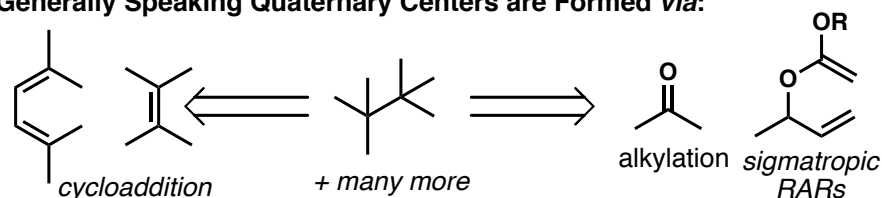
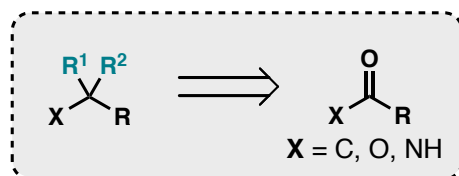
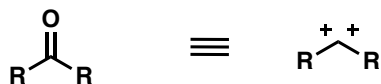
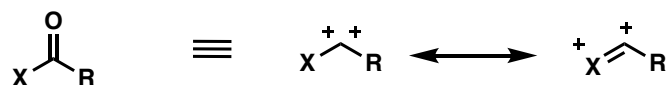


Generally Speaking Quaternary Centers are Formed via:



Reviews on quat center formation: *Adv. Synth. Catal.* **2005**, 347, 1473-1482
Chem. Rev. **2008**, 108, 2853-2873 + more

But – how can one accomplish the following transform:**Key Challenge for Ketones:** Abstraction of oxygen following 1st addition**Key Challenge for Amides/Esters:** Avoiding fragmentation/opening, activation strategy**This GM will cover the Quaternization of:**

- 1) Amides and Thioamides
- 2) Ketones
- 3) Esters

In short (1-3 step*) sequences, with focus on applications in synthesis and pharmaceuticals

This GM will not cover:

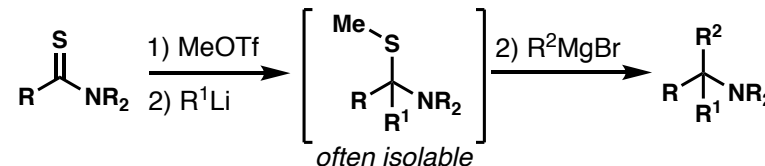
- 1) General discussion of quat center formation
- 2) Exhaustive coverage of every method for carbonyl quaternization

Key Reference: *ACIE* **2011**, 50, 96-101.

*step counts are determined by transformations directly related to the carbonyl, not distal manipulations

1) Quaternization of Amides and Thioamides**i) Methods for Activation and Organometallic Addition****Thioamide Activation and Sequential Alkylation**

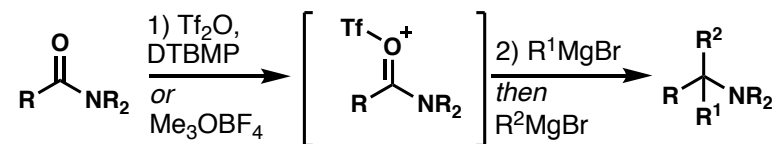
JACS **2004**, 126, 5968; *Tetrahedron* **2006**, 62, 6312



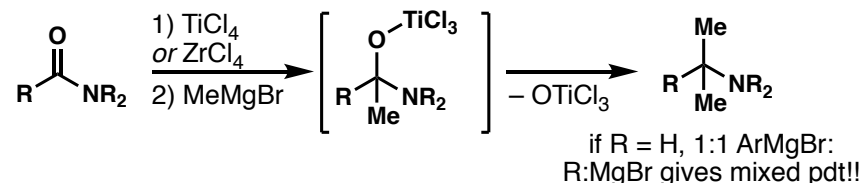
if R¹ = R² treat with xs. RMgBr or R₂CeCl₂
Org. Lett. **2008**, 10, 1417

Direct Amide Activation – Triflation or Alkylation

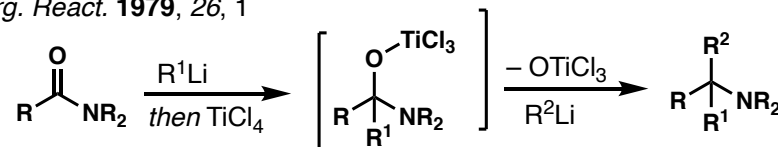
ACIE **2010**, 49, 3037

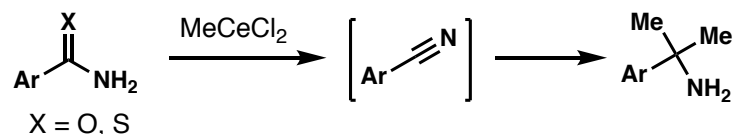
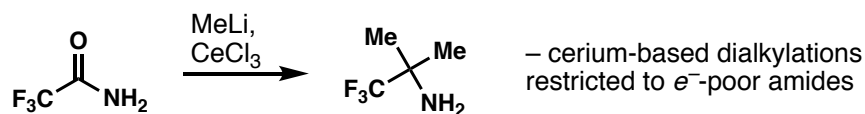
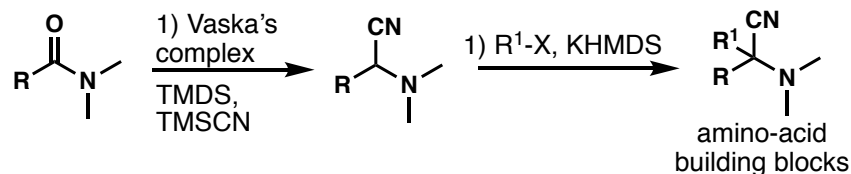
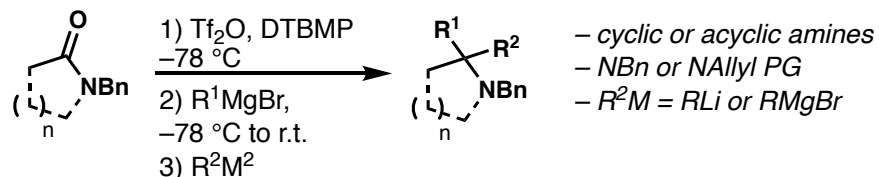
**Early TM-Amide Activation**

Eur. JOC **2008**, 5107; *Synlett* **1999**, 1, 55-56

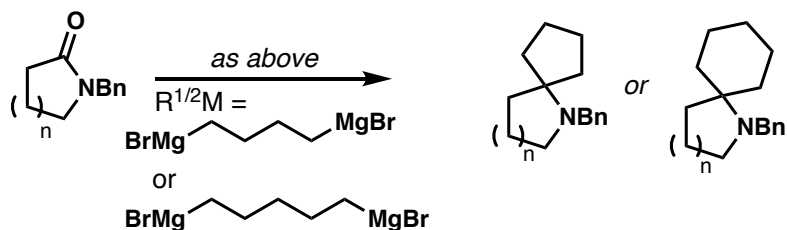
**Direct Amide 1,2-Addition–Transmetalation**

Org. React. **1979**, 26, 1

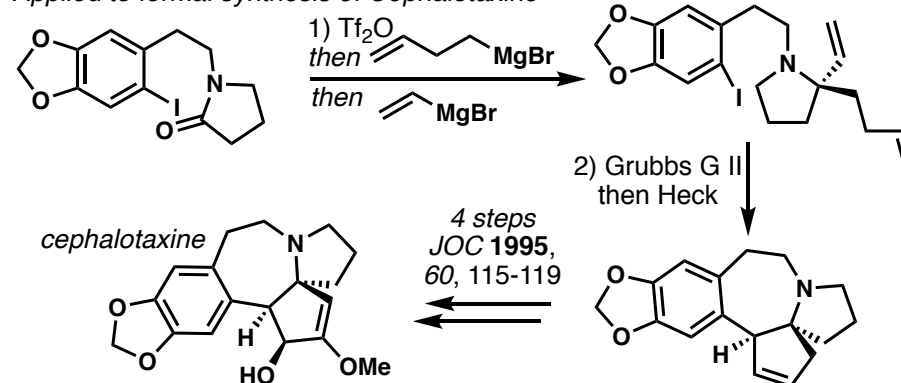
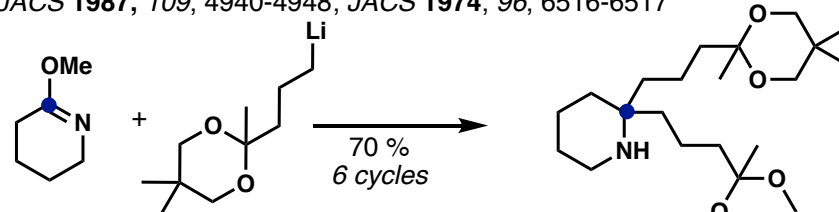
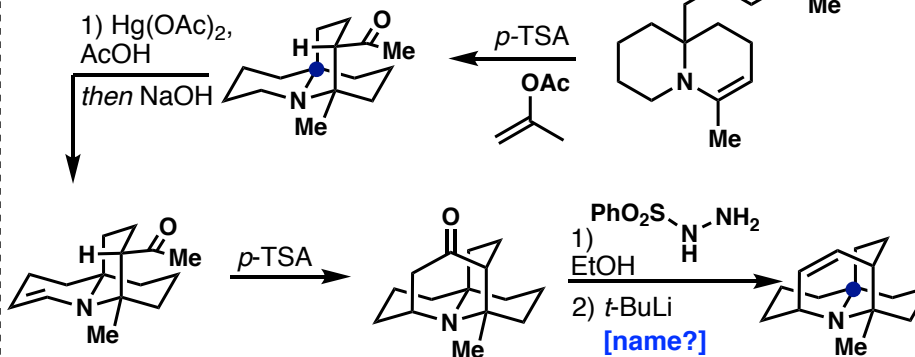


Cerium-Mediated *gem*-Dimethylation*J. Fluor. Chem.* **2002**, *117*, 9-11; *Tet. Lett.* **1997**, *38*, 1241**Reductive Strecker-based Access to Quaternized Amides***ACIE* **2017**, *56*, 3655-3659**General One-Pot *gem*-Dialkylation of Amides – *Gold mine****Chem. Eur. J.* **2013**, *19*, 13075-13086

simple access to azaspirocycles



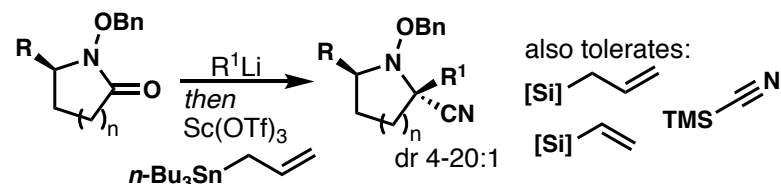
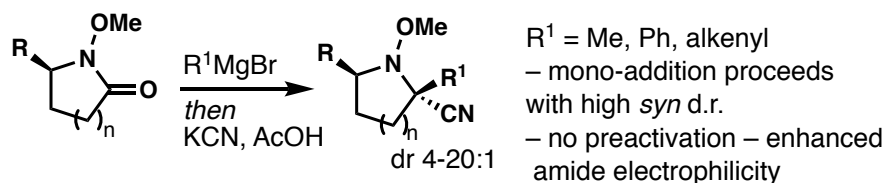
Applied to formal synthesis of Cephalotaxine

**Methylative Amide Functionalization – Synthesis of Porantherine***JACS* **1987**, *109*, 4940-4948; *JACS* **1974**, *96*, 6516-6517– poor reactivity attributed to deprotonation
– additives, alt. R-M, etc did not help

ii) Activation-Free Double Additions

N-O Amides – Diastereoselective *gem*-Dialkylation

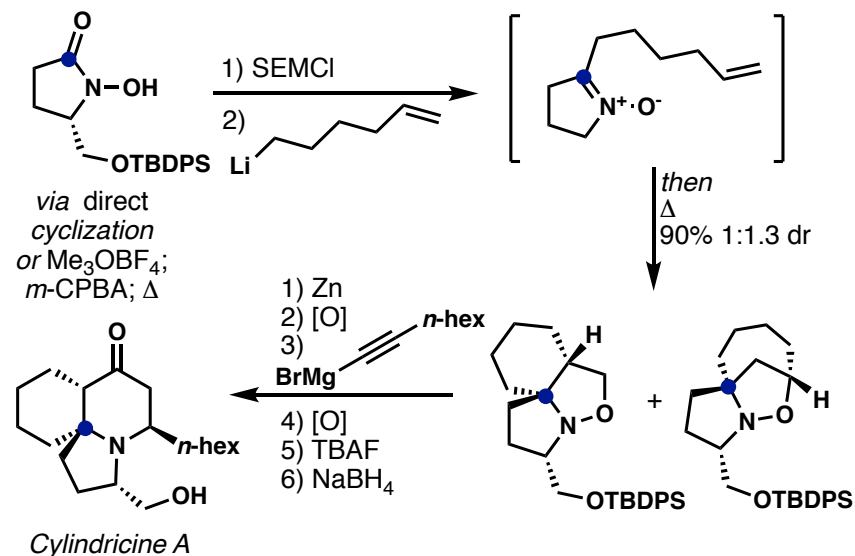
Chem. Eur. J. 2013, 19, 16746-16755; Chem. Eur. J. 2013, 19, 6778-6784



iii) Mono-Addition Followed by Intramolecular Functionalization

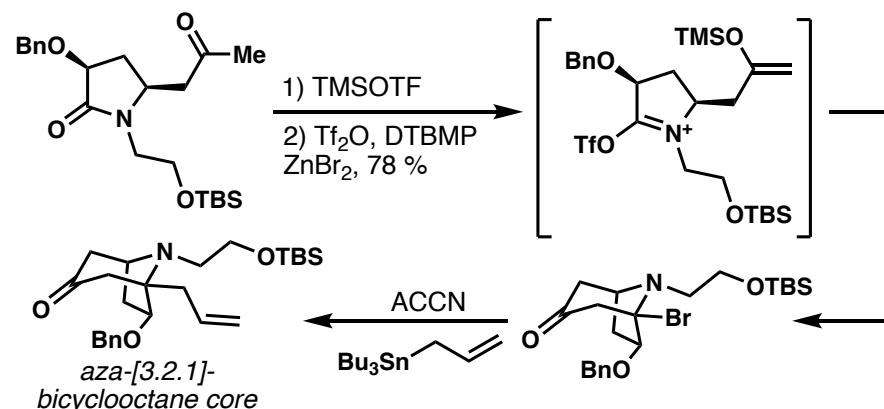
Quaternization by Cyclic Nitrone Formation-[3+2]

ACIE 2019, 58, 4381-4385



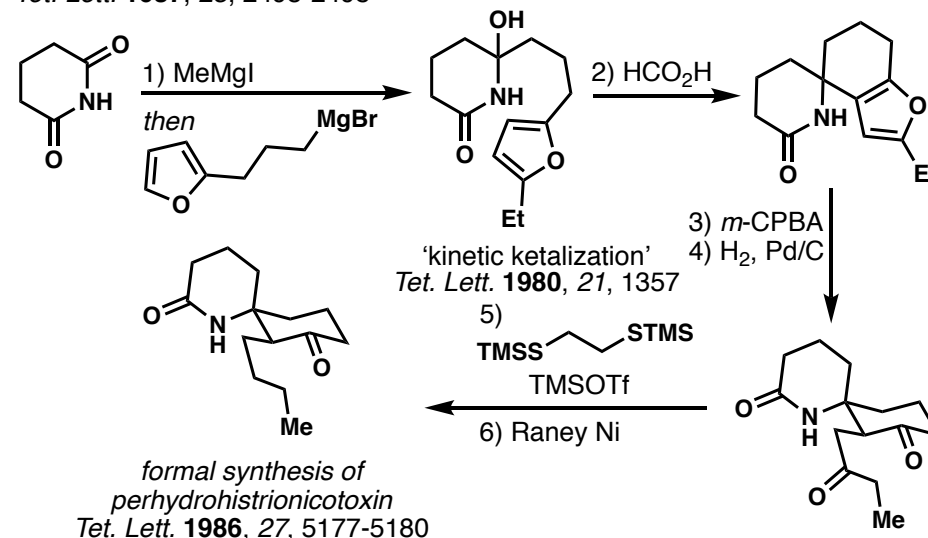
Intramolecular Mannich-type Cyclization – Methoxystemofoline

JOC 2021, 86, 11053–1107; see also: Nat Comm 2020, 11, 5314



Quaternization by Cyclization with Furan – Perhydrohistrionicotoxin

Tet. Lett. 1987, 28, 2495-2498

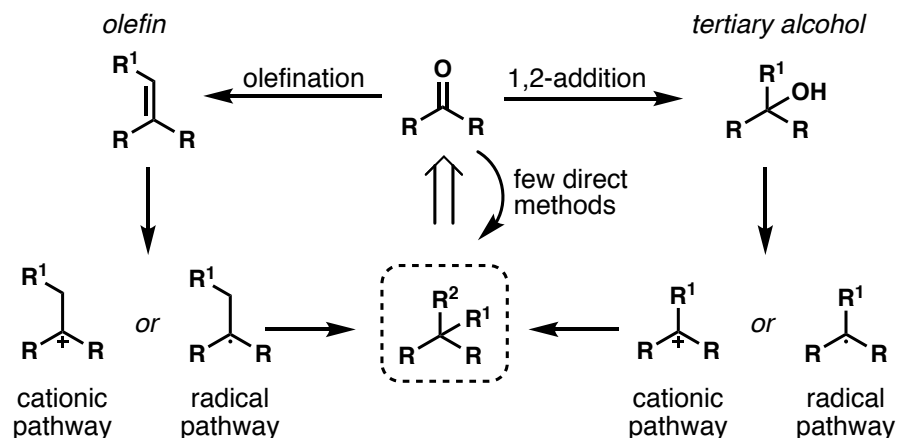


See also:

- 1) Quaternization by Cyclization with e^- -Rich Arene – Erysotramidine JOC 2015, 80, 1957-1963
- 2) Vinylogous Pictet Spengler – Lunderine A ACIE 2018, 57, 6888-6891

2) Quaternization of Ketones

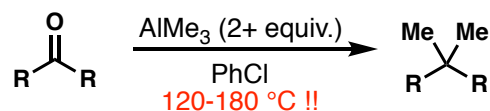
Most Common and Intuitive Disconnections



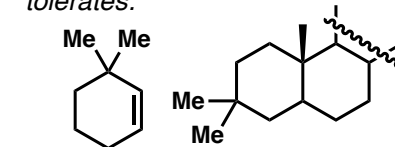
i) Direct Quaternization of Ketones

Simplicity is King: AlMe_3 *gem*-Dimethylation

Aust. J. Chem. 1974, 27, 1655-1663

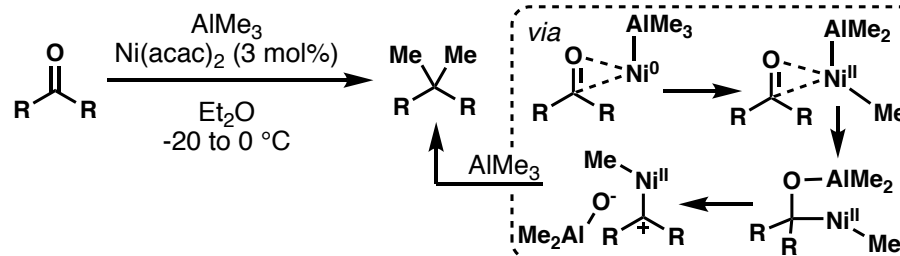


tolerates:



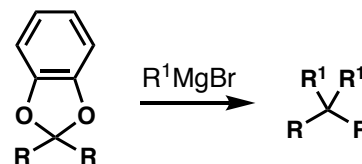
Ni-catalyzed Variant

Aust. J. Chem. 1974, 27, 2569-2576



Pyrocatechol Ketal Double-Grignard Addition

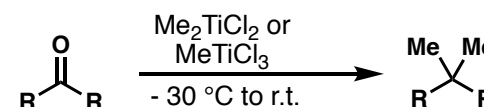
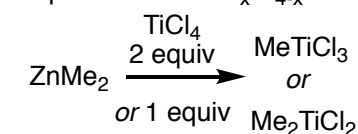
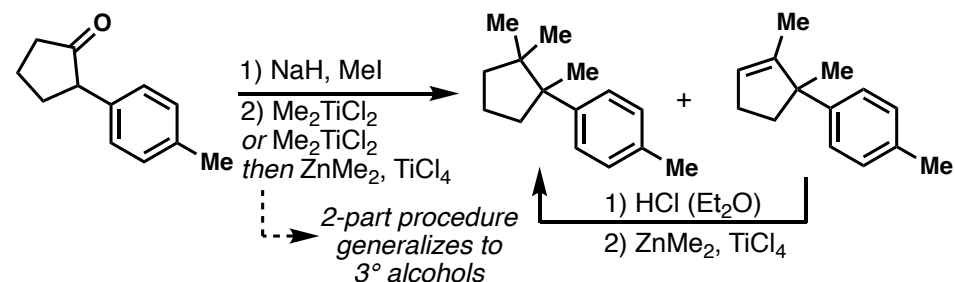
Ann. Chim. (Rome), 1970, 60, 483



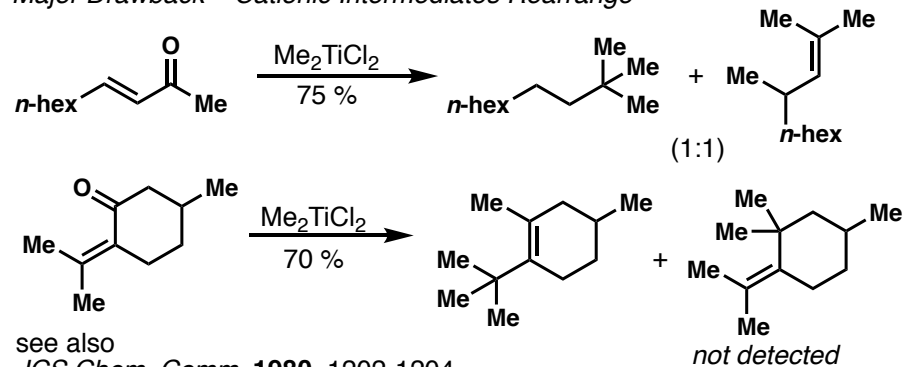
- Seemingly a forgotten procedure
- Almost no citations or use-cases

Methyl Titanium *gem*-Dimethylation

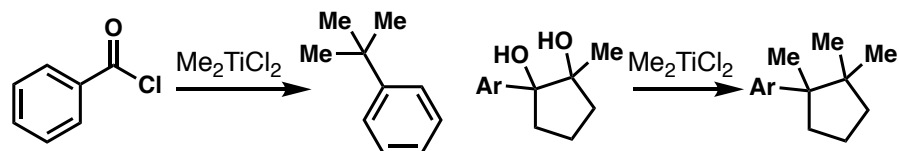
Chem. Ber. 1985, 118, 1050-1057

Preparation of $\text{TiMe}_x\text{Cl}_{4-x}$ Applied to Synthesis of Cuparene
JCS Chem. Comm. 1981, 237-239

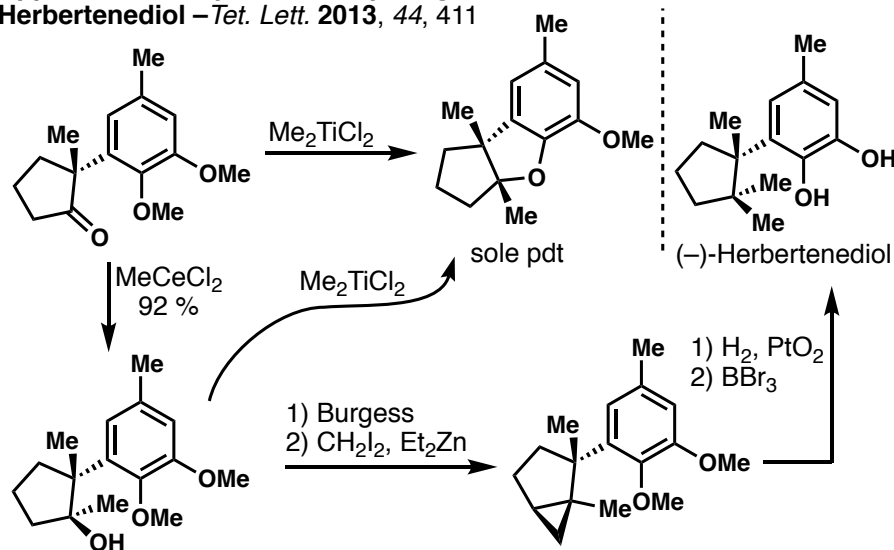
Major Drawback – Cationic Intermediates Rearrange



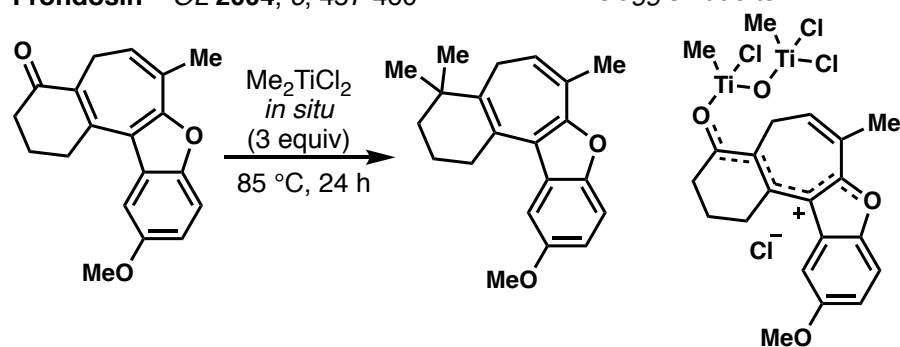
Also Applicable to Acyl Chlorides and 1,2-diols
Chem. Ber. **1985**, *118*, 1050-1057; *Synth. Comm.* **2001**, *31*, 1847-1855.



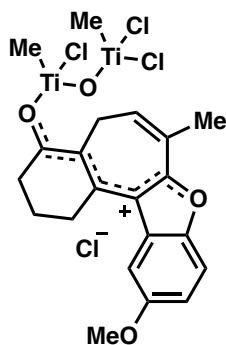
Applications in Synthesis – Sparring
 Herbertenediol – *Tet. Lett.* **2013**, *44*, 411



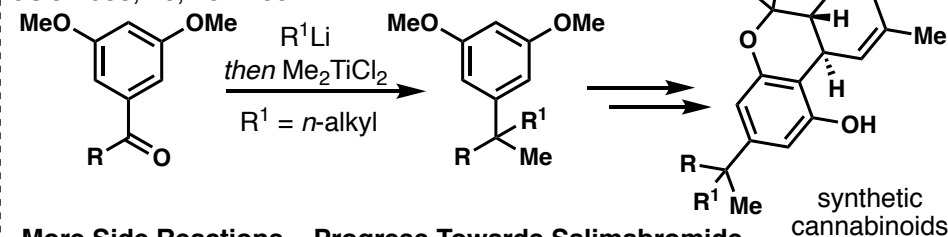
Fronodosin – *OL* **2004**, *6*, 457-460



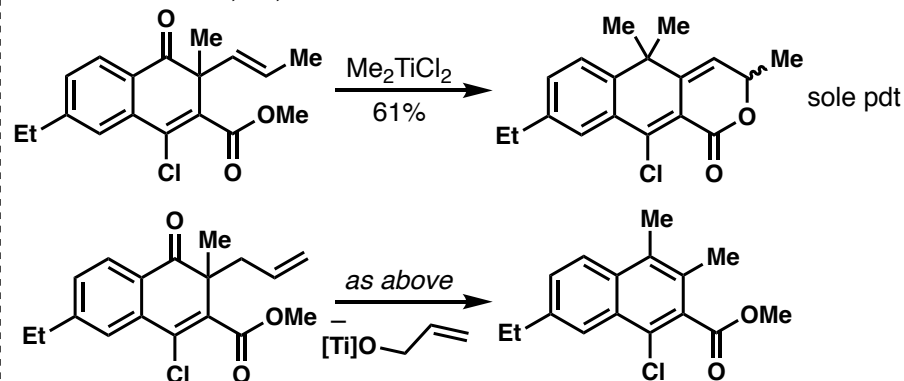
sluggish due to:



Iterative Organometallic Addition
JOC **1983**, *48*, 254-255



More Side Reactions – Progress Towards Salimabromide
Tetrahedron **2019**, *75*, 3195



Key Takeaway

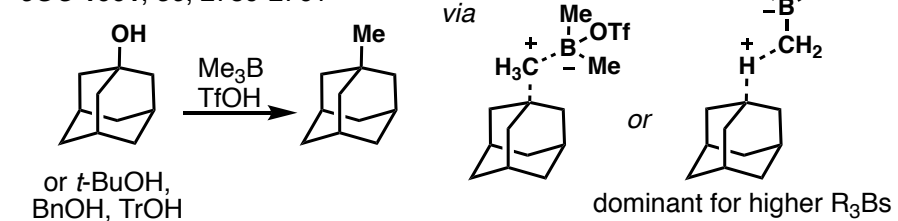
While attractive, direct quaternization of ketones is often too harsh to tolerate complex substrates

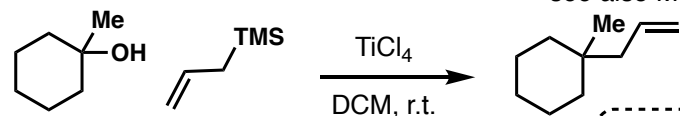
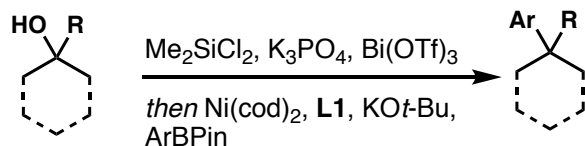
ii) Quaternization via 3° Alcohols

– Generally speaking, one can accomplish this with LA + soft Nu

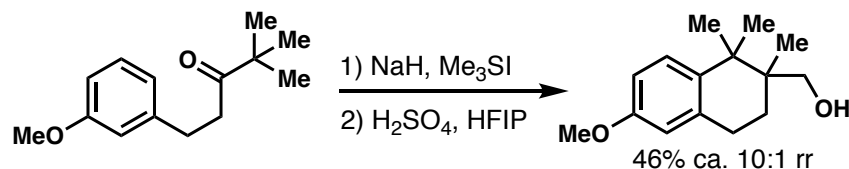
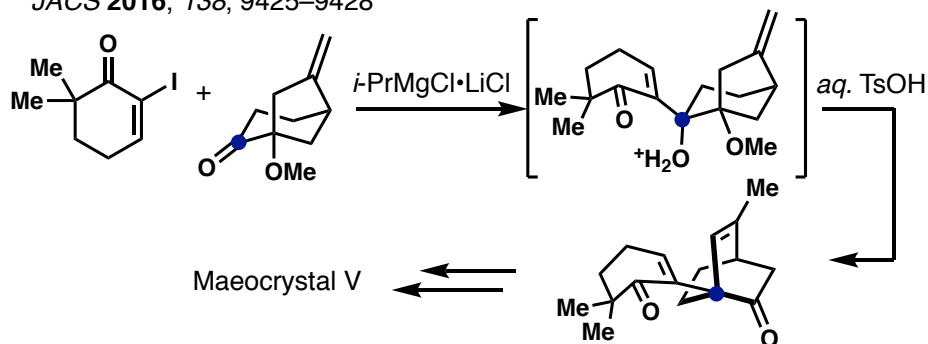
Borane-Mediated Reductive Alkylation

JOC **1991**, *56*, 2759-2761

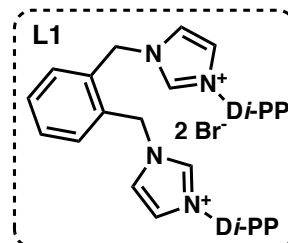


Titanium-mediated allylation
Synlett **2013**, *24*, 1275-1279**Modern Variant – Deoxygenative Suzuki**
Nat. Synth. **2023**, *2*, 663-669

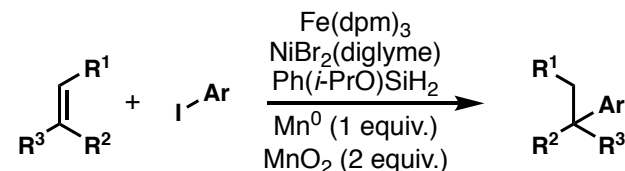
Beware Cationic Intermediates:
Rearrangements are very common, but can be strategically applied

W-M Rearrangements in the Synthesis of Salimabromide
JACS **2018**, *140*, 8444–8447**Maeocrystal V – Pinacol Rearrangement**
JACS **2016**, *138*, 9425–9428

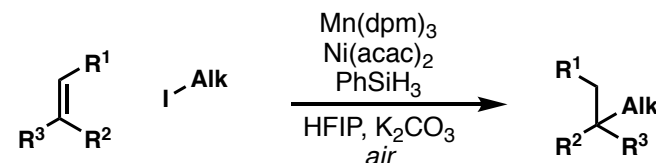
Enantioselective variant:
JACS **1992**, *114*, 2321
see also Merchant 2017 GM

**iii) Quaternization via (Radical) Olefin Functionalization**
– *Burgeoning method for accessing quaternary centers*

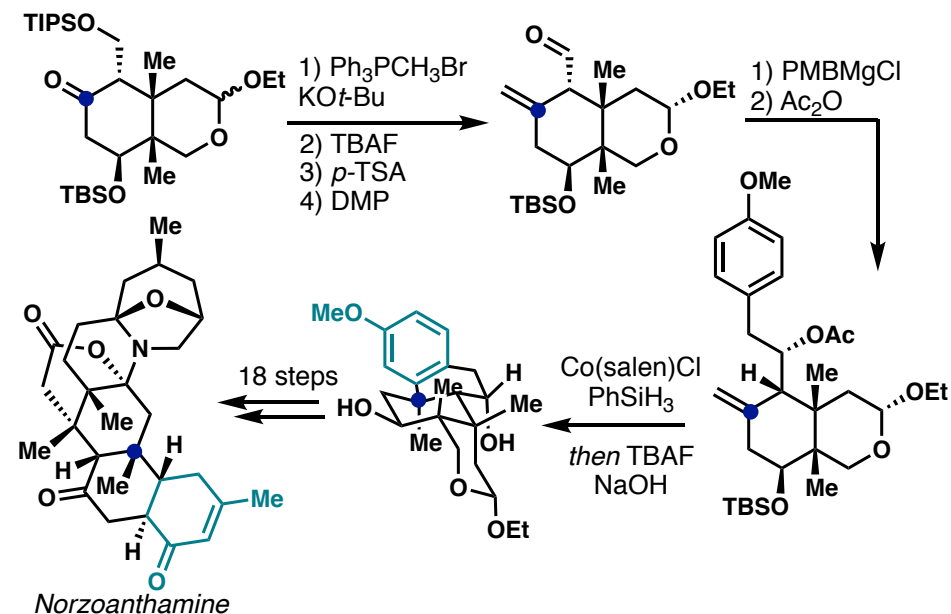
Shenvi's Hydroarylation *JACS* **2018**, *140*, 11317-11324

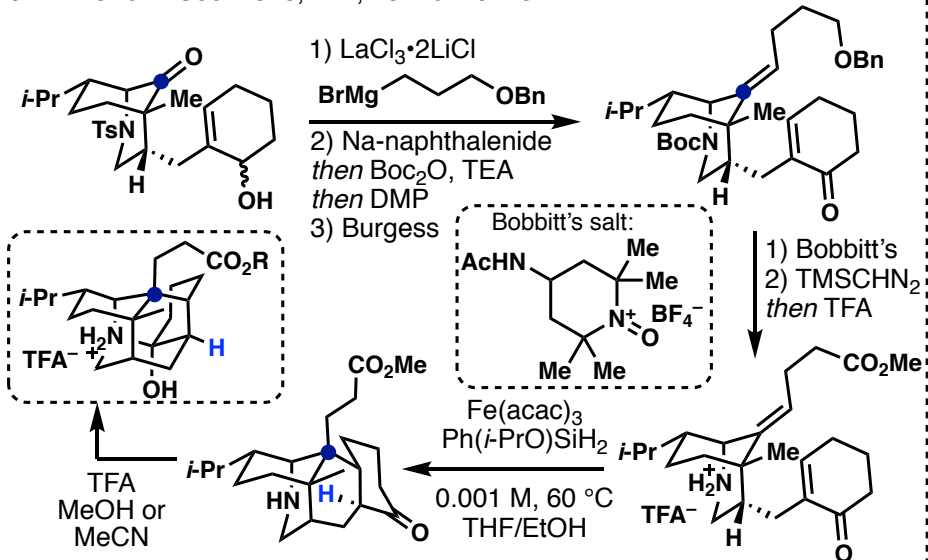
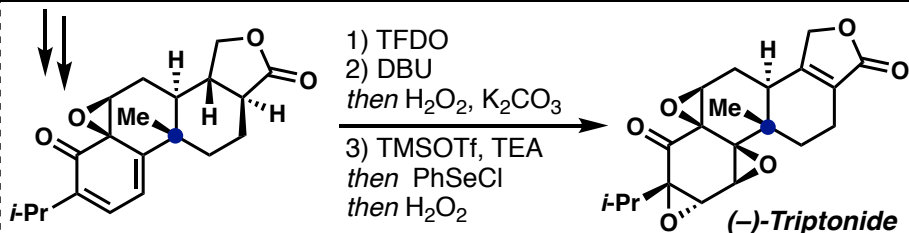
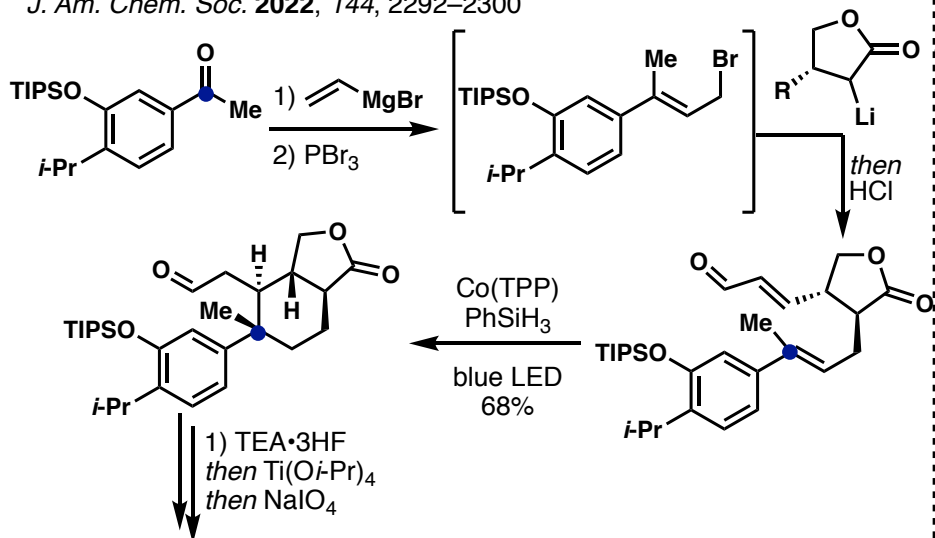
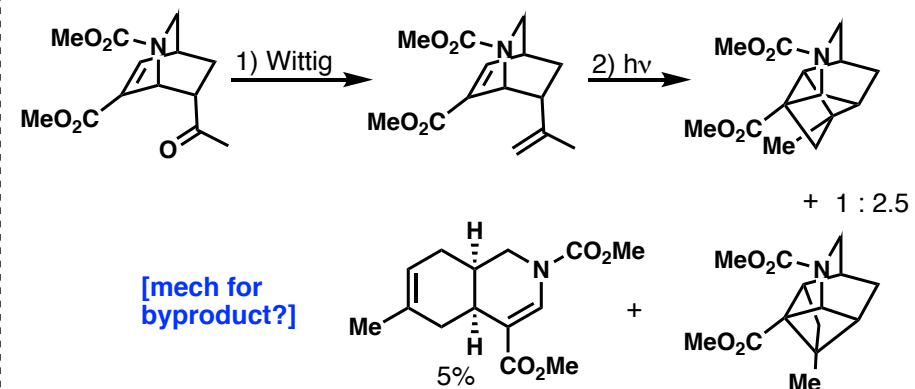


Hydroalkylation variant *JACS* **2019**, *141*, 7709-7714

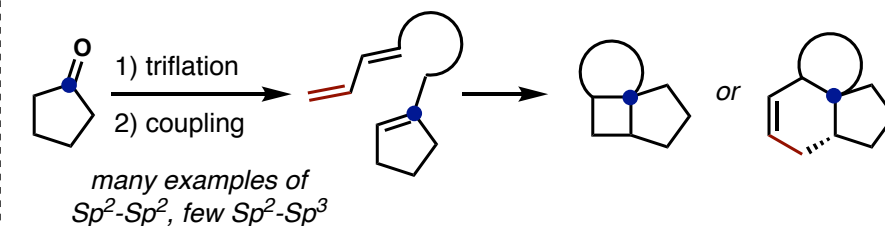


see also: our lab's work on olefin functionalization, hydromethylation, etc

HAT-based Ketone Quaternization in Gao's Norzoanthamine
ACIE **2021**, *60*, 12807-12812

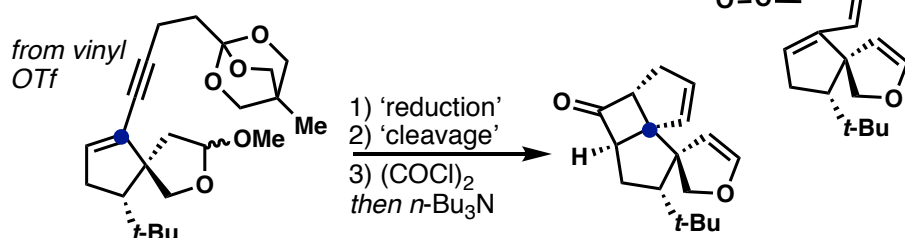
HAT Quaternization in Total Synthesis of (-)-Daphnezomines A & B –
J. Am. Chem. Soc. 2020, 142, 15240–15245

HAT Cyclization in Total Synthesis of Triptonide
J. Am. Chem. Soc. 2022, 144, 2292–2300

Cycloaddition-based Quaternization – Synthesis of Isoquinuclidines
J. Org. Chem. 2004, 69, 3758–3764

iv) Quaternization via Triflation (or other vinyl (pseudo)halides)

– Vinyl triflate handle allows for variety of subsequent quaternization steps (cycloaddition, couplings, HAT, enone difunctionalization, etc.)

a) Olefin of coupled triflate used for cycloaddition


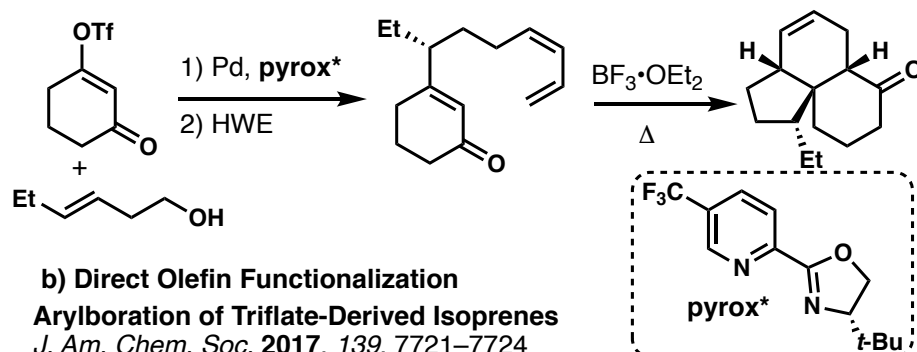
Corey's Ginkgolide B Approach

Tet. Lett. 1988, 29, 3201-3204



Enantioselective Heck Alkenylation-[4+2] for Elisabethin A Core

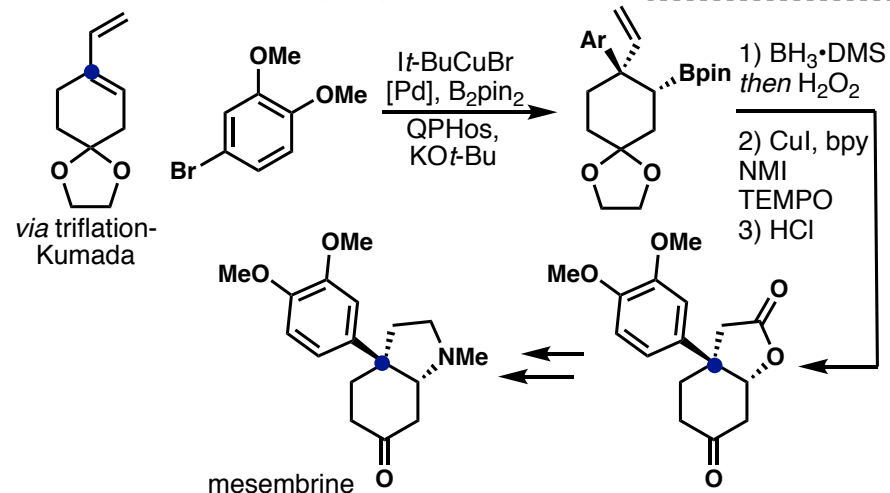
JACS 2015, 137, 3462-3465



b) Direct Olefin Functionalization

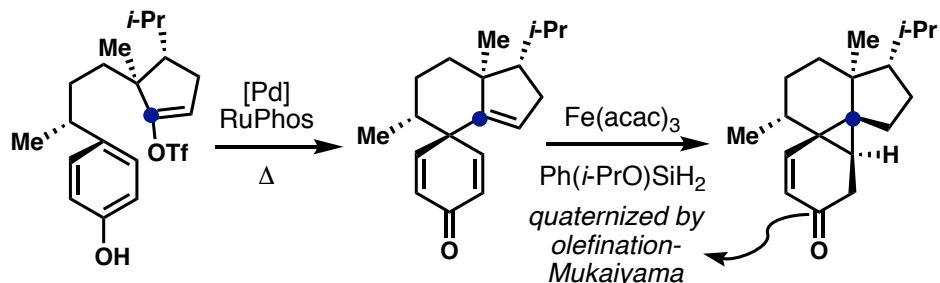
Arylboration of Triflate-Derived Isoprenes

J. Am. Chem. Soc. 2017, 139, 7721-7724



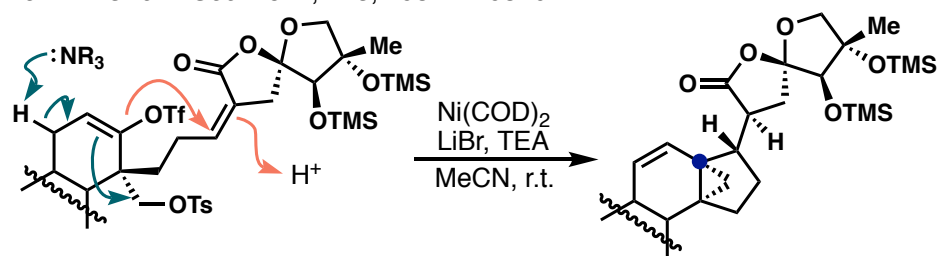
HAT-Cyclopropanation of Triflate-derived Olefin – Peyssonoside A

J. Am. Chem. Soc. 2022, 144, 19700-19703

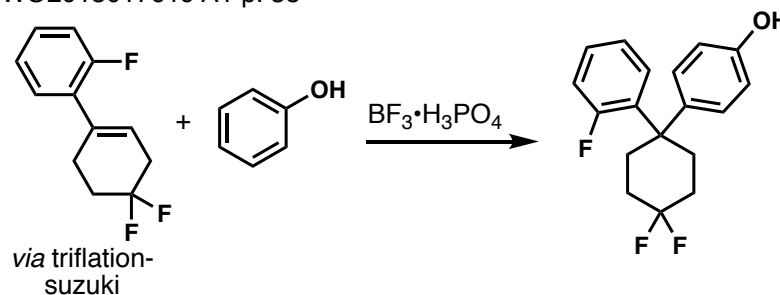
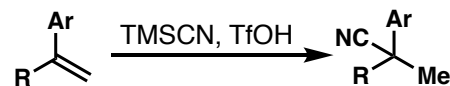


Triflate Quaternization via Cyclopropanation – Phainanoid A

J. Am. Chem. Soc. 2021, 143, 19311-19316

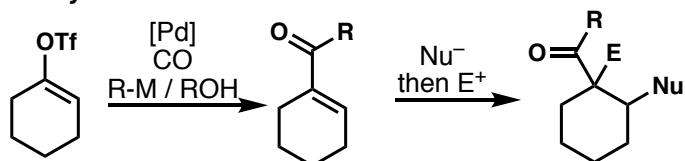


Cationic Olefin Functionalization – ERβ Modulators

Acadia Pharmaceuticals
WO2013017619 A1 p. 38also well-known with CN nucleophiles: *Org. Lett.* 2009, 11, 5286-5289

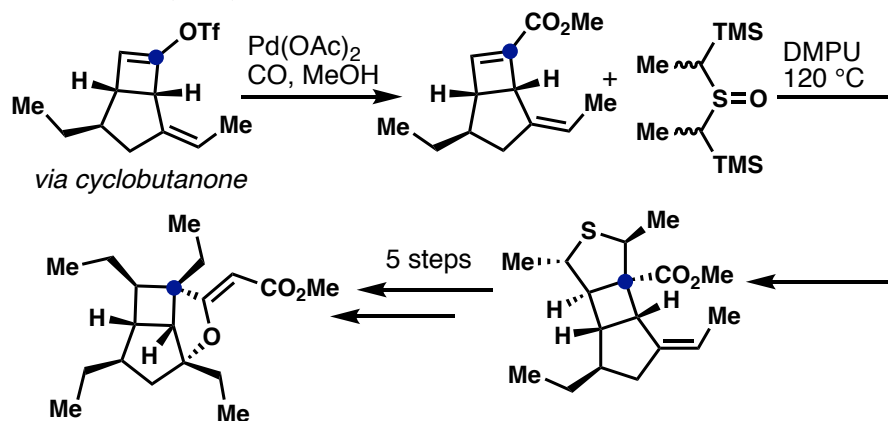
c) Functionalization of Resultant Enone

Generally:



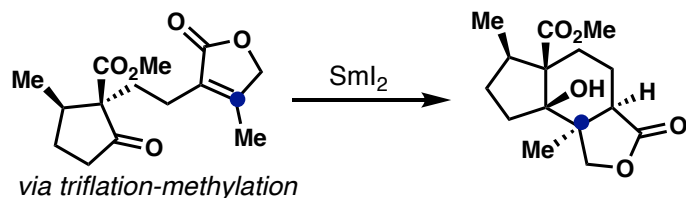
Thiocarbonyl Ylide Enone Functionalization – Hippolachnin A

JACS 2017, 139, 11706-11709



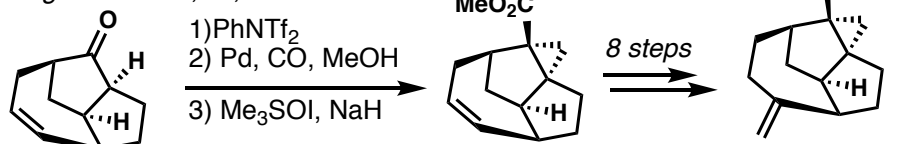
Samarium-based Quaternization – Jiadifenolide

J. Org. Chem. 2016, 81, 11017-11034

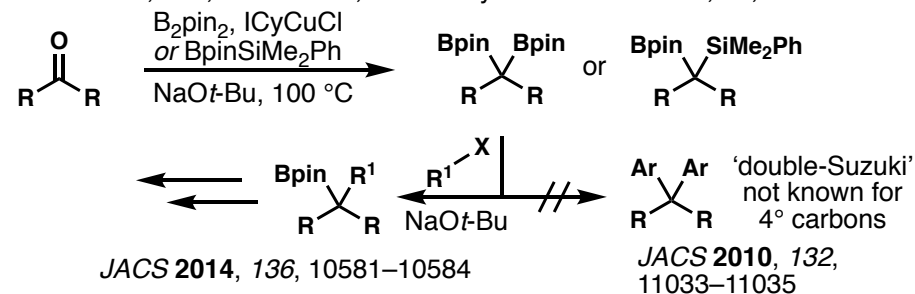


Enone Cyclopropanation – Echinopine A & B

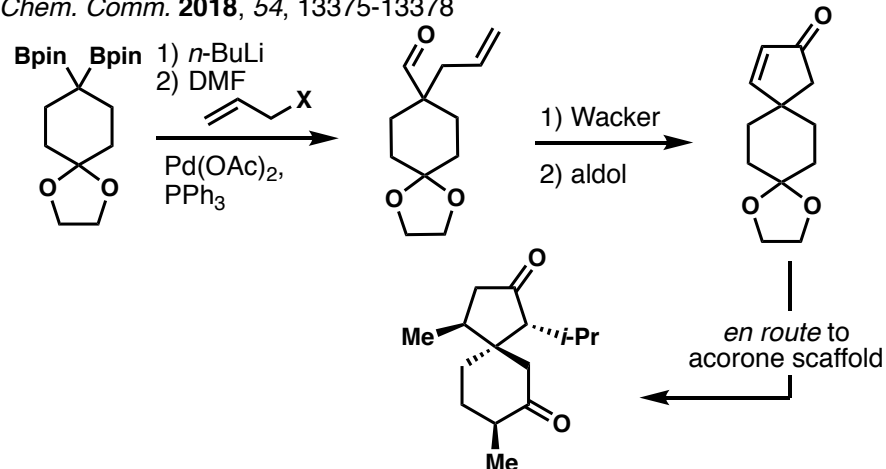
Org. Lett. 2009, 11, 5306-5309

v) Odds and Ends – *gem*-Diboronation*gem*-Diborylation and *gem*-Silylboration of Ketones

JACS 2017, 139, 5257-5264; from Ts-hydrazone: OL 2014, 16, 448-451

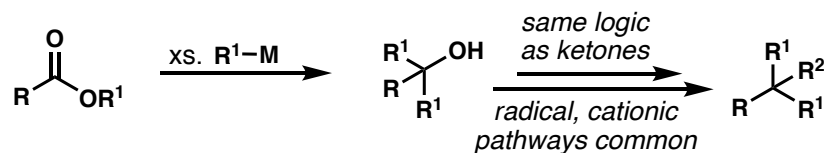
Allyl-Formylation *gem*-diboron Functionalization

Chem. Comm. 2018, 54, 13375-13378



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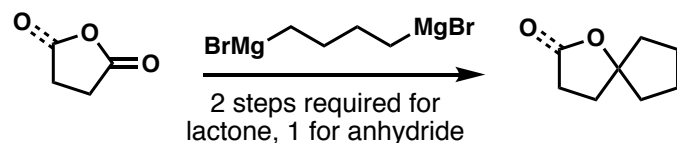
3) Quaternization of Esters



Double-Addition to Esters

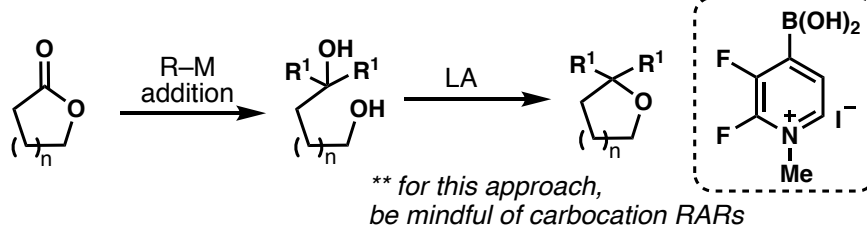
JOC 1987, 52, 569-580

+ 100s of patent examples

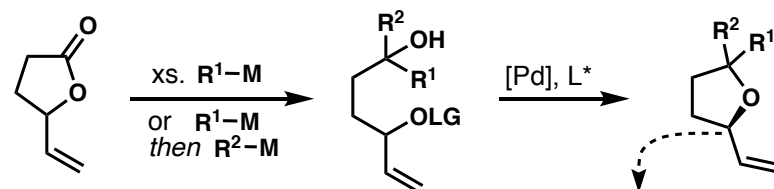


(Lewis) Acid Cyclization of 3° Alcohol

ACIE 2012, 51, 6187-6190 (a mild, modern example)

Tsuji-Trost/ π -Allyl Cyclization

Generically:



Org. Lett. 2009, 11, 3124–3127

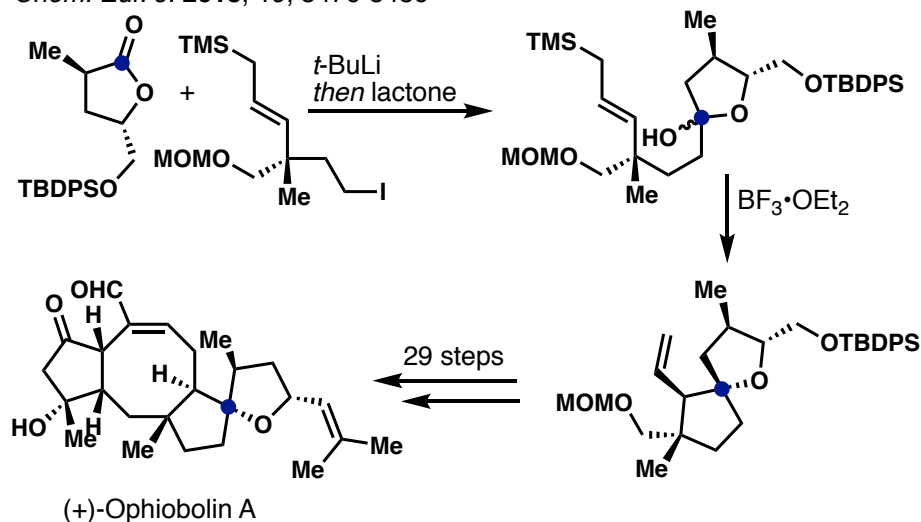
see also cyclopamine:

JACS 2023, 145, 21760-21765

stereocontrol
usually at this site

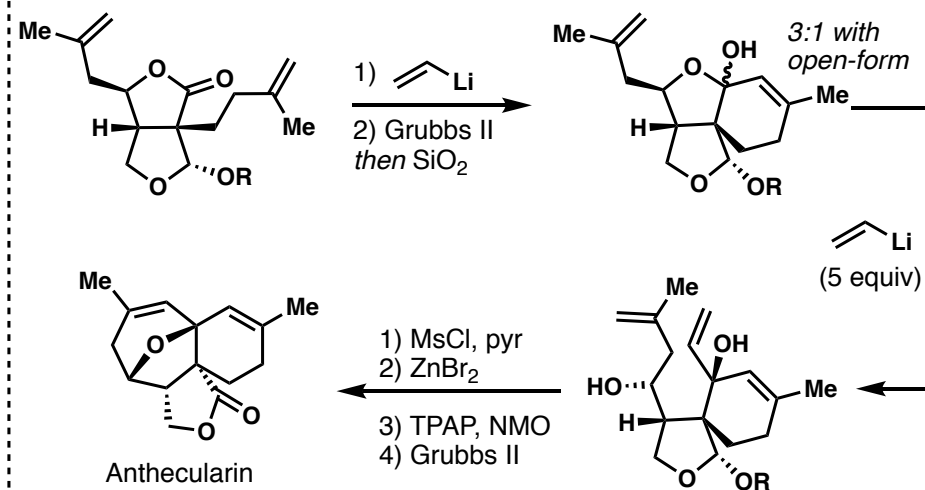
Total Synthesis of Ophiobolin A

Chem. Eur. J. 2013, 19, 5476-5486



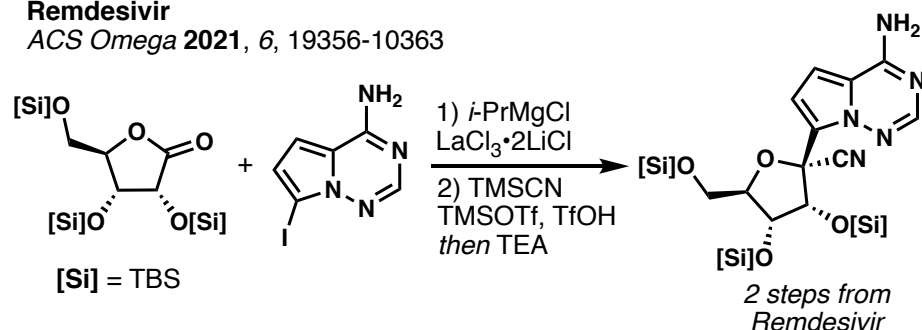
Total Synthesis of Anthecularin

Org. Lett. 2018, 20, 3888-3891



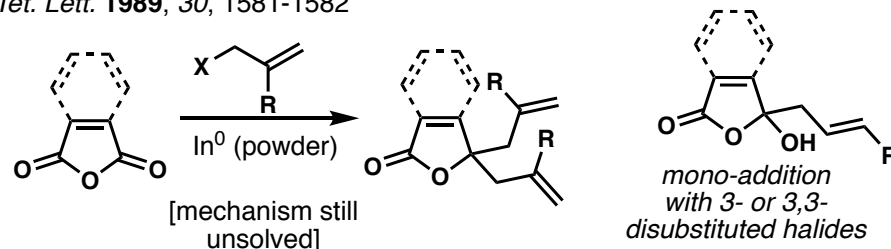
Remdesivir

ACS Omega 2021, 6, 19356-10363



Exotic Examples – Indium-Mediated Double Addition

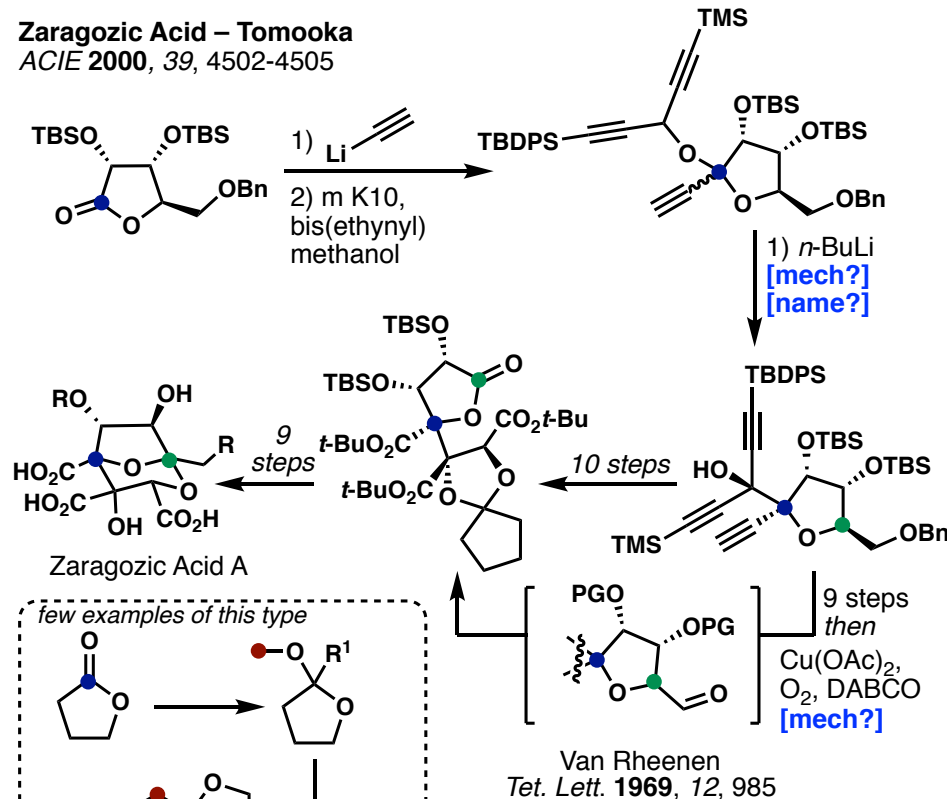
Tet. Lett. 1989, 30, 1581-1582



– Also known with tri-allyl aluminum: Tet. Lett. 2007, 48 6348-6351

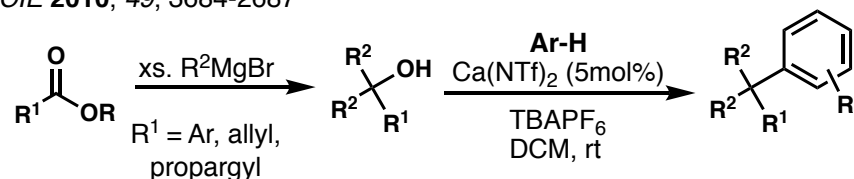
Zaragozic Acid – Tomooka

ACIE 2000, 39, 4502-4505



Exotic Examples – Calcium-catalyzed Arylation of 3° Alcohols

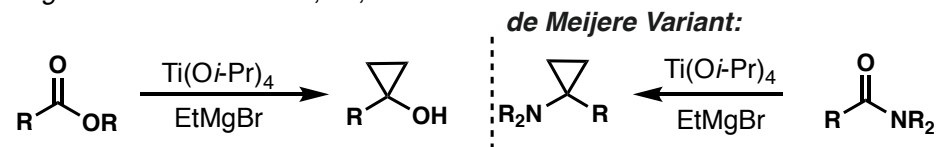
ACIE 2010, 49, 3684-2687



The Venerable Kulinkovich Cyclopropanation

Excellent Review: Chem. Rev. 2003, 103, 2597-2632

Org. Biomol. Chem. 2012, 10, 7649-7665



From Olefinic Coupling Partners

JACS 1996, 118, 4198-4199

alcohol-directed: Eur JOC 2014, 1, 181-187; Tet. Lett. 2015, 56, 3298-3300

