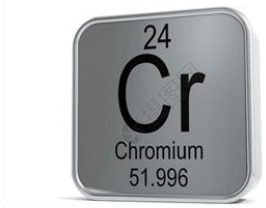
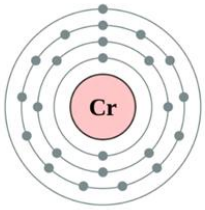
Kang Shen

The NHK and Related Reactions

Hu Lab @WestlakeU



IUPAC: Chromium Atom number: 24
Oxidation state: II, III, V,VI
m.p. 1857 °C b.p. 2672 °C density: 7.19 g/cm^3
Soluble in dilute sulfuric acid, dilute hydrochloric acid, insoluble in water, nitric acid, aqua regia



History:

1.In 1766, Lehmann, a professor of chemistry in St. Petersburg, Russia, analyzed chromium and determined that it contained lead.

2. In 1919, the structure of the resulting bis(benzene)chromium species was determinated of the structure of the resulting bis(benzene)chromium species.[1]

$$5\ C_6H_5MgBr + 4CrCl_3 = (C_5H_5)_5CrBr + 2\ MgBr_2 + 3MgCl_2 + 3\ CrCl_2$$

3. In 1957, Anet and Leblanc were the first to prepare aqueous solutions of benzylchro mium compounds by reaction of Cr(II) with benzyl chloride.

4. Nozaki and Hiyama et al. screened of the reactivity of benzylchromium and related reagents in 1977 that triggered an explosive development of this particular branch of organometallic chemistry.

5. Takai, Nozaki and Hiyama found that organochromium species can add selectively to an aldehyde moiety without affecting the ketone or cyano group.

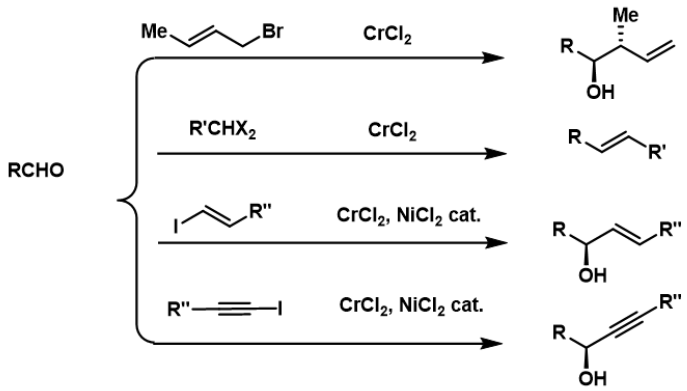
6.In 1986, Kishi et al. and Nozaki et al. discovered that traces of nickel salts exert a catalytic effect on the formation of the C-Cr(III) bond.

Furstner, Chem. Rev. 1999, 99, 991

Preparation:

1. transmetallation from RLi, RZnX, RMgX
   Cr (III) low solubility in ethereal solvents

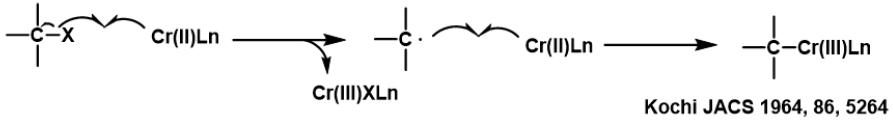
2. redution of C-X



Reduction of organic halides

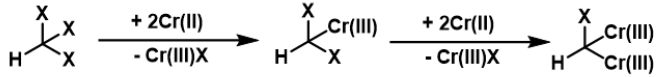
$$PhCH_2X > RCOCH_2X > CH_2{=}CHCH_2X > R_3CX > R_2CHX > RCH_2X > R^1R^2C{=}CR^3X > ArX$$

(X = I > Br > Cl)



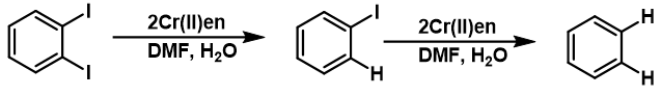
Kochi JACS 1964, 86, 5264

Polyhalides:



Takai JACS, 1986, 108, 7408

Aryl halides:



NR in aproyic solvents
Takai JACS 1986, 108, 6048

The NHK and Related Reactions

The nature of carbon-chrominm bonds

1. thermal stability

RCr(III)Cl (THF)n

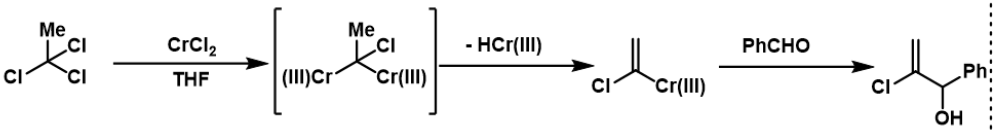
iBu > iPr > Et > Me

Ikeda J. organomet. Chem 1972, 37, 317.

Decylchromium dichioride

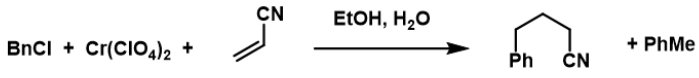
0 °C stable
20 °C slow homolysis
65 °C rapid homolysis

Zeiss J. organomet. Chem 1971,26,101



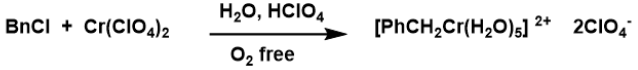
Miokoski JACS 2001, 123, 9196

2. hydrolysis



20 %

Sustmann chem. Ber 1993, 126, 1759.



Anet Can. J. Chem. 1959, 37, 58

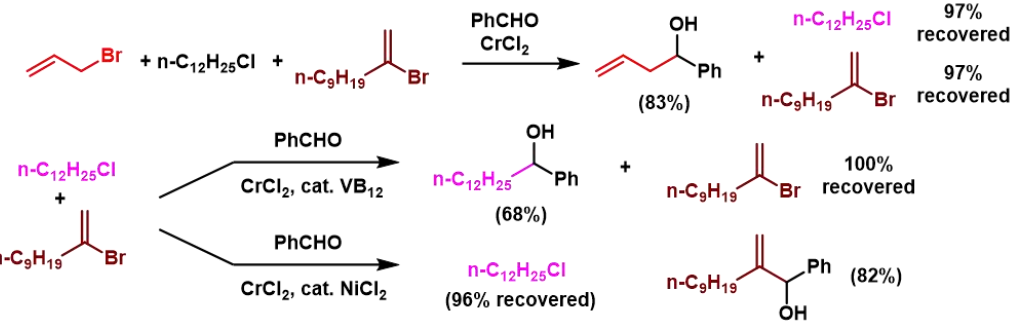
3. nucleophilicity

Excess

70 % (yield are based on PhMgBr)

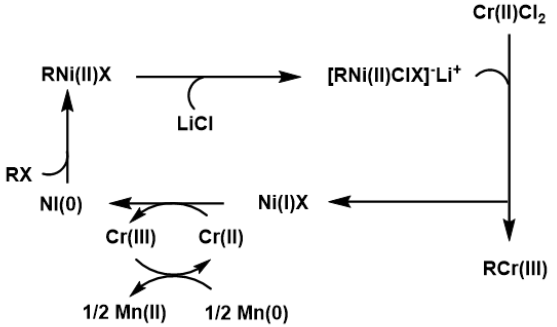
Zeiss J. organomet. Chem 1965, 4, 397

Chemoselectivity



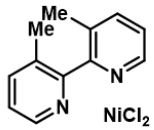
Utimoto JOC 1989, 54, 4732

Alkenyl/Aryl chromium addition to aldehyde [$NiCl_2$, $Pd(OAc)_2$]



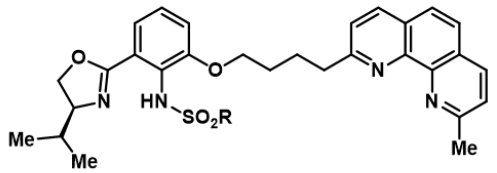
"$NiCl_2$ and$Pd(OAc)_2$ have a dramatic effect"

Kishi JACS 1986, 108, 5644



Kishi OL 2004, 24, 5421

1 and 5 mol % catalyst-loading



Kishi 2009,131,42, 15393

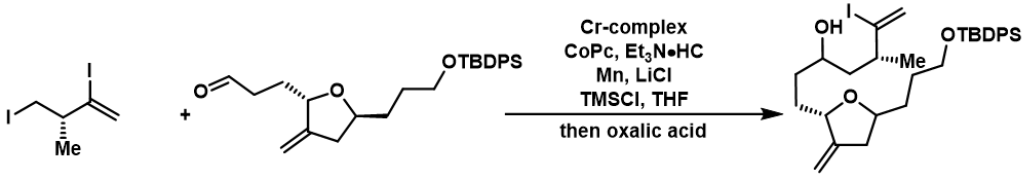
the molar ratio of coupling partners

The NHK and Related Reactions

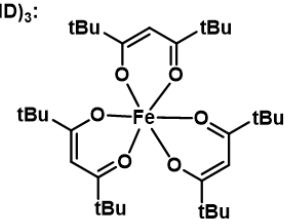
PhI	PhCHO	85% 62-88% 66%	A B C
PhBr	PhCHO	31% 57%	A C

A:$CrCl_2$ (4 equiv), DMF, rt.
B:$CrCl_2$ (15 mol %), Mn powder, chlorosilane, DMF/DME (20/3), 50 °C.
C:$CrCl_2$ (10 mol %), $Pd(OAc)_2$ (0.1 mol %), PPh_3 (0.4 mol %), constant current conditions, $LiClO_4$ as supporting electrolyte in DMF

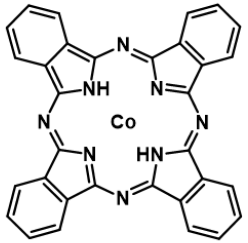
Alkyl chromium addition to aldehyde [$Fe(TMHD)_3$, CoPc]

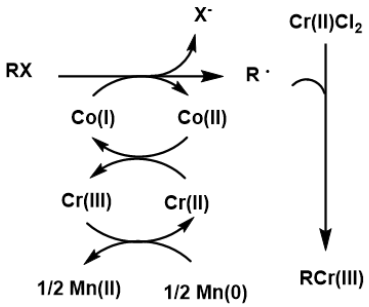


$Fe(TMHD)_3$:



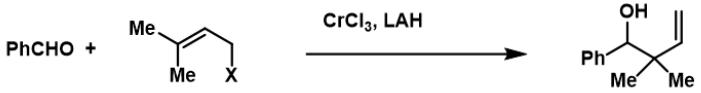
CoPc:





Kishi OL 2004, 4, 25, 4435
Kishi JACS 2004, 126, 39, 12248

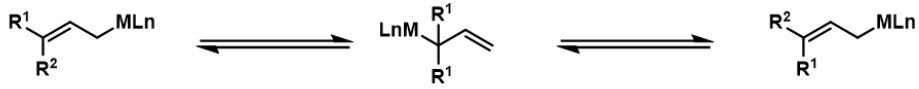
Allyl chromium addition to Aldehyde:



X = Br, THF, rt 90%
X = $OP(O)(OEt)_2$, DMF, 90 °C, 97%

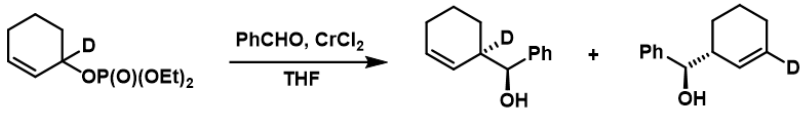
Nozaki BCSJ 1982, 55, 561.

Regioselectivty:



reactive site

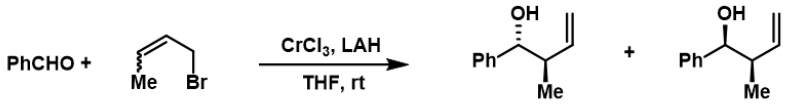
Equlibrum rate: AllyLi, AllyMgBr > $AllyBR'_2$



1:1

Takai JSOJ, 1988, 46, 66.

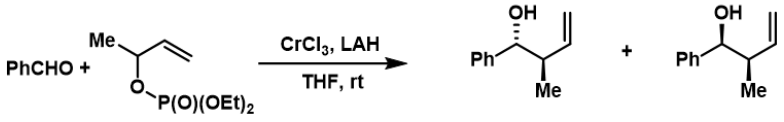
Diastereoselectivity:



(E)-crotyl bromide 96%, anti:syn = 100:0
(Z)-crotyl bromide 87%, anti:syn = 100:0

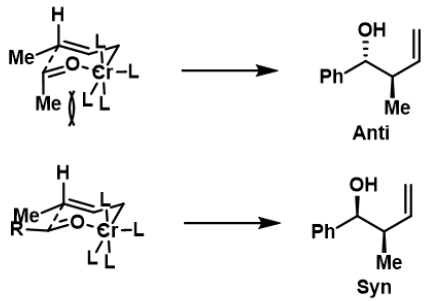
Heathcock, TL 1978, 1685

The NHK and Related Reactions

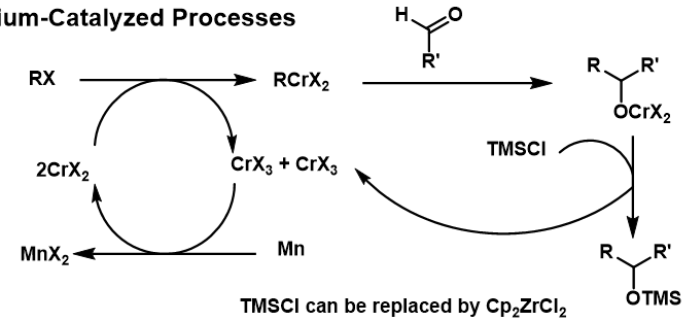


73%, anti:syn = 89:11

Takai JSOJ, 1988, 46, 66.



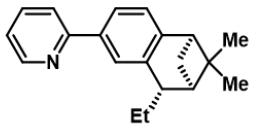
Chromium-Catalyzed Processes



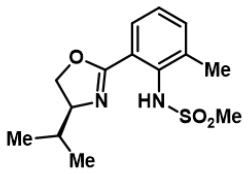
TMSCl can be replaced by Cp_2ZrCl_2

Kishi OL 2004, 6, 26, 5031.

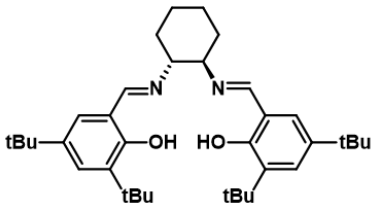
Asymmetric addition



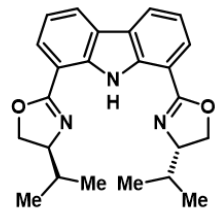
Kishi (1996)



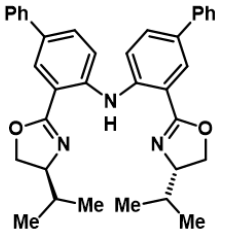
Kishi (2002)



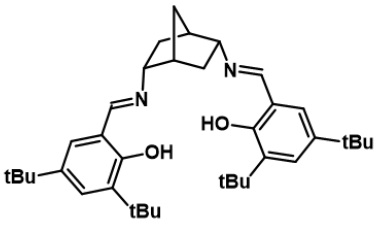
Cozzi and Umani-Rouchi(1999)



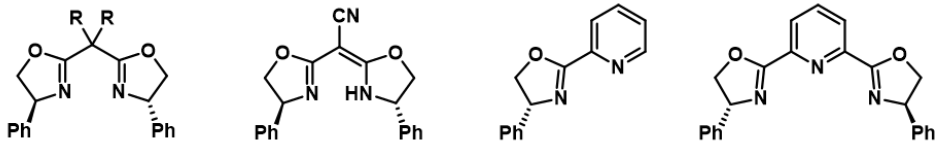
Guiry (2003)



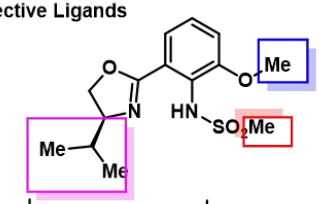
Nakada (2003)



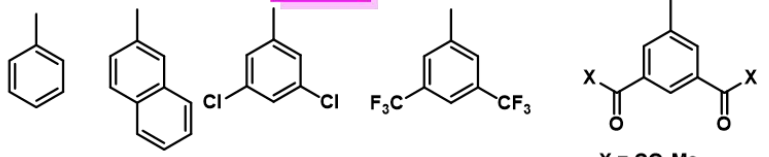
Berkessel and Paterson (2003)



Toolbox Approach to the Search for Effective Ligands

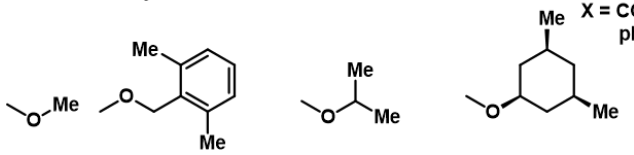


Red

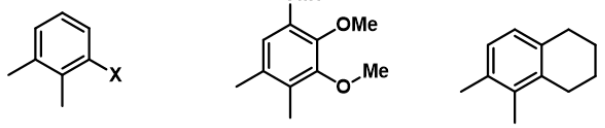


X = CO_2Me, phenothiazine

Blue



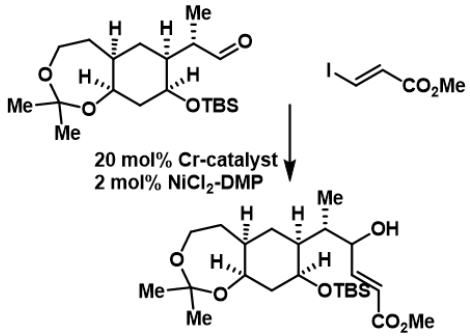
Purple

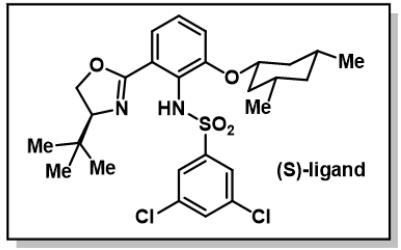


X = H, Me, OMe

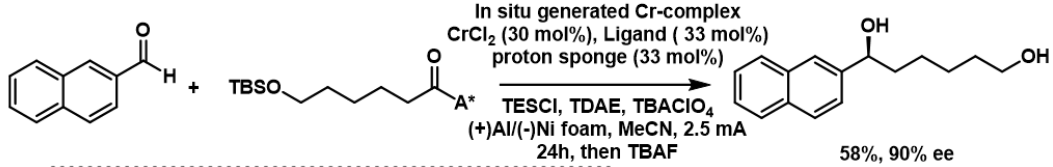
Kishi JACS 2009, 131, 15387

The NHK and Related Reactions



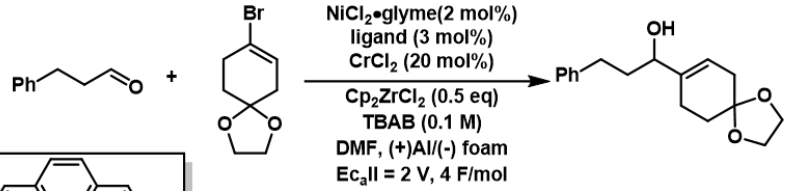


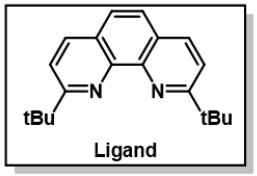
non-asymetric ligands 1.1:1
(S)-ligand dr 60:1
(R)-ligand dr 1:27

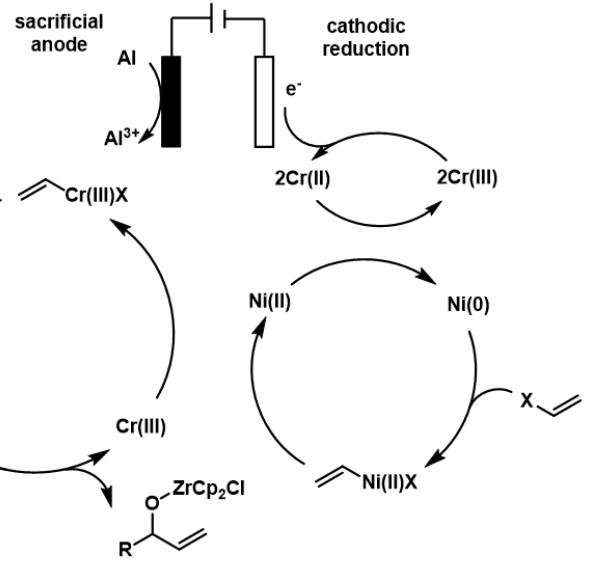


58%, 90% ee

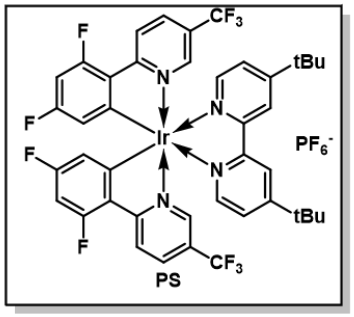
Research progress in recent years

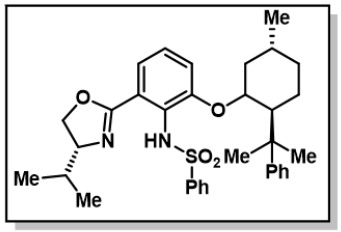




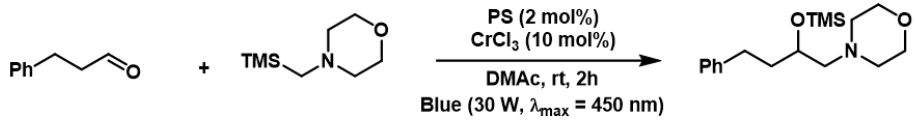


Baran JACS 2021, 143, 9478

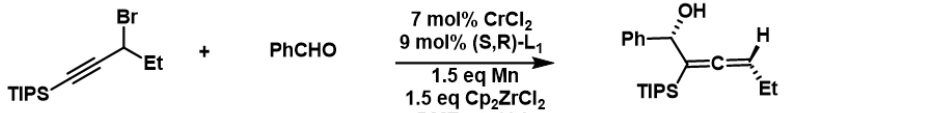




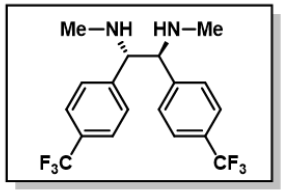
Baran JCAS 2024, 146, 4872

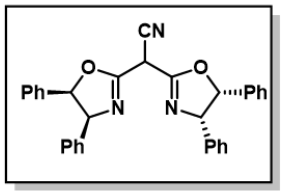


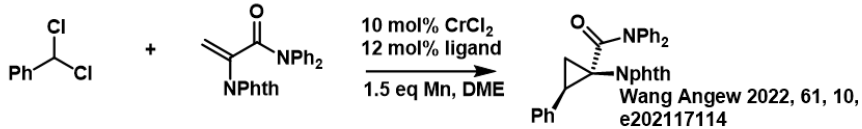
Glorius JCAS 2020, 142, 2168



Wang Angew 2022, 61, e202117114

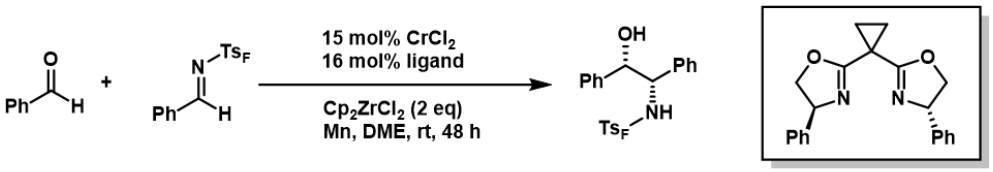


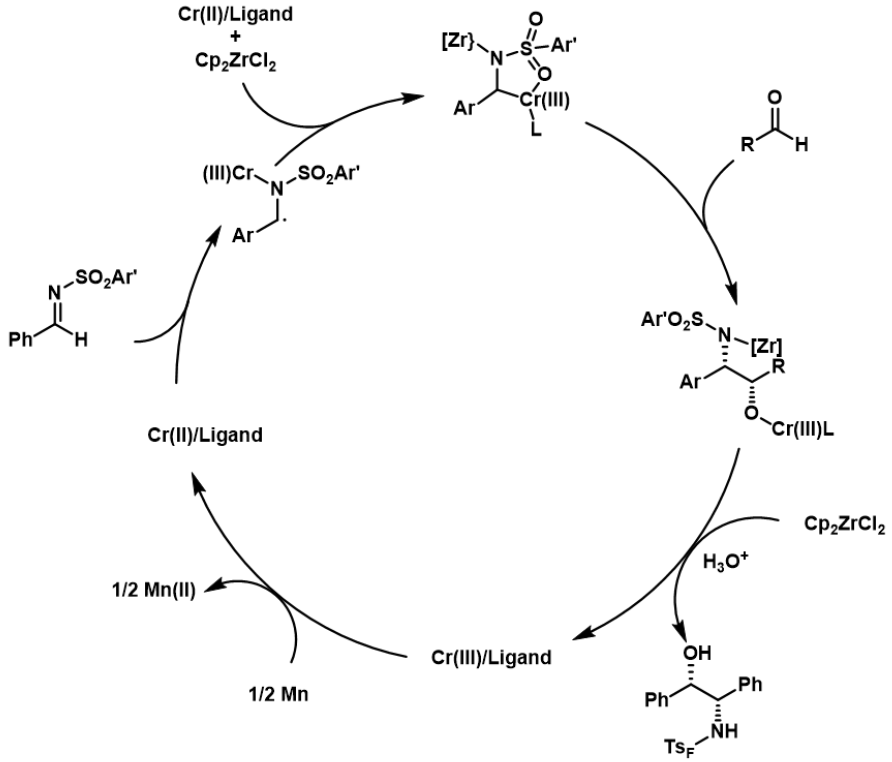




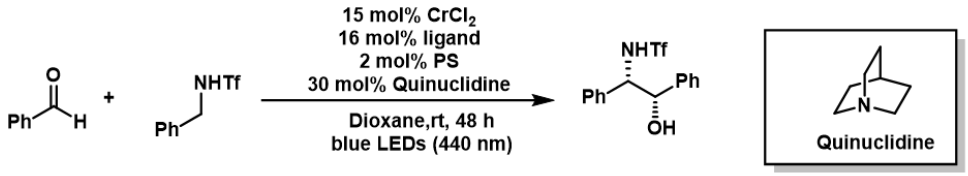
Wang Angew 2022, 61, 10, e202117114

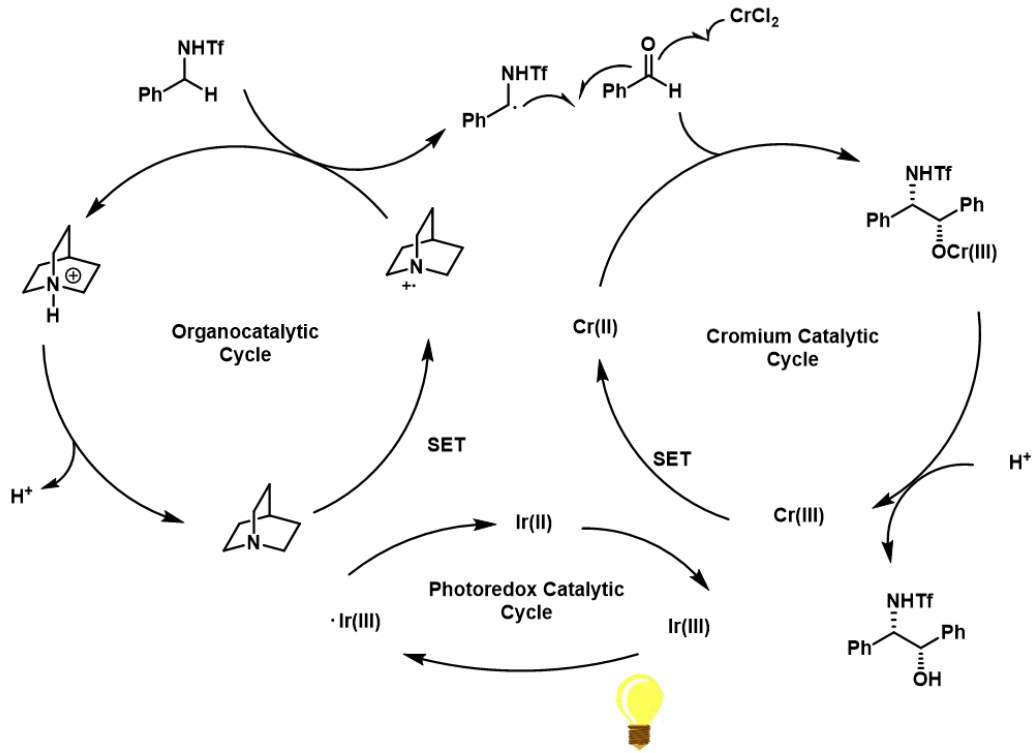
The NHK and Related Reactions





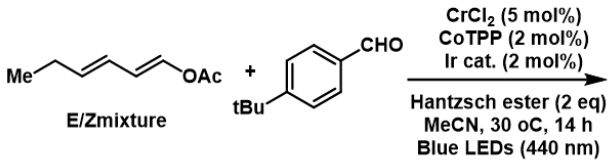
Wang JACS 2023, 145, 38, 20775

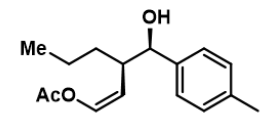




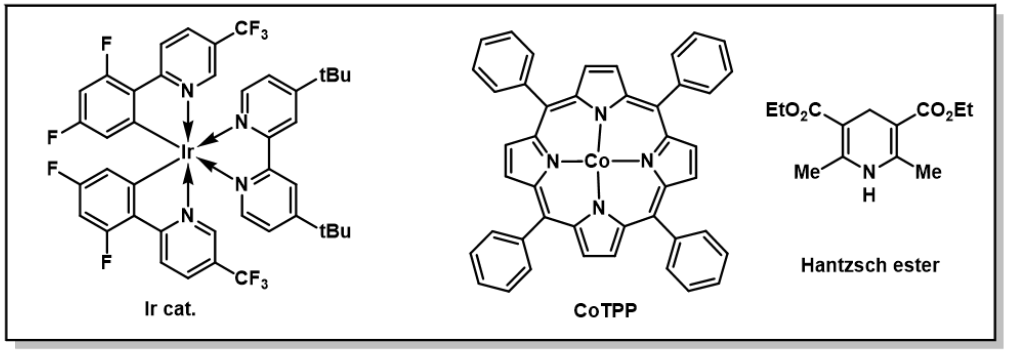
Wang JACS 2024, 146, 5316

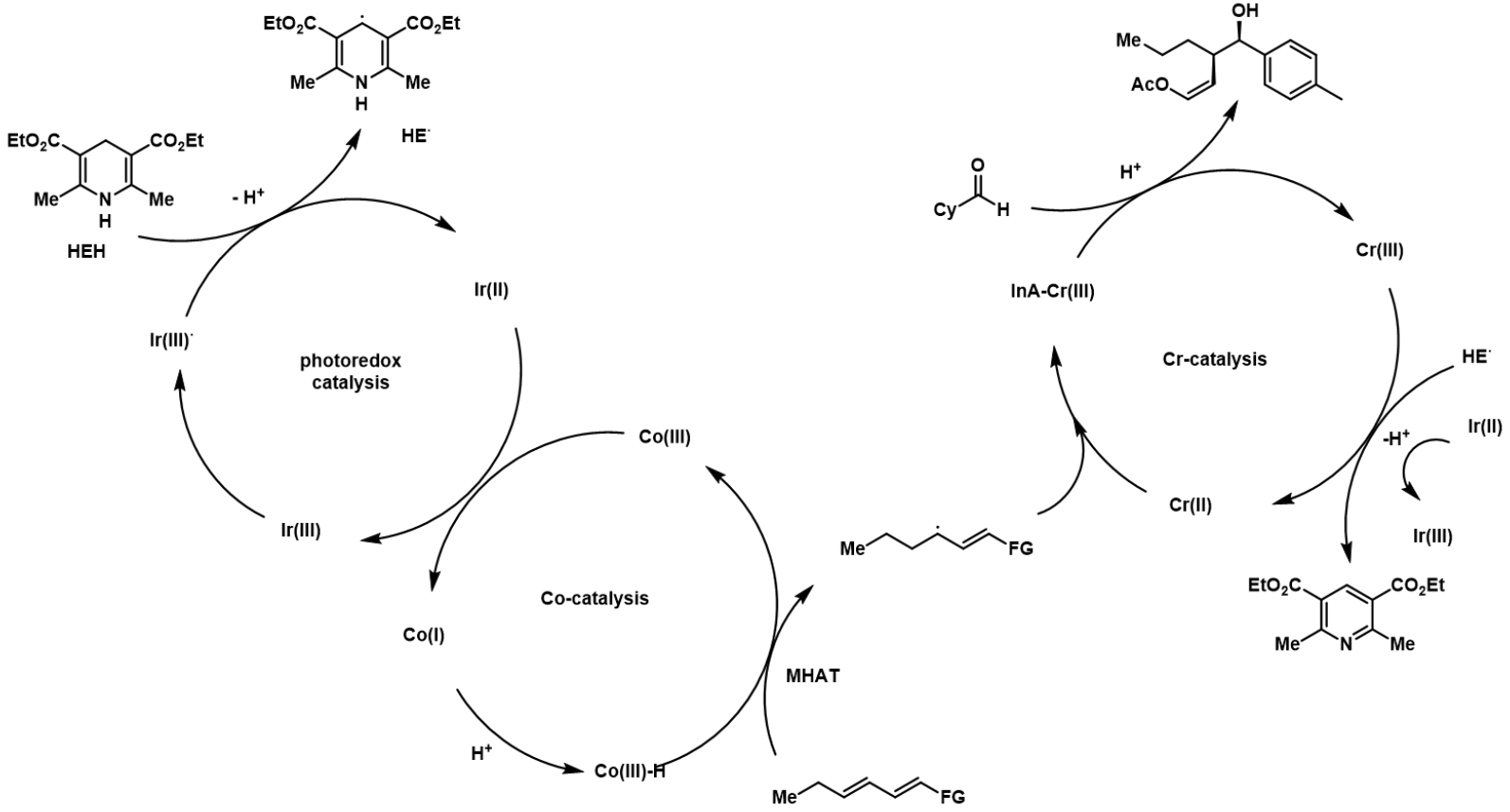
The NHK and Related Reactions

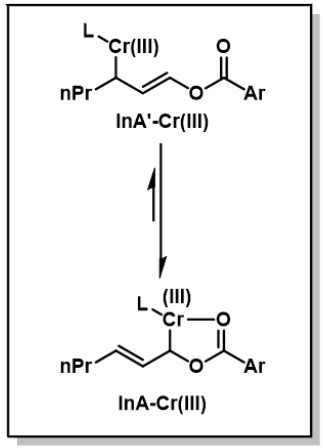


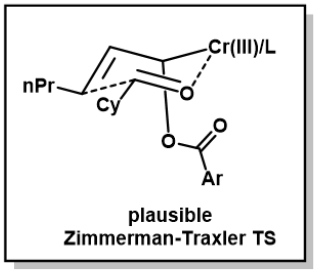


99% yield
anti-Z selectivity, > 20:1 dr





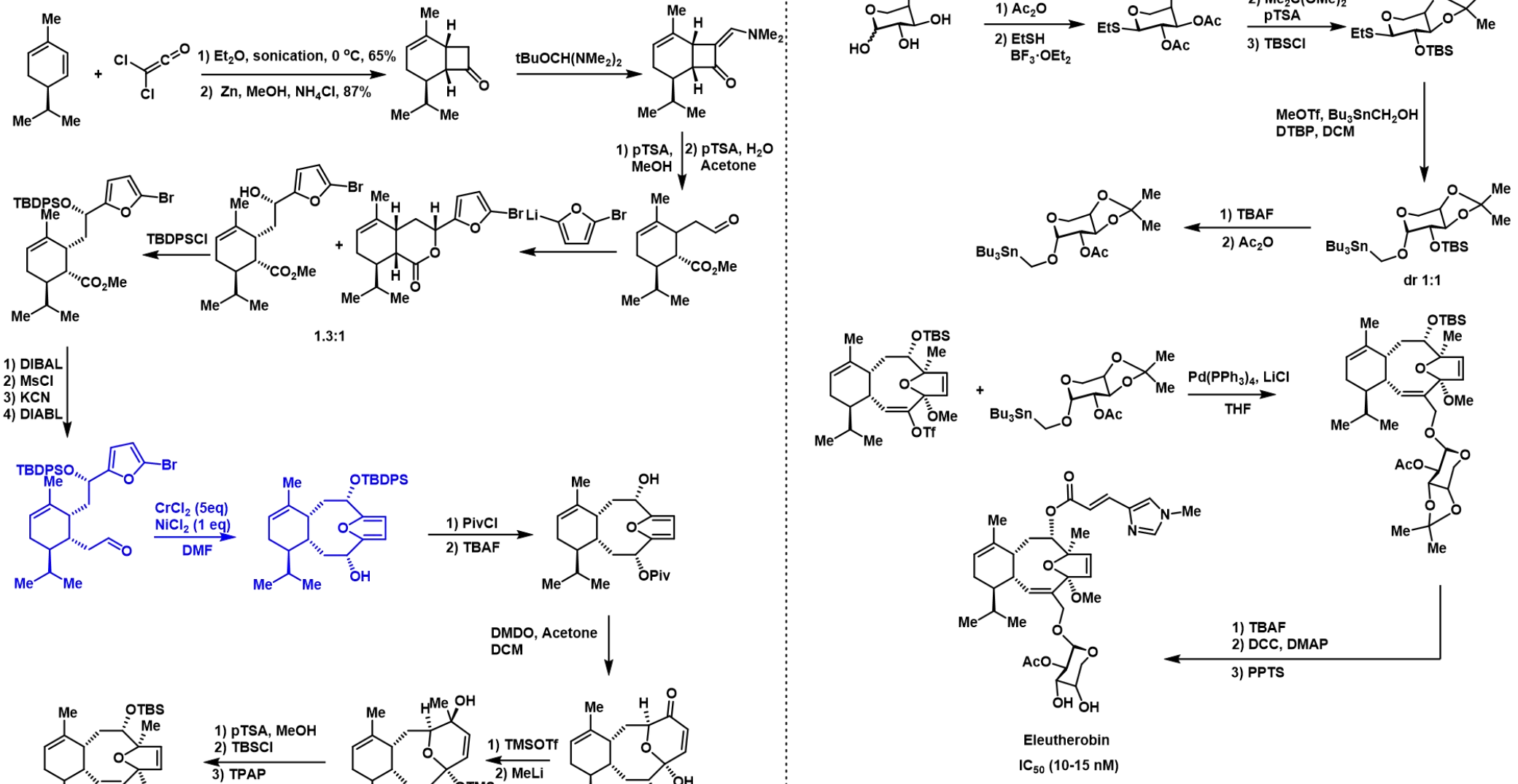




Wang Chem 2024 10, 998.

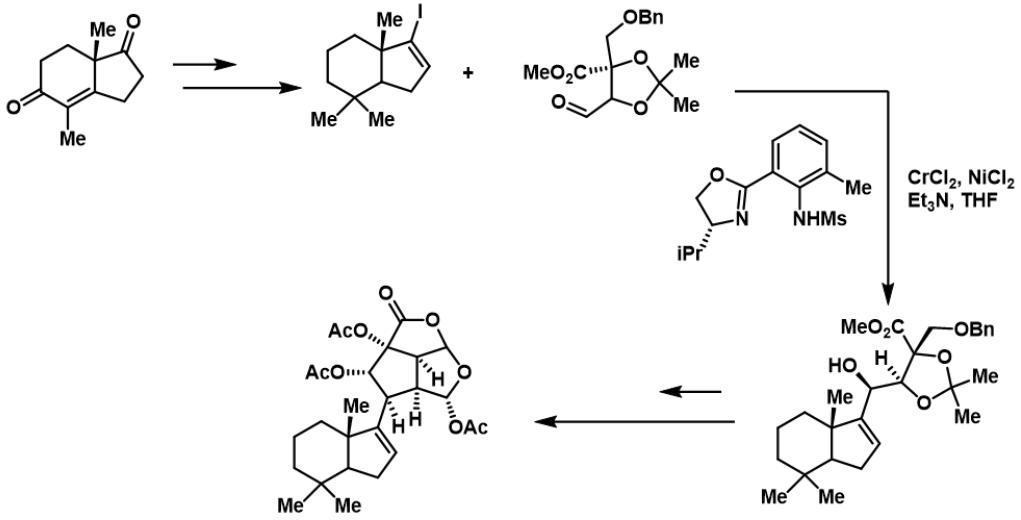
The NHK and Related Reactions

Synthetic application:



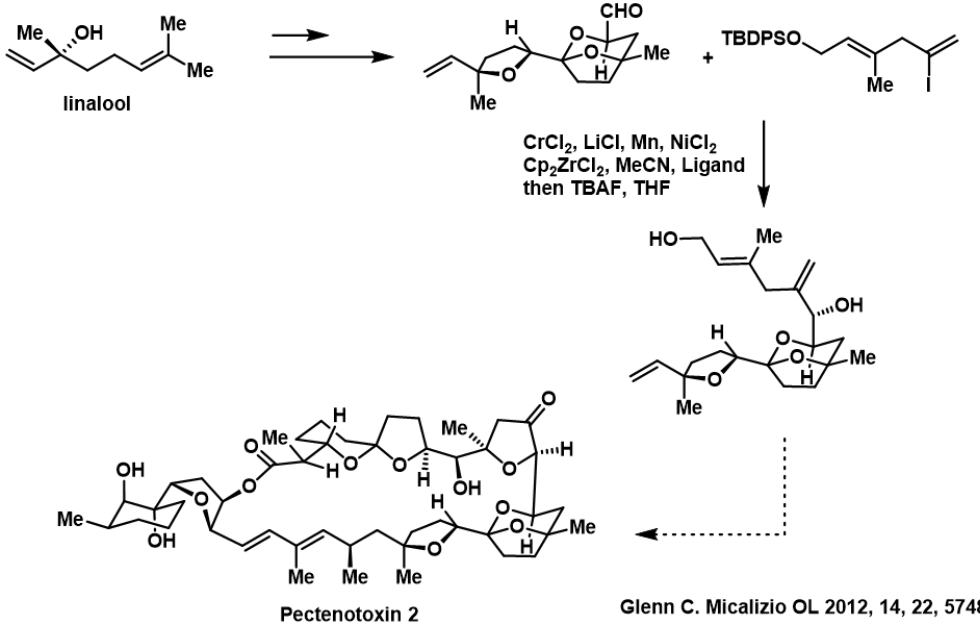
Danishefsky JACS 1999, 121, 28, 6563

The NHK and Related Reactions



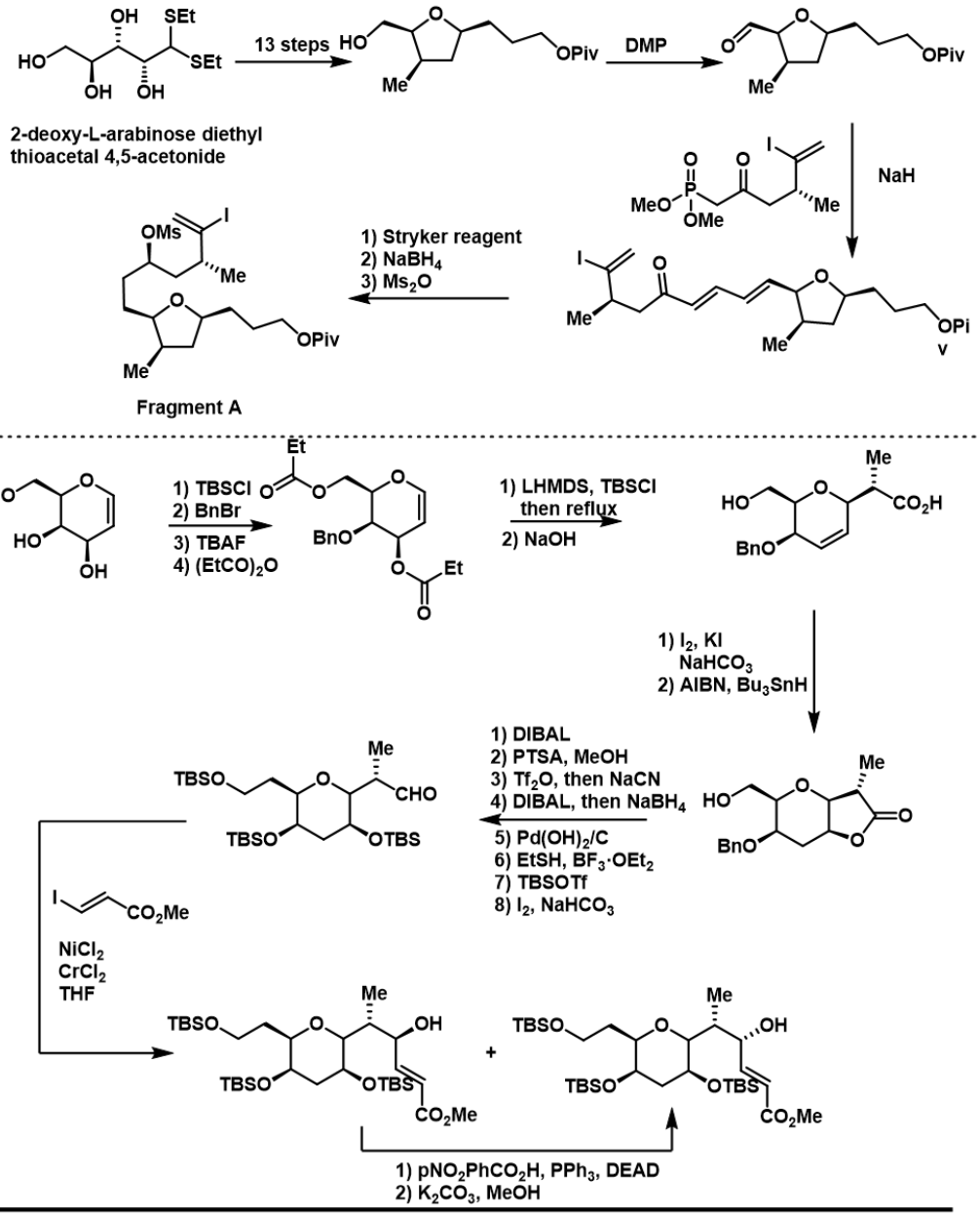
chromodorolide B

Overman JACS 2016, 138, 7, 2186

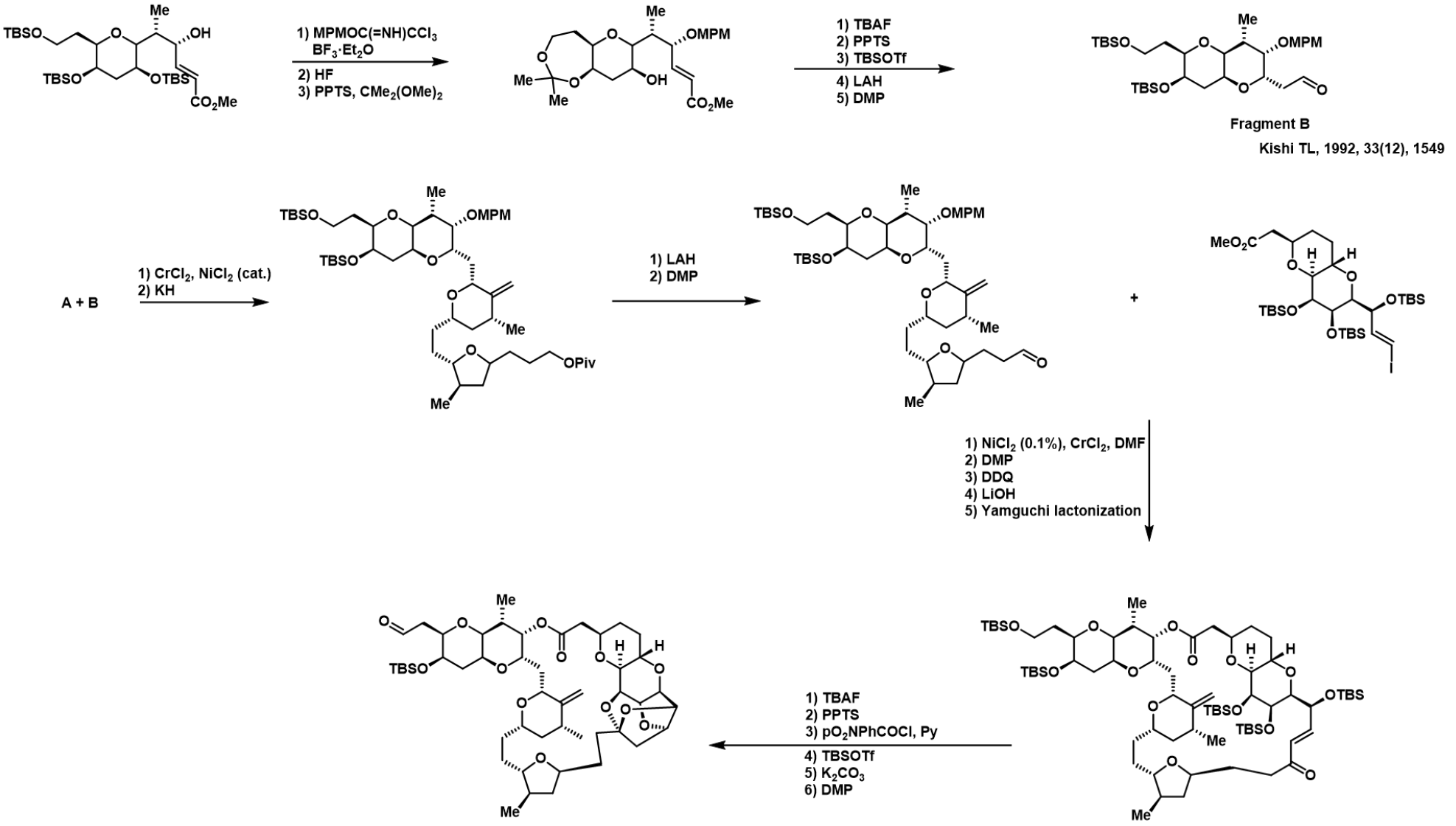


Pectenotoxin 2

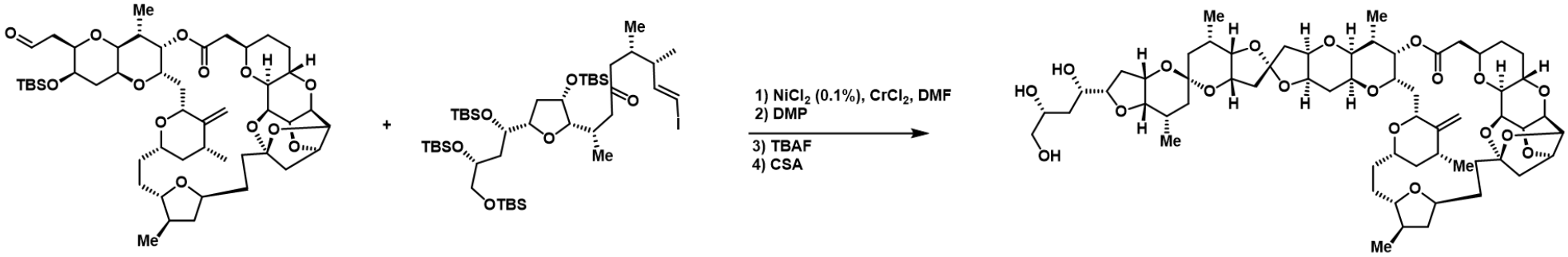
Glenn C. Micalizio OL 2012, 14, 22, 5748



The NHK and Related Reactions

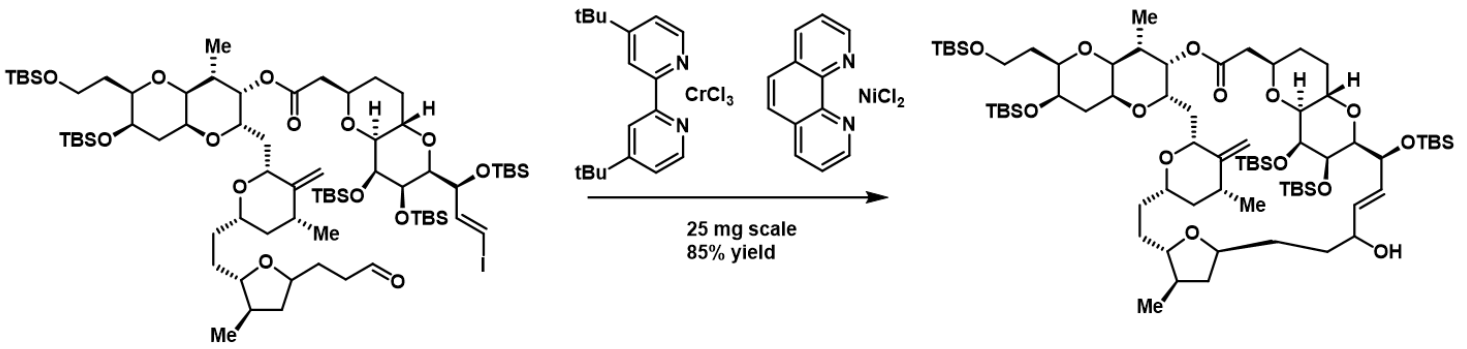


The NHK and Related Reactions



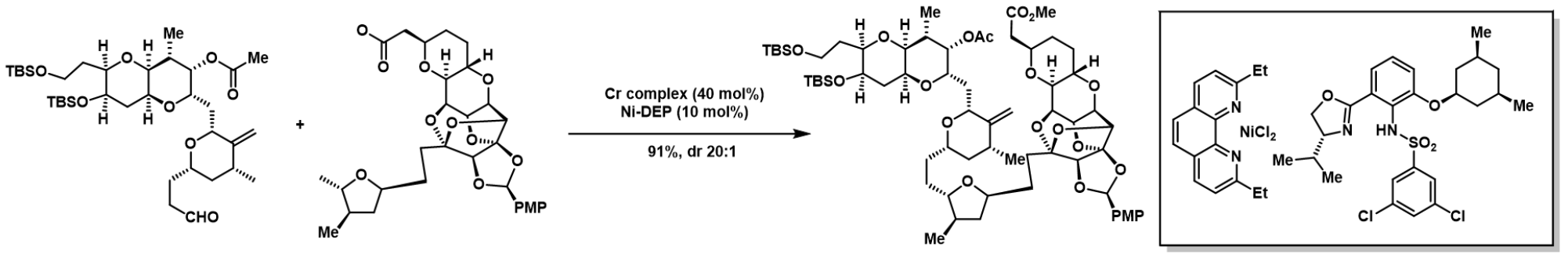
Halichondrin B

Kishi JACS 1992, 114, 3162



Catalytic Ni/Cr-Mediated Macrocyclization without Use of High-DilutionTechniques

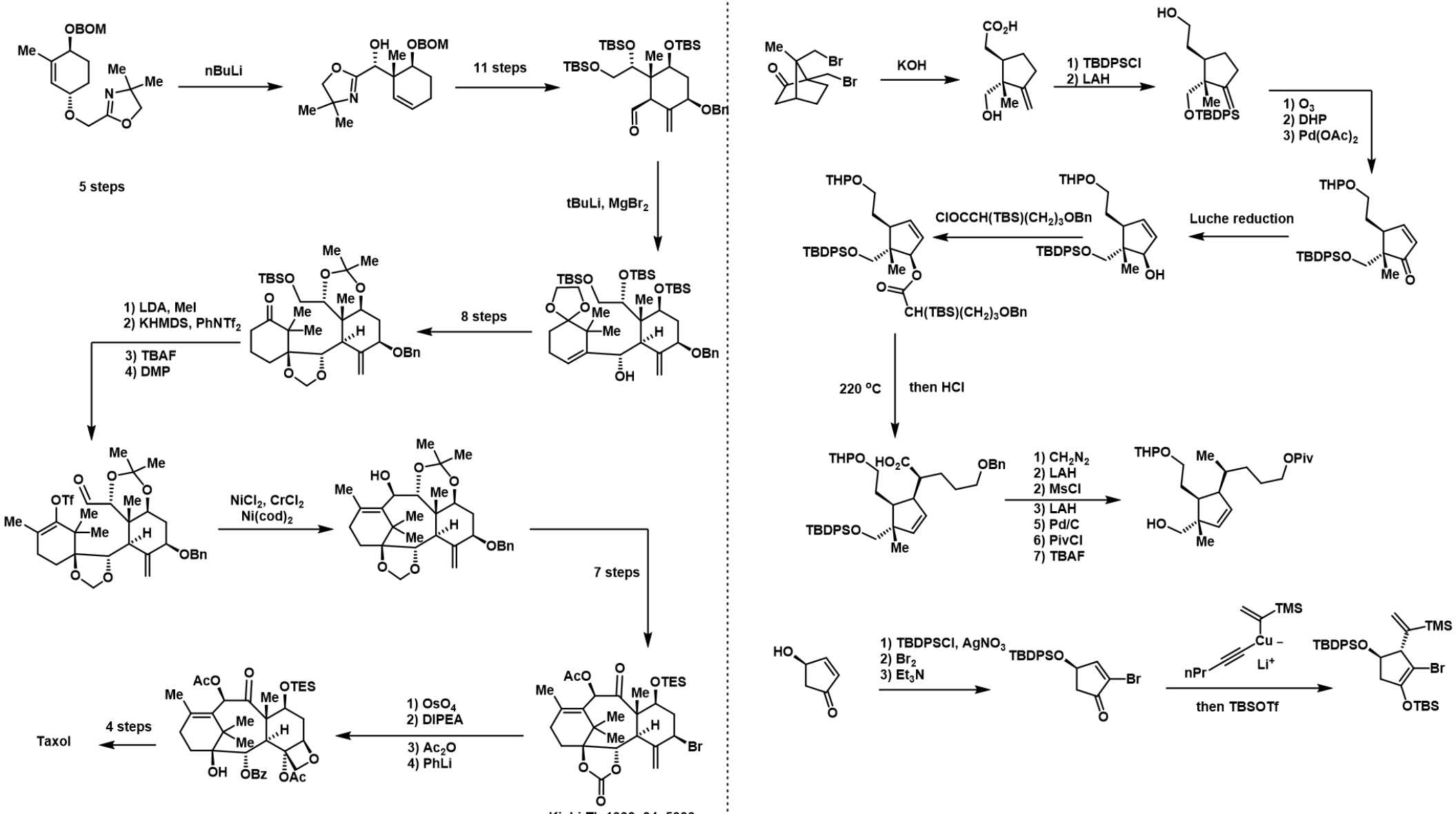
Kishi JACS 2005,127, 15382



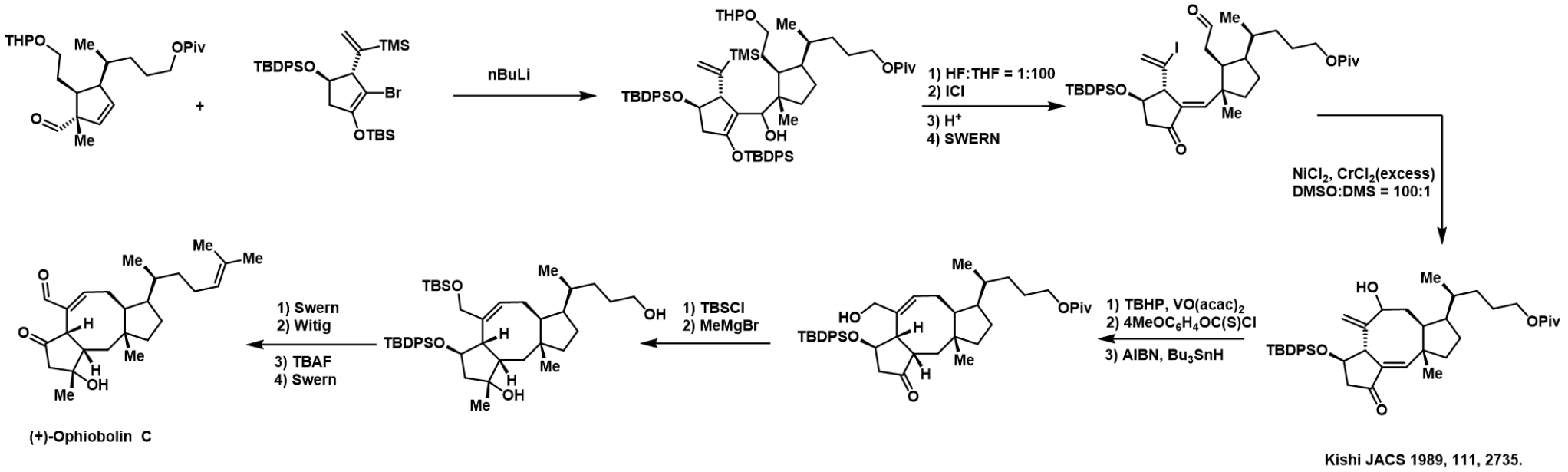
Total Synthesis of Halichondrin A

Kishi JACS 2014, 136, 5171.

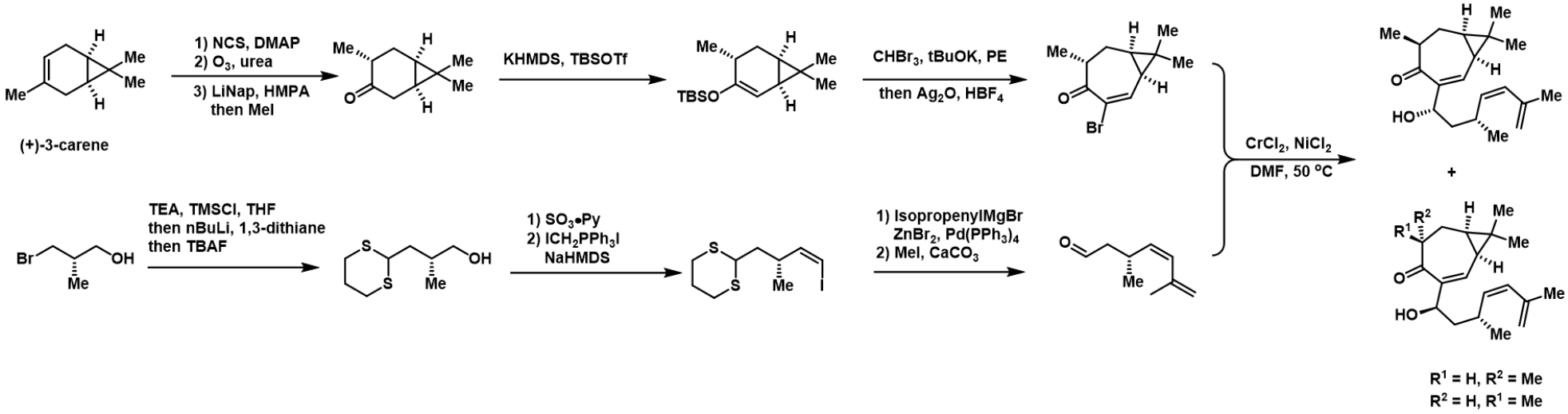
The NHK and Related Reactions



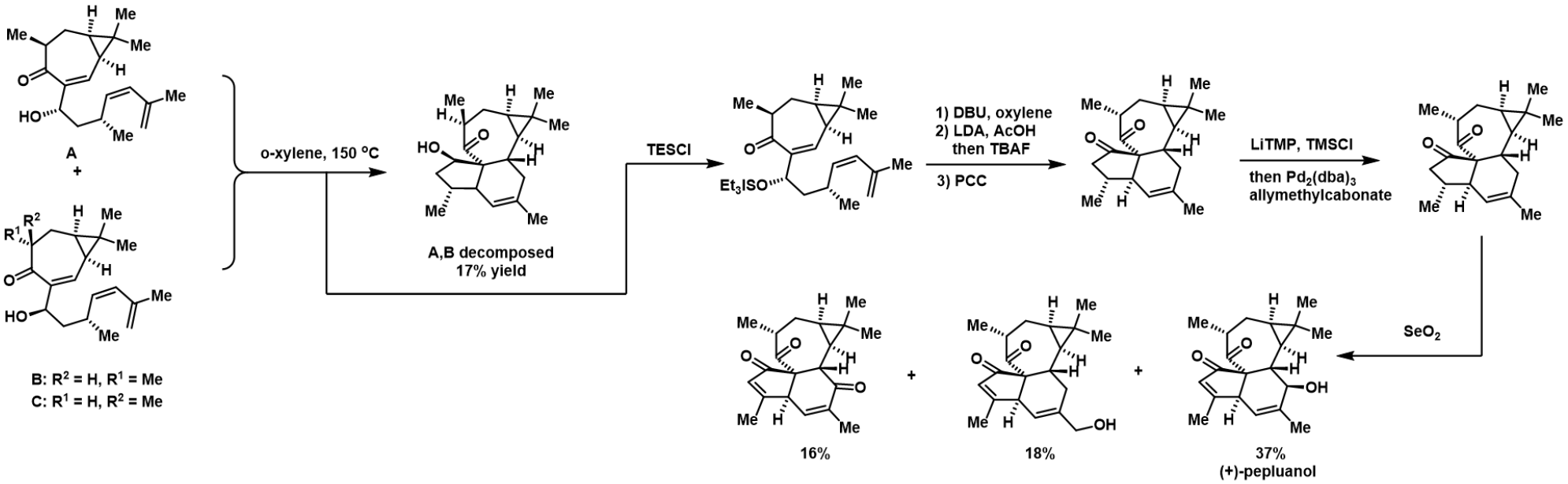
The NHK and Related Reactions



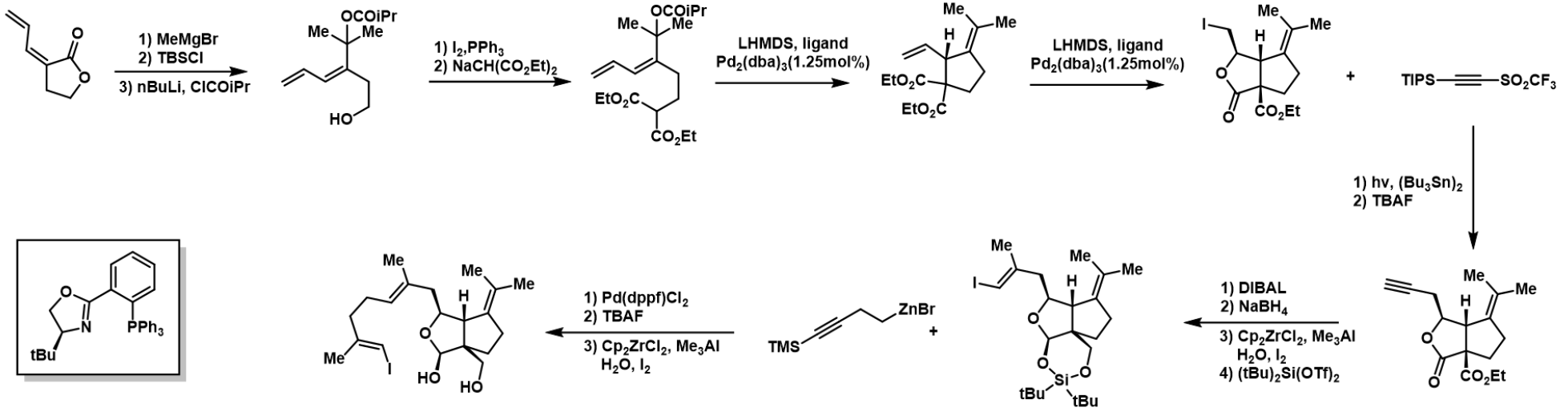
Kishi JACS 1989, 111, 2735.



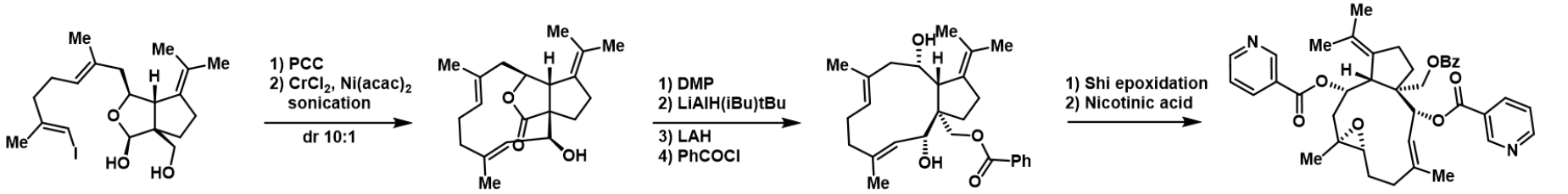
The NHK and Related Reactions



Gaich JACS 2021, 143, 11934



The NHK and Related Reactions



Ent-Nigellamine A_2

Ready JACS 2006, 128, 7428