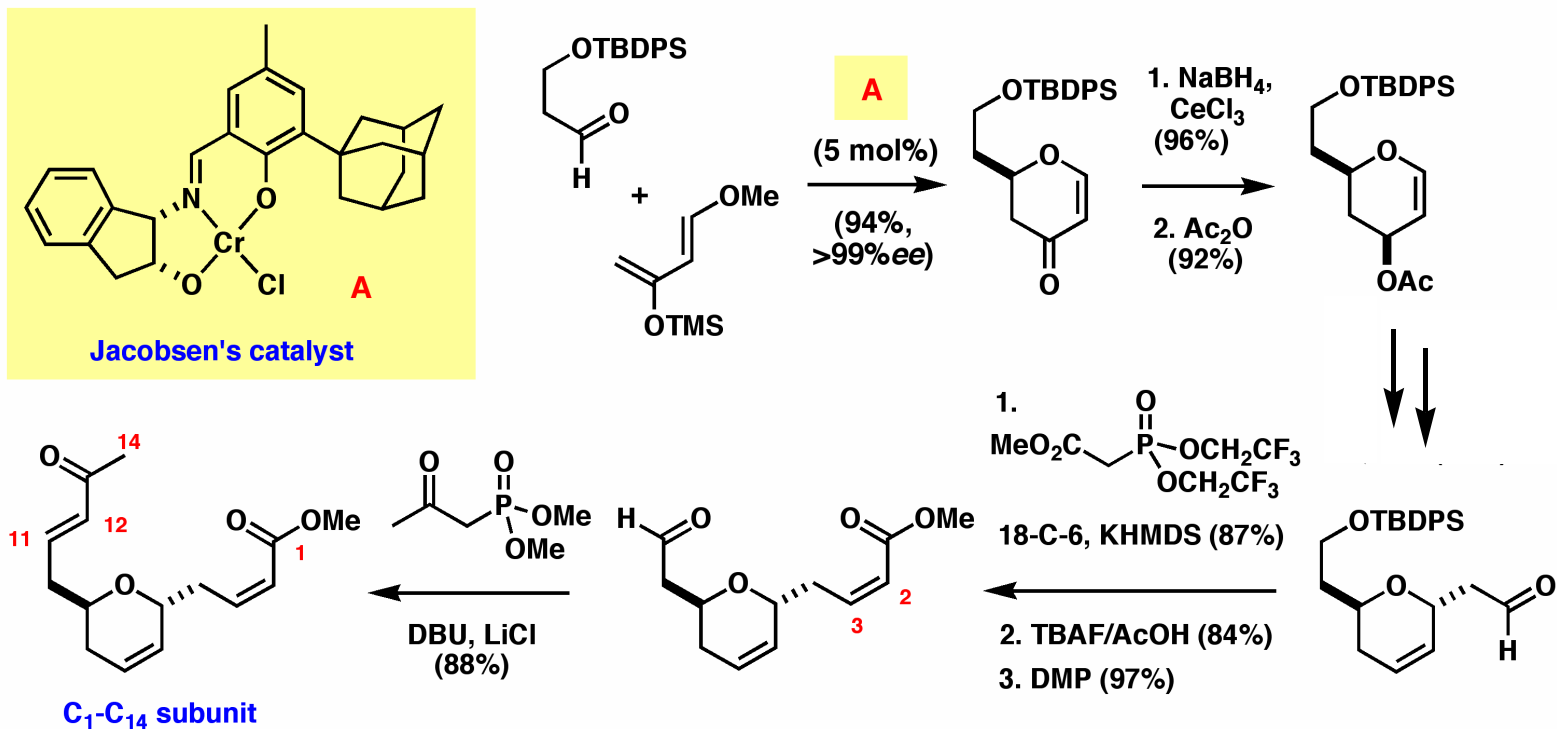
- **20-Membered macrolide isolated from marine sponges (*Faciospongia rimosa*, *Hyatella sp.* and *Spongia mycofijiensis*); low natural abundance**
- **Potent antimitotic agent, acting like Taxol® (paclitaxel) by microtubule stabilisation and disruption of mitotic spindle formation, but having different binding site on tubulin**
- **Inhibits proliferation of paclitaxel-resistant and MDR cancer cell lines at low nanomolar concentrations**

Laulimalide Analogues: Synthetic Planning



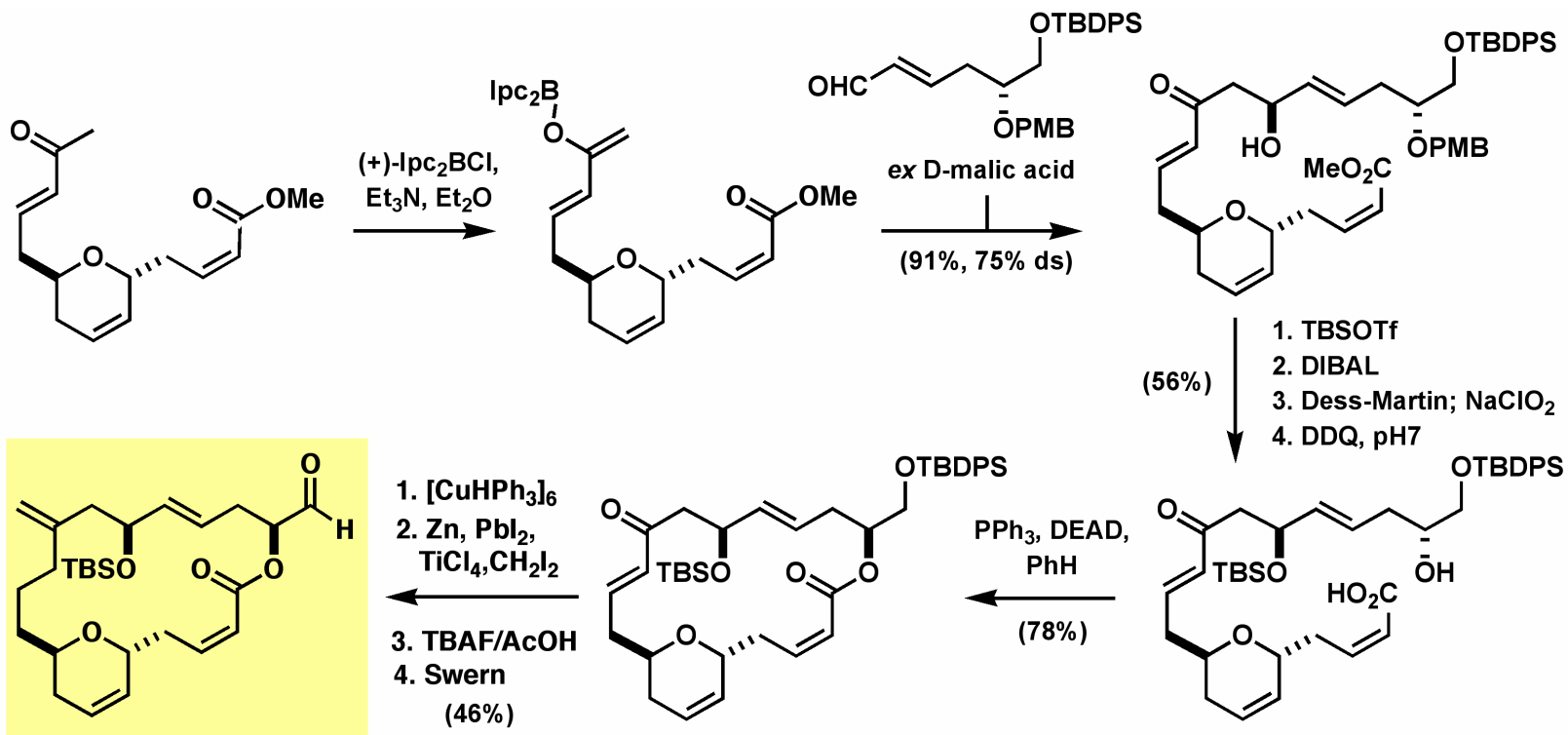
Wo ist die Nozaki-Hiyama-Kishi-Reaktion?

Laulimalide Analogues: Preparation of the C₁-C₁₄ Fragment



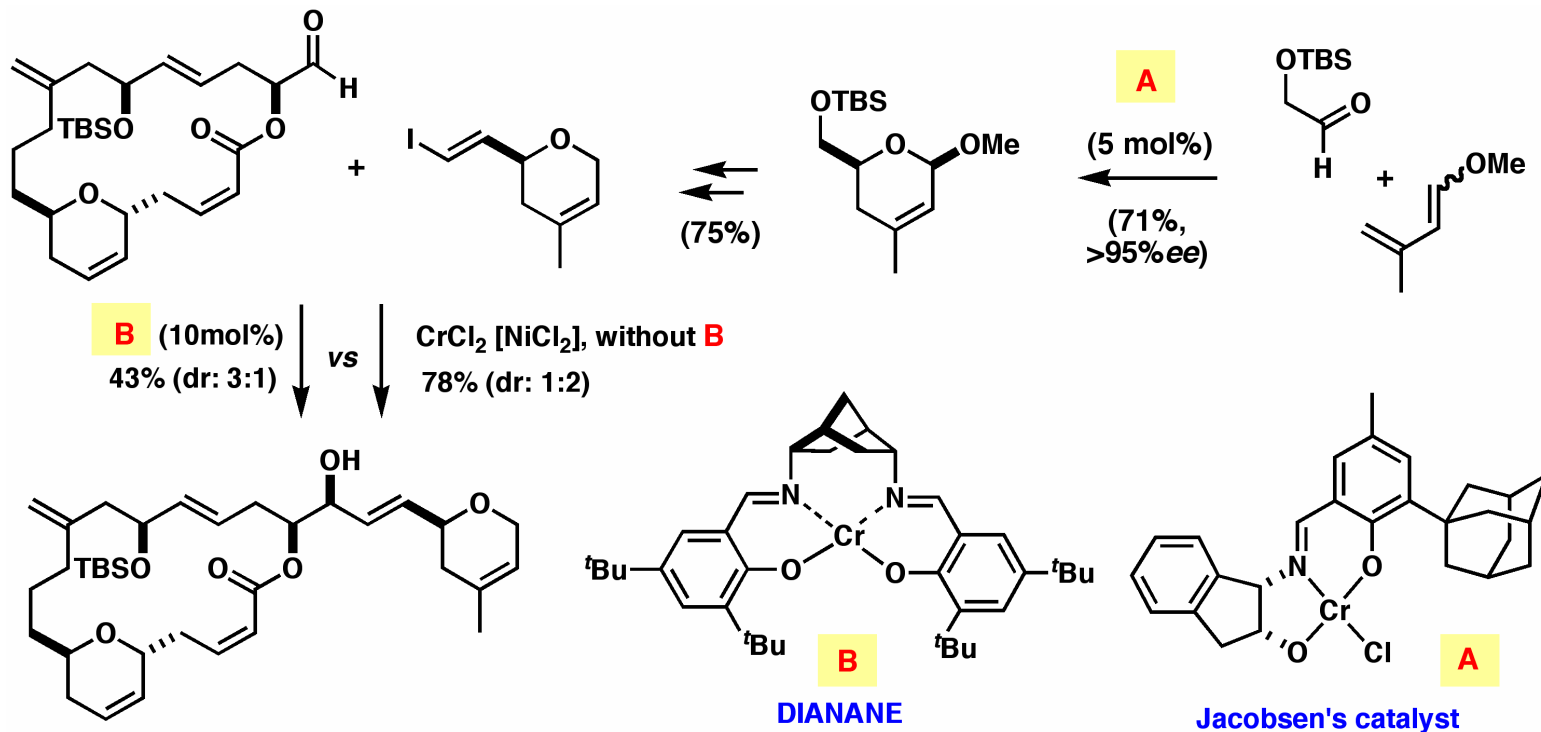
- *Jacobsen HDA chemistry and Ferrier-rearrangement for construction of dihydropyran*
- *Still-Gennari olefination for introduction of the (Z)-enoate*

Laulimalide Analogues: Synthesis of the Macrocycle



- *Diastereoselective aldol coupling using chiral boron enolate methodology*
- *Smooth macrolactonisation under Mitsunobu-type conditions*

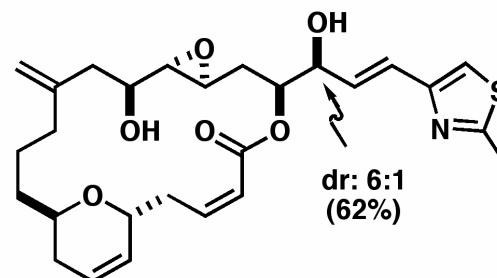
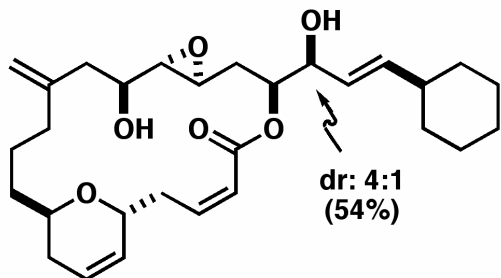
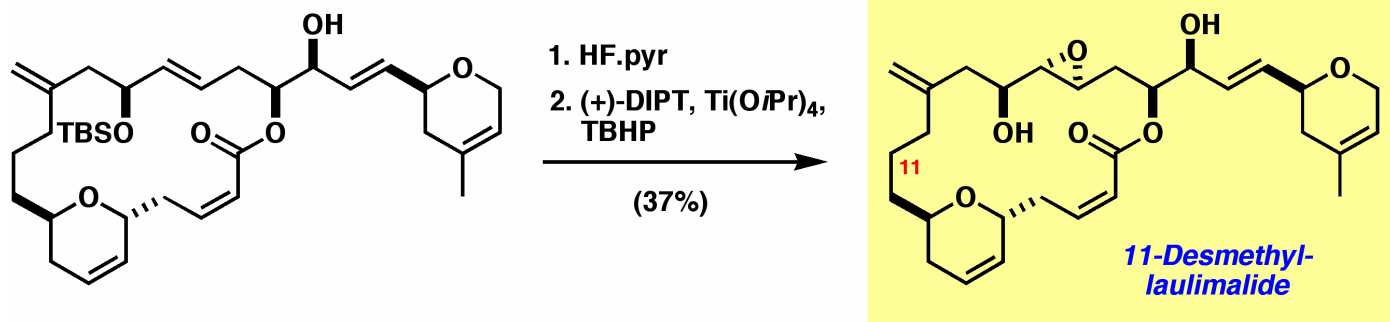
Laulimalide Analogues: Asymmetric Nozaki-Kishi Coupling



- *Jacobsen HDA reaction for construction of side chain dihydropyran*
- *Asymmetric Nozaki-Kishi coupling to overcome unfavourable substrate selectivity*

Berkessel, A.; Menche, D.; Sklorz, C.; Schröder, M.; Paterson, I. *Angew. Chem. Int. Ed.* 2003, 42, 1032.

Laulimalide Analogues: Completion of the Synthesis



- *Diversification of side chain by asymmetric Nozaki-Kishi coupling*
- *11-Desmethyl-laulimalide equipotent to Laulimalide against MCF7 Cancer Cell Line*

Paterson, I.; Bergmann, H.; Menche, D.; Berkessel, A. *Org. Lett.* 2004, 6, 1293.