

## Module 4 Reactions with Miscellaneous Reagents

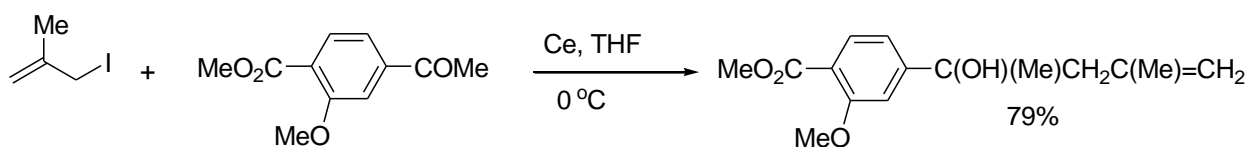
### Lecture 34

#### 4.1 Cerium Compounds

Cerium compounds are widely used in organic synthesis. This section covers some of the important processes.

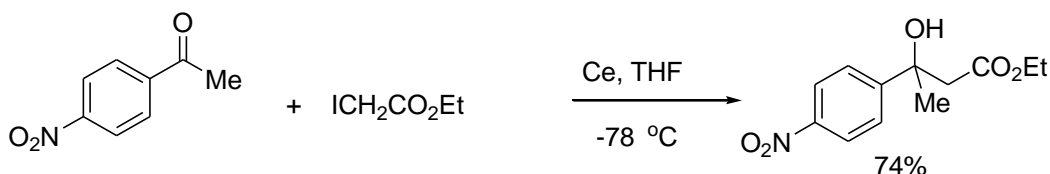
##### 4.1.1 Cerium (Ce)

Cerium powder is air sensitive and is stored in mineral oil or under argon. It is a reagent for the Barbier reaction of alkyl halides with carbonyl compounds. The addition can be performed chemoselectively in the presence of functional groups such as nitriles, nitro compounds and esters (Scheme 1).



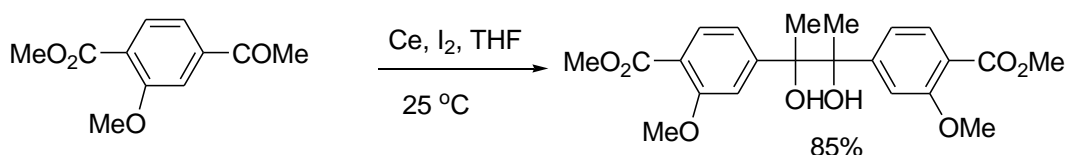
Scheme 1

The reaction conditions are also effective for the Reformatsky reaction of α-haloesters with ketones (Scheme 2).



Scheme 2

The reductive coupling of carbonyl compounds can also be accomplished using the combination of cerium and I<sub>2</sub> at ambient temperature (Scheme 3).



Scheme 3

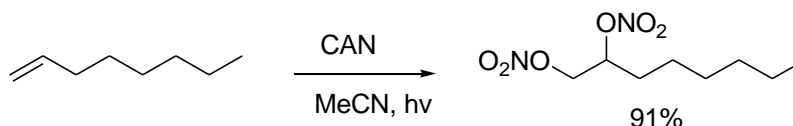
#### 4.1.2 Cerium(IV) Ammonium Nitrate ((NH<sub>4</sub>)<sub>2</sub>Ce(NO<sub>3</sub>)<sub>6</sub>)

Cerium(IV) ammonium nitrate (CAN) is an orange colour strong oxidizing agent and soluble in water and to smaller extent in polar solvent. Thus, the reaction is often performed in a mixed solvent such as aqueous CH<sub>3</sub>CN. During the reaction, the consumption of the CAN can be judged by the fading of an orange colour to pale yellow, if the substrate or products are not strongly coloured. Some of the important processes of the CAN oxidations follow.

T.-L. Ho, *Encyclopedia of Reagents for Organic Synthesis*, John Wiley and Sons, Inc., L. A. Paquette, Ed., New York, 1995, **2**, 1029.

#### Oxidation of Alkenes

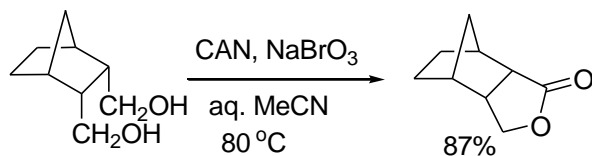
The oxidation of alkenes is solvent dependant. Terminal alkenes can be dinitroxyated in high yield (Scheme 4).



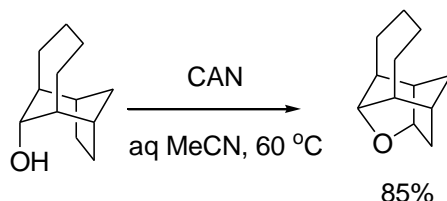
Scheme 4

#### Oxidation of Alcohols and Phenols

A secondary alcohol can be selectively oxidized to ketones in the presence of a primary alcohol. Under these conditions, 1,4-primary diols can be converted into lactones (Scheme 5). The formation of tetrahydrofuran predominates in molecules, which are favourable to  $\delta$ -hydrogen abstraction by an alkoxyl radical (Scheme 6). In the case of phenols, quinones are formed.



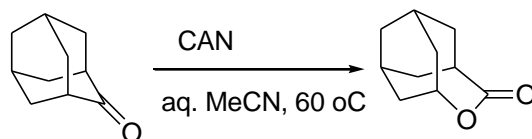
Scheme 5



Scheme 6

### Oxidation of Cage Ketones

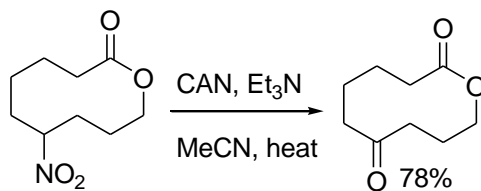
The CAN oxidation of aldehydes and ketones is of much of less synthetic importance compared to that with other methods. However, cage ketones can be oxidized using CAN to give lactones in good yield (Scheme 7).



Scheme 7

### Oxidation of Nitroalkanes

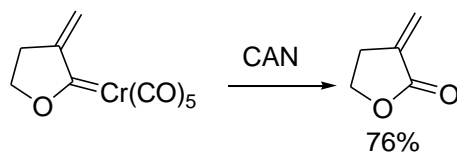
The CAN oxidation affords an alternative method to the Nef reaction. For an example, nitromacrolide can be selectively oxidized in good yield (Scheme 8).



Scheme 8

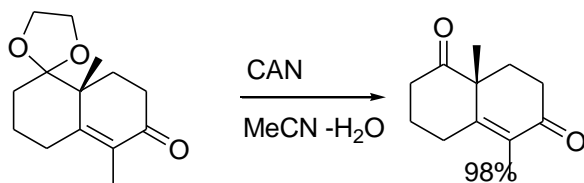
### Oxidative Cleavage of Organometallic Compounds

CAN is useful reagent for the oxidative cleavage of  $\sigma$ - and  $\pi$ -complexes. For an example, chromium-carbene complex can be oxidatively cleaved to afford  $\pi$ -methylene- $\gamma$ -butyrolactone in good yield (Scheme 9).

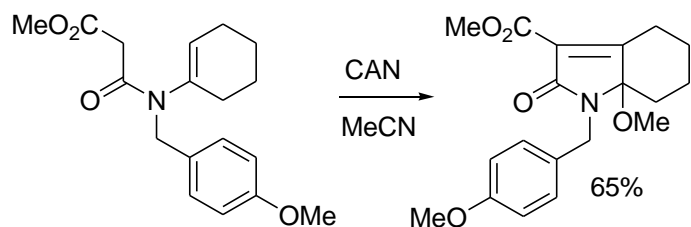


Scheme 9

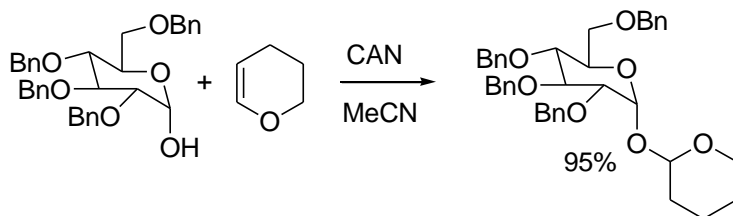
**Examples:**



A. Ates, A. Gauthier, B. Leroy, J.-M. Planncher, Y. Quesnel, I. E. Marko, *Tetrahedron Lett.* **1999**, 40, 1799.



S. J. Clark, C. P. Dell, J. M. McDonagh, J. Geden, P. Mawdsley, *Org. Lett.* **2003**, 5, 2063.



K. Pitchamuthu, Y. D. Vankar, *J. Org. Chem.* **2001**, 66, 7511.

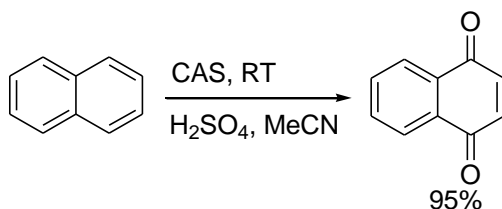
### 4.1.3 Cerium(IV) Ammonium Sulfate ( $\text{Ce}(\text{NH}_4)_4(\text{SO}_4)_4 \cdot 2\text{H}_2\text{O}$ )

CAN is the most extensively utilized cerium(IV) oxidizing agent, but cerium(IV) ammonium sulfate (CAS) is a versatile substitute when complications occur due to the involvement of nitrate ligands, resulting in side products such as nitrate esters.

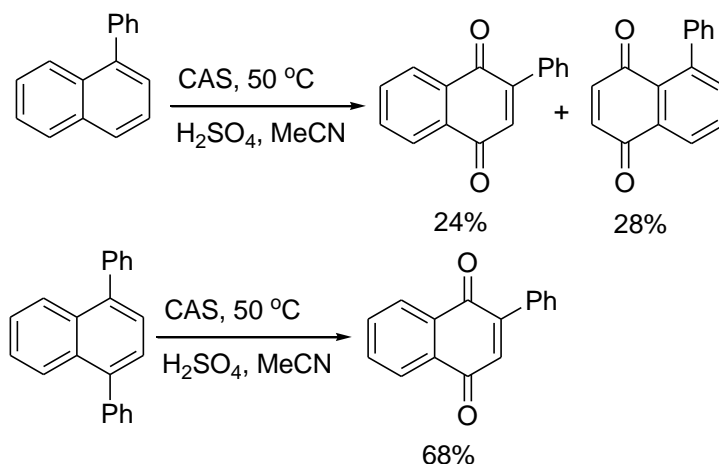
M. Periasamy, U. Radhakrishnan, *Encyclopedia of Reagents for Organic Synthesis*, John Wiley and Sons, Inc., L. A. Paquette, Ed., New York, 1995, **2**, 1029.

#### Oxidation of Aromatic Rings

The most important use of CAS is the oxidation of aromatic rings to quinones. CAN oxidizes polyaromatic rings only in moderate yields. Furthermore, these reactions often give nitrate esters as by-products. In contrast, CAS usually oxidizes aromatic rings to quinones in good yields. For example, naphthalene is oxidized to 1,4-naphthaquinone by CAS in a mixture of  $\text{H}_2\text{SO}_4$  and MeCN (Scheme 10). A similar result is observed with polycyclic aromatic compounds such as



Scheme 10

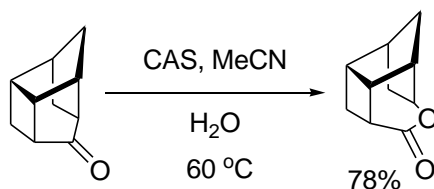


Scheme 11

phenanthrene and anthracene. Whereas the oxidation of 1-phenyl and 1,4-diphenylnaphthalene react to form some substituted naphthaquinones through rearrangement depending on the reaction conditions (Scheme 11).

### Baeyer-Villiger Oxidation

The CAS oxidation of bishomocubaneone gives the corresponding lactone (Scheme 12). This is obtained only as a minor product in the peroxy acid promoted Baeyer-Villiger oxidation conditions.



Scheme 12

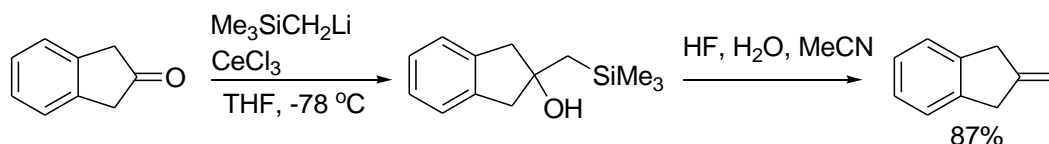
### 4.1.3 Cerium(III) Chloride ( $\text{CeCl}_3 \cdot 7\text{H}_2\text{O}$ )

Cerium(III) chloride is a mild Lewis acid. For some applications, it must be anhydrous. Some of the important transformations follow.

#### 1,2-Addition Reactions

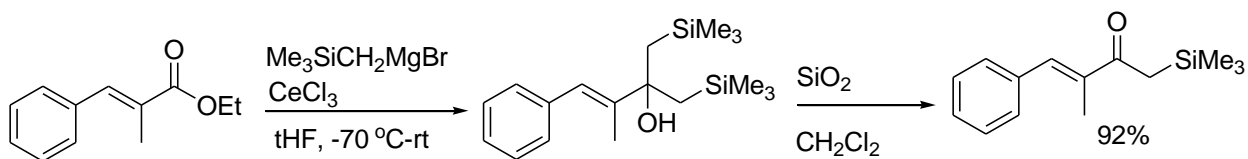
Organocerium reagents are conveniently prepared from the reactions of lithium compounds with anhydrous  $\text{CeCl}_3$  in THF. They are highly oxophilic and significantly less basic than RLi and RMgBr. Thus, 1,2-addition with enolizable ketones can be performed. Although alkyl and vinyl cerates are often employed,  $\text{Cl}_2\text{CeCH}_2\text{CN}$ ,  $\text{Cl}_2\text{CeCH}_2\text{CO}_2\text{R}$  and  $\text{Cl}_2\text{CeCH}_2\text{SiMe}_3$  are known to be equally effective. Some of the examples follow:

The methylation of enolizable ketones can be accomplished in high yield (Scheme 13).



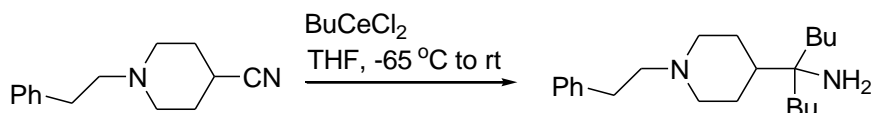
Scheme 13

□□-Unsaturated esters can be converted into allylsilanes in high yield (Scheme 14).



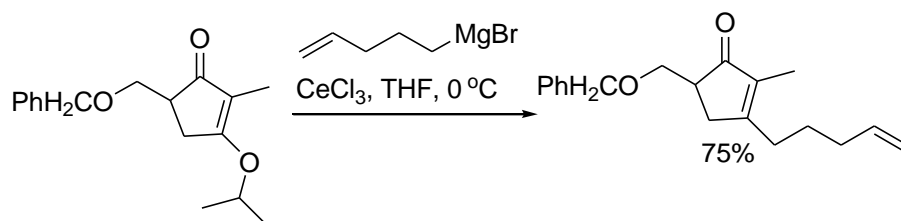
Scheme 14

High levels of steric hinderance can be tolerated (Scheme 15).



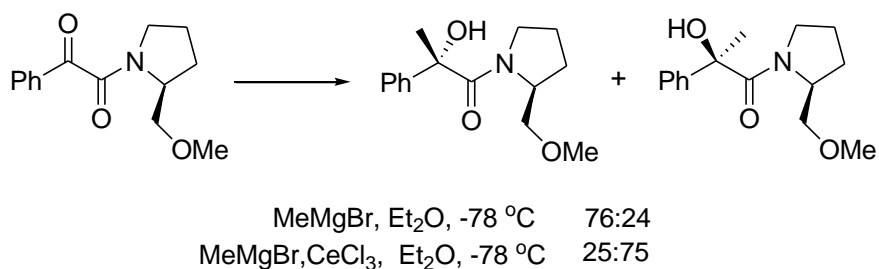
Scheme 15

CeCl<sub>3</sub> can be used as promoter to improve the addition of alkyl Grignard to give vinylogous ester (Scheme 16).



Scheme 16

In the addition of Grignard reagent to chiral  $\alpha$ -keto amides, the stereoselectivity can be reversed using CeCl<sub>3</sub> (Scheme 17).



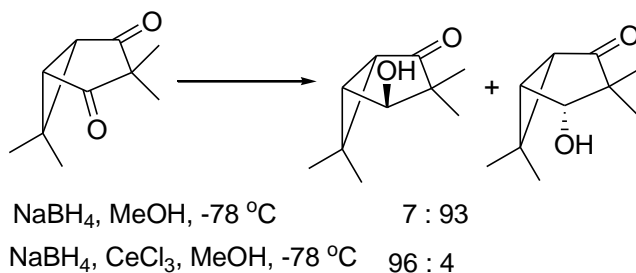
Scheme 17

### Selective Reductions

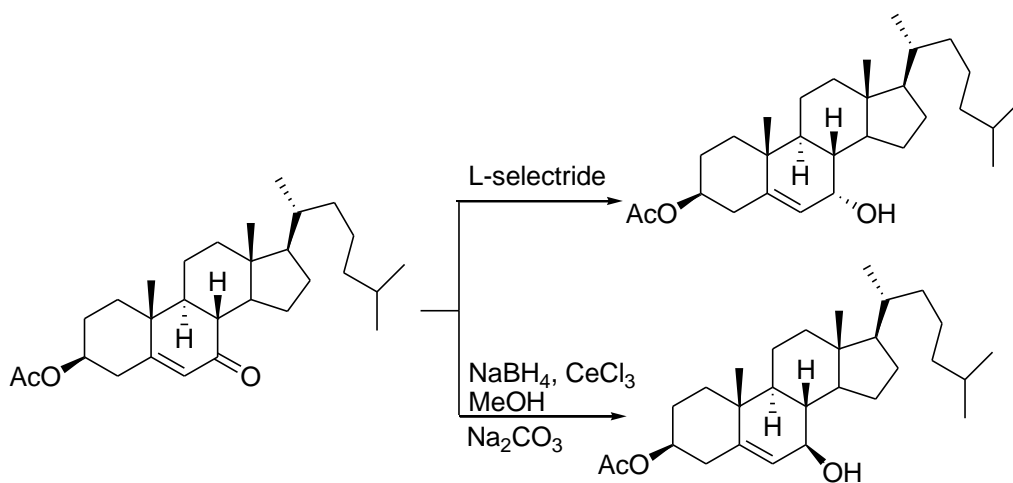
The Lewis acidity of CeCl<sub>3</sub> plays important role with metal hydrides in the reduction of carbonyl compounds. The combination of NaBH<sub>4</sub> and CeCl<sub>3</sub>·7H<sub>2</sub>O is used for the selective reduction of carbonyl compounds. The reaction is called

Luche Reduction. For examples, the stereochemistry can be reversed in the reduction of bicyclic ketone using  $\text{NaBH}_4\text{-CeCl}_3$  (Scheme 18-19).

L. A. Paquette, Encyclopedia of Reagents for Organic Synthesis, John Wiley and Sons, Inc., L. A. Paquette, Ed., New York, 1995, **2**, 1031.

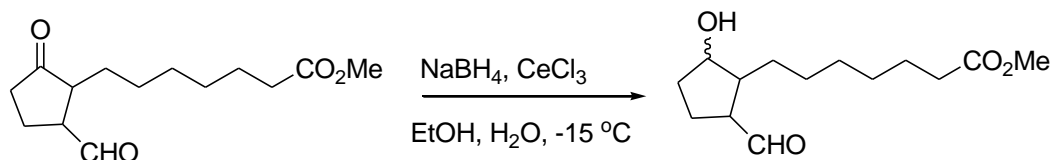


Scheme 18



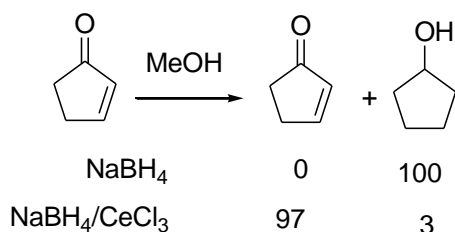
Scheme 19

The above described reagent can also be used for the chemoselective reduction of ketones in the presence of aldehyde functional group (Scheme 20).

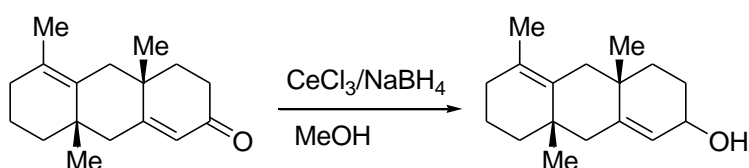


Scheme 20



**Examples:**

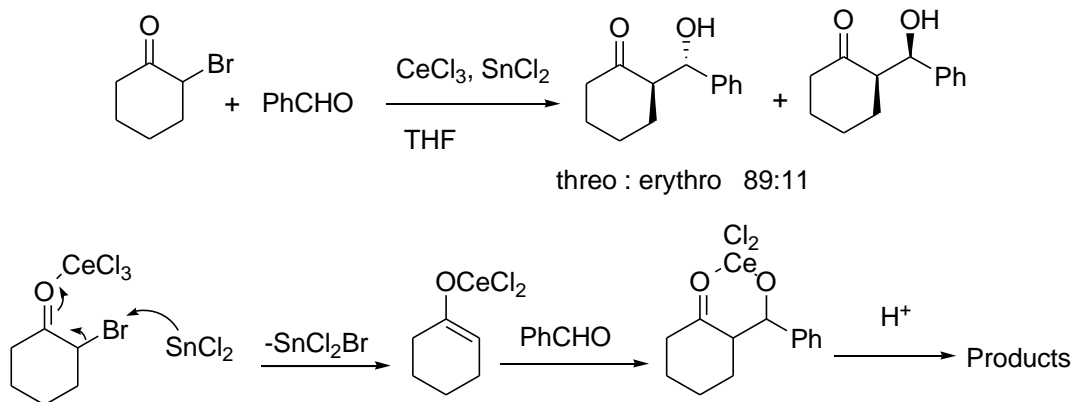
J. I. Luche, *J. Am. Chem. Soc.* **1978**, 100, 2226.



L. A. Paquette, D. T. Belmont, Y.-L. Hsu, *J. Org. Chem.* **1985**, 50, 4667.

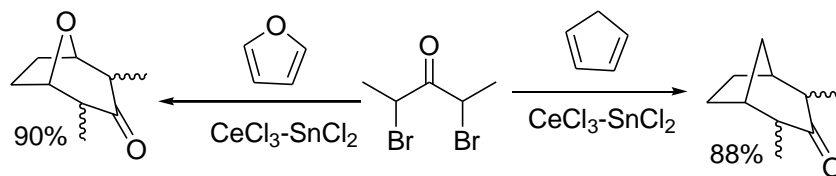
**Aldol and (3+4)-Cycloaddition Reactions**

The combination of  $\text{CeCl}_3\text{-SnCl}_2$  is widely used for the aldol reactions of  $\alpha$ -bromoketones with aldehydes to afford  $\beta$ -hydroxy ketones in good to excellent yields (Scheme 21). The success of the reaction is attributed to activation of the carbonyl group by Lewis acidic  $\text{CeCl}_3$  that promotes the reduction of bromine by  $\text{SnCl}_2$ .



Scheme 21

The above described combined reagent also promotes the (3+4)-cycloaddition of  $\alpha,\alpha$ -dibromo ketones with 1,3-dienes under mild conditions (Scheme 22).



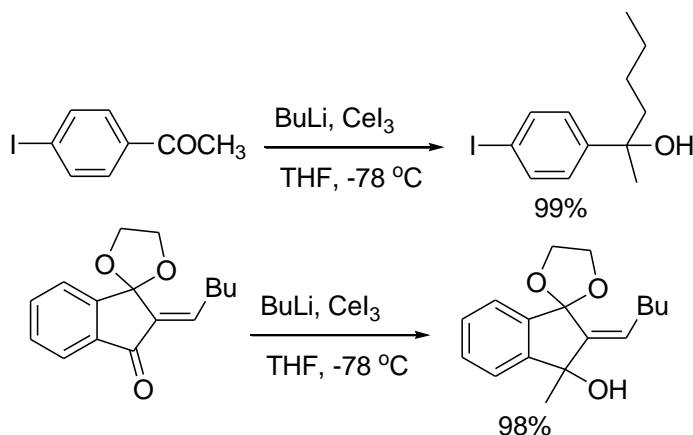
Scheme 22

#### 4.1.4 Cerium(III) Iodide ( $\text{CeI}_3$ )

$\text{CeI}_3$  is extremely hygroscopic and turns brown when exposed to air due to liberation of iodine. The reagent is to be stored under nitrogen and handled in a glove bag.

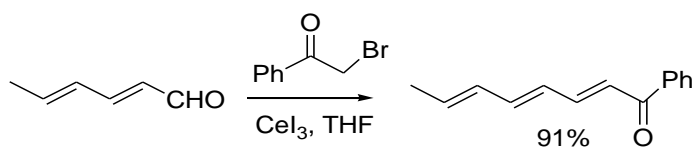
#### 1,2-Addition and Aldol Reactions

As  $\text{CeCl}_3$ ,  $\text{CeI}_3$  reacts with organolithium compounds in THF to give organocerium compounds that can be used for the 1,2-addition of ketones (Scheme 23).



Scheme 23

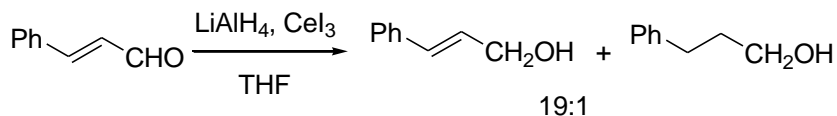
Cross-aldol reaction of  $\alpha$ -halo ketones with aldehydes can be accomplished using  $\text{CeI}_3$  at room temperature (Scheme 24). Ketones do not react under these conditions.



Scheme 24

**Selective Reduction**

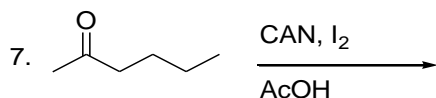
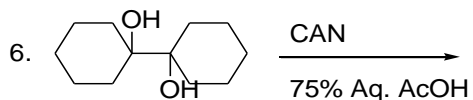
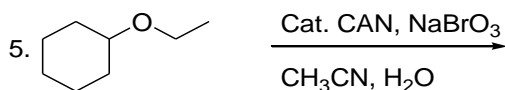
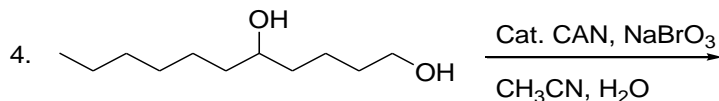
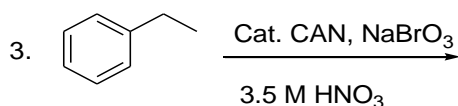
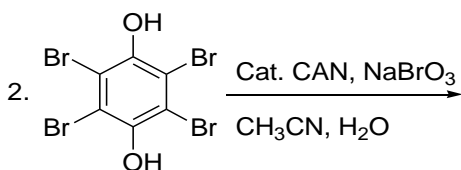
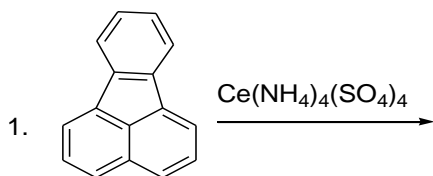
$\alpha,\beta$ -Unsaturated carbonyl compounds can be subjected to selective 1,2-reduction using  $\text{CeI}_3\text{-LiAlH}_4$  in THF (Scheme 25).



Scheme 25

**Problems:**

Write the major products for the following reactions.



## Text Books

M. B. Smith, *Organic Synthesis*, 2<sup>nd</sup> Ed., McGraw Hill, Singapore, 2004.

## Lecture 35

### 4.2 Samarium and Ytterbium Compounds

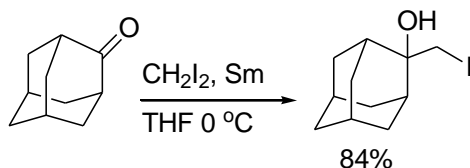
Samarium and ytterbium compounds find wide applications in organic synthesis. This section covers most of the important processes.

#### 4.2.1.1 Samarium (Sm)

Samarium in combination with dihalomethane is used to iodomethylate ketones and aldehydes. These reaction conditions are also effective for the transformation of esters and  $\alpha$ -haloketones to cyclopropanols, and directed cyclopropanation of allylic alcohols.

#### Iodomethylation of Ketones and Aldehydes

A wide variety of aldehydes and ketones can be converted into iodohydrins using samarium and diiodomethane in excellent yield (Scheme 1). Under these conditions, hindered ketones do not react, while  $\alpha,\beta$ -unsaturated carbonyl compounds afford the desired products in moderate yield.

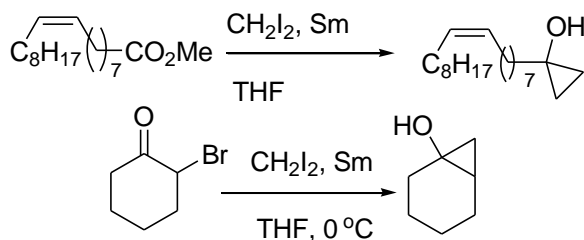


## Scheme 1

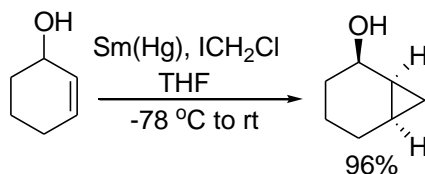
## Cyclopropanation

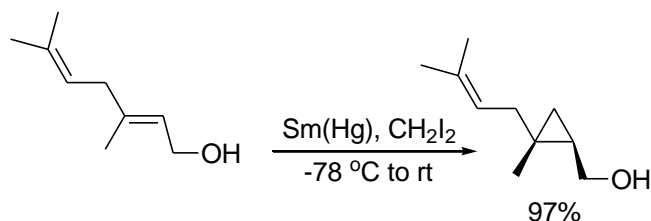
Using the above conditions, esters and  $\alpha$ -halo ketones can be converted into cyclopropanols, thereby affording a one-carbon homologation (Scheme 2). The reactions occur *via* Simmons-Smith-type cyclopropanation of the samarium enolate.

Directed cyclopropanation of allylic alcohols can be efficiently accomplished using  $\text{Sm}(\text{Hg})$  and dihalomethane under mild conditions (Scheme 2). Many functional groups such as isolated alkenes, homoallylic alcohols are inert under these conditions. Compared to Simmons-Smith and related reagents, the present protocol performs the cyclopropanation stereospecifically. For example, cyclopropanation of geraniol can be accomplished with complete stereospecificity in excellent yield (Scheme 3).

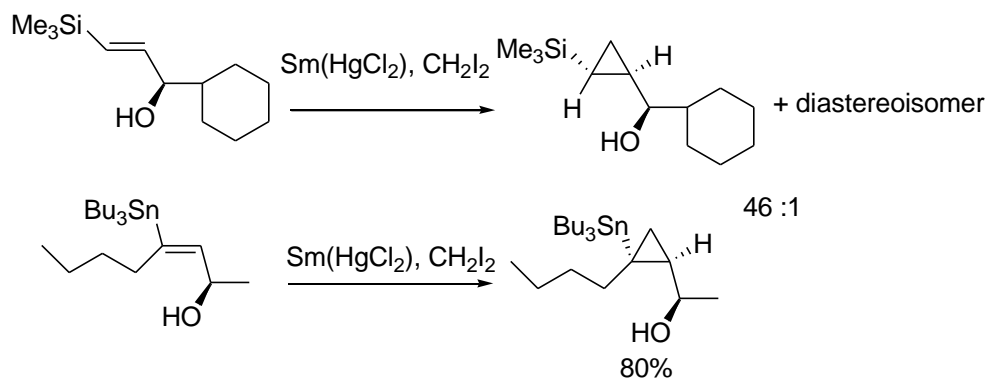


Scheme 2





Scheme 3



Scheme 4

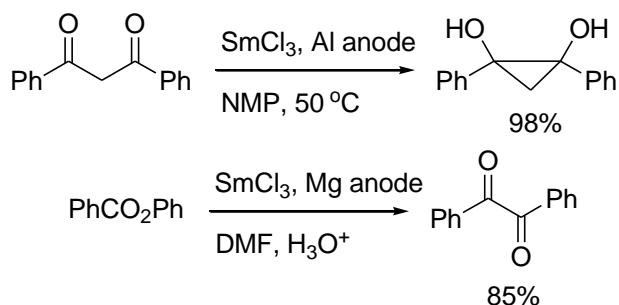
Alkenes containing tin or silicon substituents also react with excellent diastereoselectivity under similar reaction conditions, affording highly functionalized cyclopropanes (Scheme 4).

#### 4.2.1.2 Samarium(III) Chloride ( $\text{SmCl}_3$ )

$\text{SmCl}_3$  is air and moisture sensitive and the reactions are to be performed under inert atmosphere.

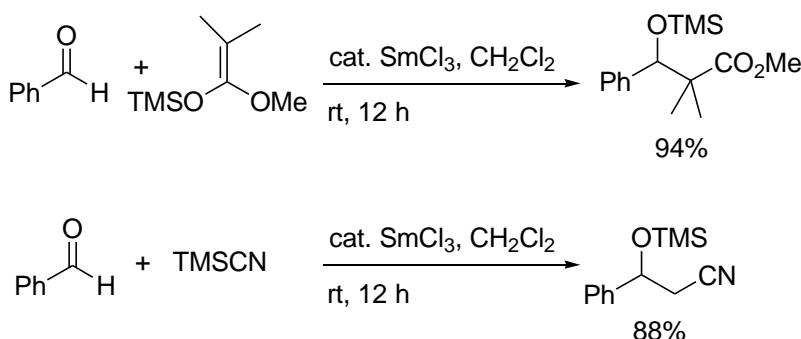
#### Carbon-Carbon Bond Formation

$\text{Sm(II)}$  species generated by the electrochemical reduction of  $\text{SmCl}_3$  promotes the coupling of carbonyl compounds to give cyclopropane diols (Scheme 5). The process is, however, limited to carbonyls having aromatic functionality.



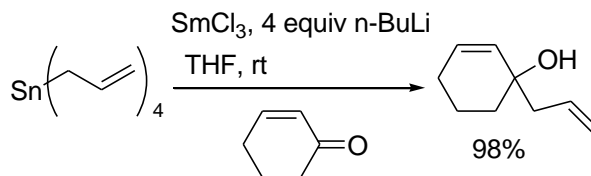
Scheme 5

Using catalytic amount of  $\text{SmCl}_3$ , aldol reaction of silyl enol ether with aldehydes can be performed at ambient temperature (Scheme 6). These reaction conditions are also effective for cyanohydrins synthesis from aldehydes and  $\text{TMSCN}$ .



Scheme 6

1,2-Allylation of  $\alpha,\beta$ -unsaturated carbonyl compounds can be accomplished using  $\text{SmCl}_3$ ,  $n\text{-BuLi}$  and tetraallylstannane at ambient temperature (Scheme 7).

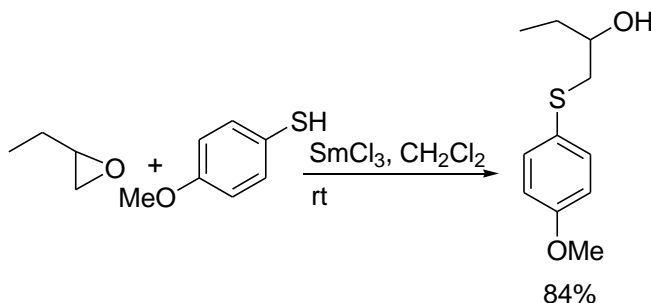


Scheme 7

## Epoxide Ring Opening and Protecting Group Removal

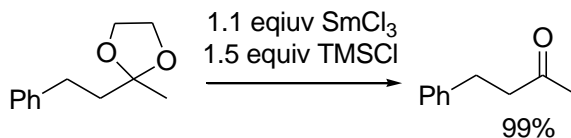
$\text{SmCl}_3$  catalyzes the reaction of epoxide with thiol nucleophiles to give thioalcohol in high yield (Scheme 8). The process is regio- and stereoselective and takes

place in shorter reaction time as compared to the other Lewis acid catalyzed systems.



Scheme 8

$\text{SmCl}_3$  can be used for the cleavage of acetals to give carbonyl compounds (Scheme 9). The transformation of acetals to aldehydes is slower than that to ketones. Thus, the present method can be employed for the chemoselective removal of acetal protecting groups. Acid-sensitive functional groups such as *t*-butyldimethylsilyl ethers and methoxy methyl ethers are inert to these reaction conditions.



Scheme 9

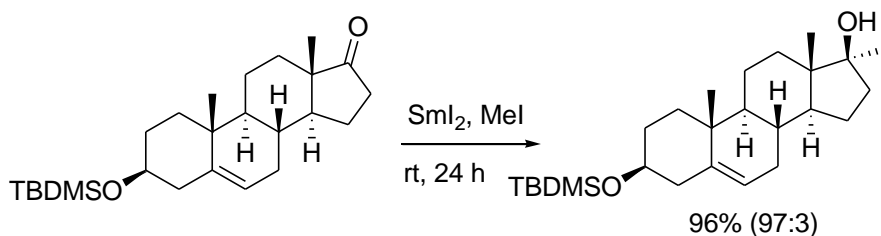
#### 4.2.1.3 Samarium(II) Iodide ( $\text{SmI}_2$ )

$\text{SmI}_2$  is air sensitive and should be handled under inert atmosphere. It may be stored over THF for longer period.

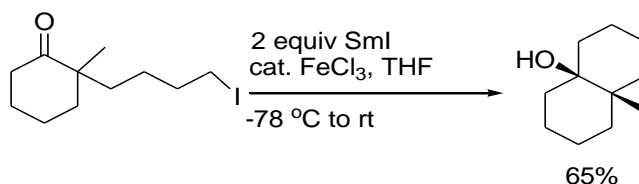
#### Barbier-Type Reactions

$\text{SmI}_2$  is quite useful in promoting Barbier-type reactions between aldehydes or ketones and a variety of organic halides (Scheme 10). The reaction time and temperature can be reduced by adding catalytic amount of  $\text{FeCl}_3$  or HMPA. For example, annulations of six member ring occur





Scheme 9

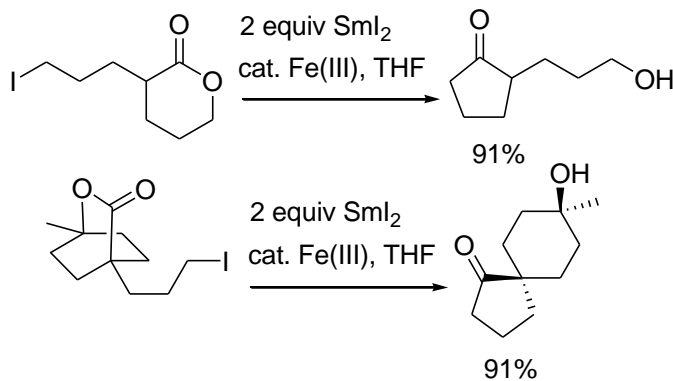


Scheme 10

with excellent diastereoselectivity *via* an intramolecular Barbier-type reaction in the presence of catalytic  $\text{FeCl}_3$  at mild conditions (Scheme 10). Moreover, this method provides effective route for the construction of fused bicyclic systems.

### Nucleophilic Acyl Substitutions

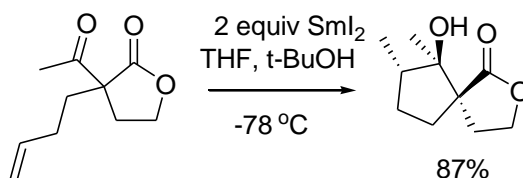
The above described reaction conditions can be used to facilitate the selective intramolecular acyl substitution of halo esters (Scheme 11). Unlike the organolithium reagents,  $\text{Sml}$ -promoted nucleophilic substitutions don't proceed with double addition to the carbonyl.



Scheme 11

## Ketone-Alkene Coupling Reactions

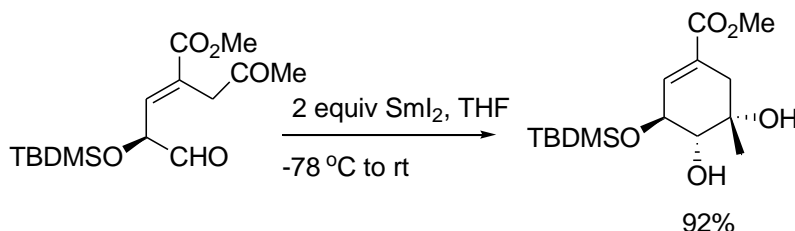
Ketyl radicals generated from reduction of ketones or aldehydes with  $\text{SmI}_2$  can be coupled both inter- and intramolecularly to a variety of alkenic species. Excellent diastereoselectivities are accomplished in intramolecular coupling reactions. For example, ketone–alkene cyclization can be pursued in a stereocontrolled manner (Scheme 12).



Scheme 12

## Pinacolic Coupling Reactions

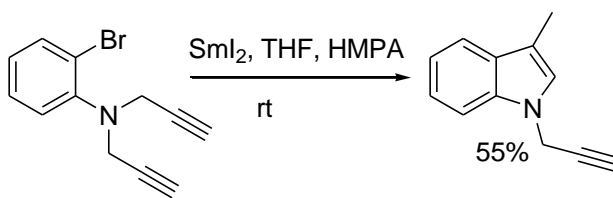
Both aldehydes and ketones are coupled in the presence of  $\text{SmI}_2$  to give pinacol. The reaction is carried out in the absence of proton source. Intramolecular reactions proceed with excellent diastereoselectivity (Scheme 13).



Scheme 13

## Radical Addition to Alkenes and Alkynes

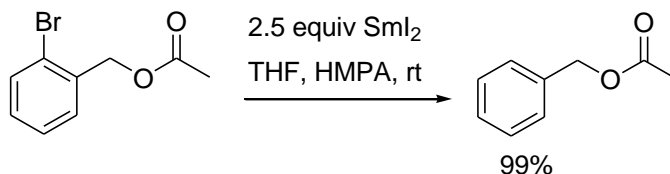
$\text{SmI}_2$  can mediate the cyclization of aryl radicals onto alkene and alkyne acceptors to give an excellent route to the synthesis of heterocycles (Scheme 14). This protocol affords an effective route to construct more highly functionalized frameworks through sequential radical cyclization.



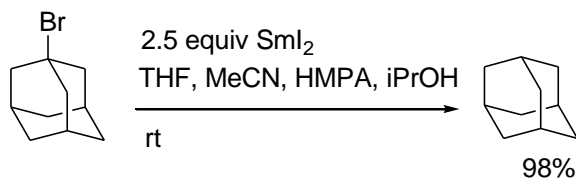
Scheme 14

## Reduction Reactions

$\text{SmI}_2$  reduces alkyl halides to give hydrocarbons in the presence of proton source (Scheme 15). The reactivity order of alkyl halides is  $\text{R-I} > \text{R-Br} > \text{R-Cl}$ . This method provides effective route to reduce the substrates in which the halide is resistant to reduction by hydride reducing agents (Scheme 16).

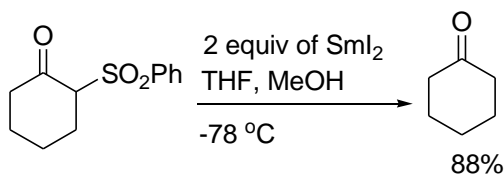


Scheme 15

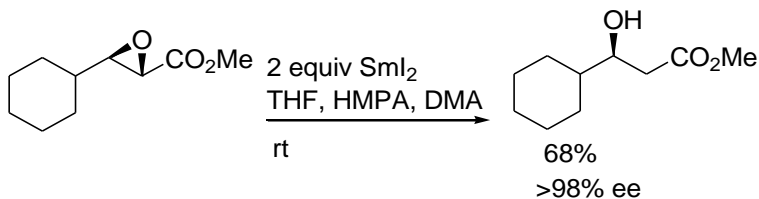


Scheme 16

Under similar conditions, the reduction of  $\alpha$ -heterosubstituted carbonyl compounds can be accomplished. A wide range of substrates proceeds reaction to give unsubstituted ketones under mild conditions (Scheme 17). These conditions can also be applied for the reductive cleavage of  $\alpha$ -alkoxy ketones to give the corresponding  $\beta$ -hydroxy carbonyl compounds (Scheme 18).

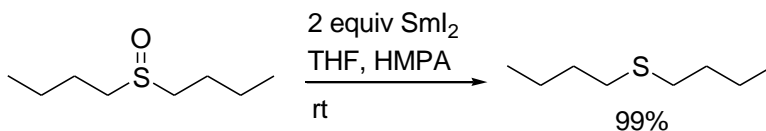


Scheme 17



Scheme 18

$\text{Sml}_2$  can also be used for the reduction of sulfoxide and sulfones to give sulfides under mild conditions (Scheme 19).



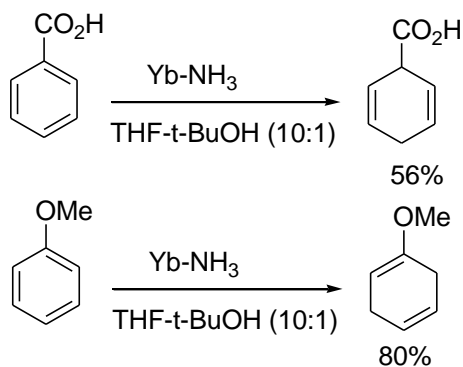
Scheme 19

#### 4.2.2.1 Ytterbium (Yb)

Yb can be used for Birch type of reduction of aromatic and alkenic compounds, coupling of aldehydes and ketones to give pinacol and formation of organoytterbium reagents that can react with ketones, epoxides and nitriles to afford functionalized compounds.

#### Reduction Reactions

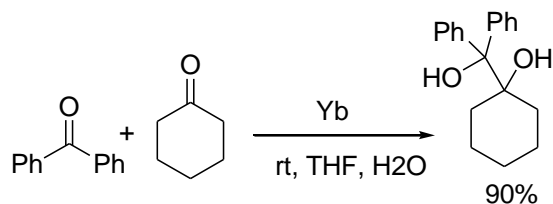
Solutions of Yb in ammonia have properties similar to that of alkali metal-ammonia solutions and can reduce aromatic and alkenic compounds like Birch reduction (Scheme 20).



Scheme 20

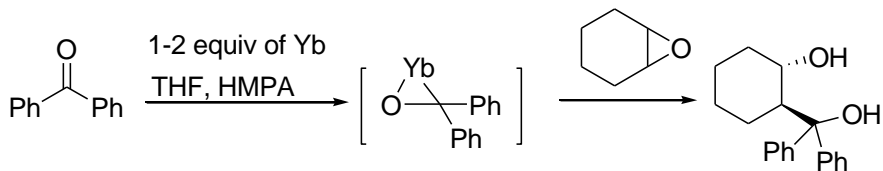
### Carbon-Carbon Bond Formation

Yb promotes pinacolic coupling of diaryl ketones with aldehydes and ketones (Scheme 21). However, it is limited due to the requirement of one of the pinacolic partner must contain aromatic functionality.



Scheme 21

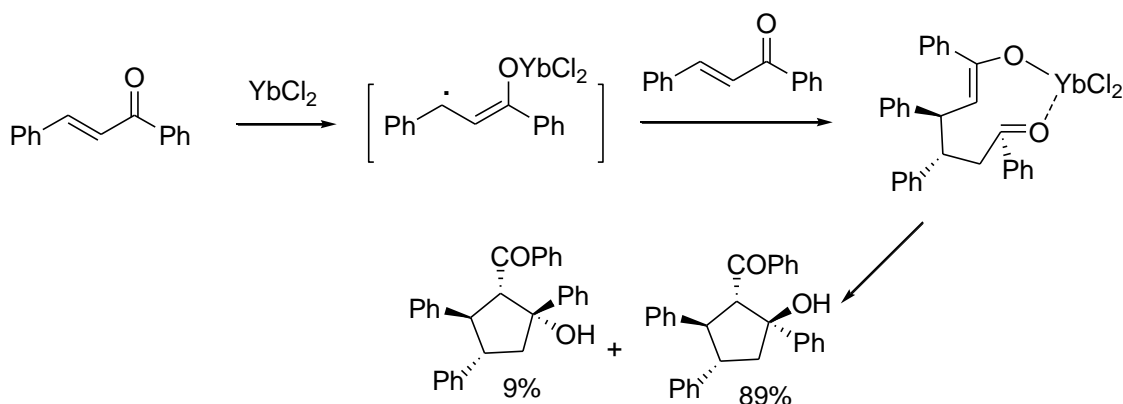
Organoytterbium complex derived from Yb and aryl ketone can be reacted with electrophiles such as ketones, epoxides, nitriles and carbon dioxide to afford the corresponding pinacol, 1,3-diol,  $\alpha$ -hydroxy ketone, and  $\alpha$ -hydroxy carboxylic acid, respectively (Scheme 22).



Scheme 22

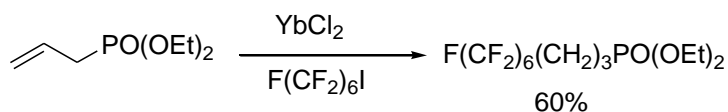
### 4.2.2.2 Ytterbium(II) Chloride (YbCl<sub>2</sub>)

The reductive dimerization of  $\alpha,\beta$ -unsaturated ketones and hydroperfluoroalkylation of alkenes have accomplished in the presence of YbCl<sub>2</sub>. For example, chalcone undergoes dimerization to give cyclopentanols (Scheme 23). The reaction involves a single electron-transfer to the conjugated system, followed by addition of the resulting enolate radical to the starting material. The reaction shows significant diastereoselectivity.



Scheme 23

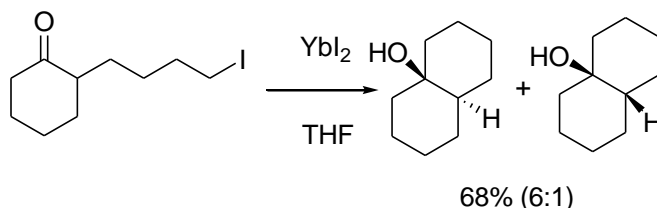
Addition of perfluoroalkyl iodide to alkenes containing ester, ether, alcohol, and phosphonate proceeds in the presence of YbCl<sub>2</sub> in good yield (Scheme 24).



Scheme 24

### 4.2.2.2 Ytterbium(II) Iodide (YbI<sub>2</sub>)

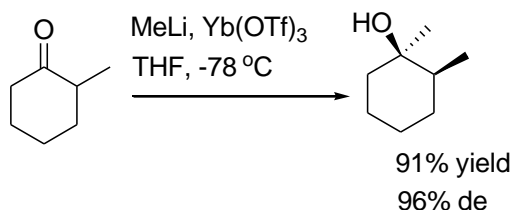
YbI<sub>2</sub> has been used for the reductive cyclization of halo ketones to afford five, six and seven membered rings (Scheme 25). The reactions show better diastereoselectivity compared to that with SmI<sub>2</sub> reactions.



Scheme 25

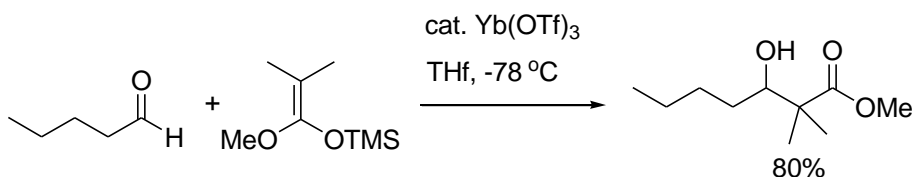
#### 4.2.2.3 Ytterbium(III) Trifluoromethanesulfonate ( $\text{Yb}(\text{OSO}_2\text{CF}_3)_3$ )

Organoytterbium triflates derived from organolithium and  $\text{Yb}(\text{OTf})_3$  exhibits greater diastereoselectivity in carbonyl addition to chiral aldehydes and ketones. For example, 2-methylcyclohexanone with the methylytterbium reagent gives a mixture of diastereoisomers in 98:2, resulting from the favoured equatorial attack of the bulky organolanthanide reagent (Scheme 26).



Scheme 26

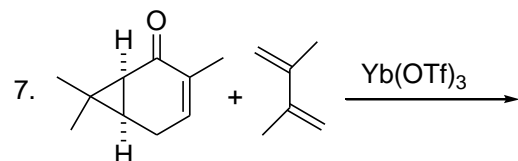
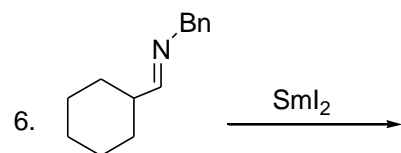
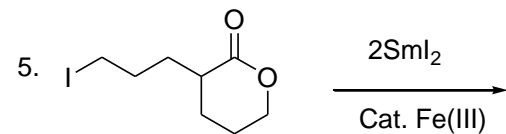
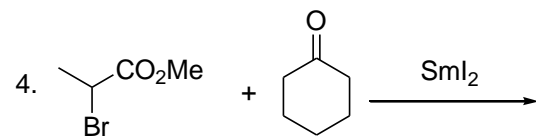
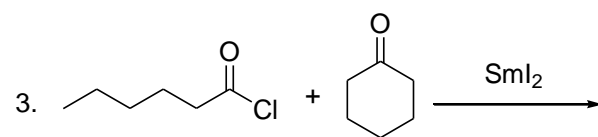
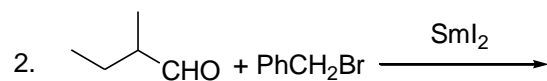
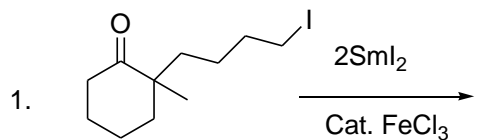
$\text{Yb}(\text{OTf})_3$  has been extensively used as Lewis acid catalyst for aldol reactions (Scheme 27). Unlike other Lewis acid catalysts, water does not interfere with the reactions when  $\text{Yb}(\text{OTf})_3$  is employed. In addition, molecules with free hydroxyl and nitrogen functionalities are compatible and do not coordinate with  $\text{Yb}(\text{OTf})_3$ . Furthermore, the catalyst may be recovered from the aqueous solution and recycled.



Scheme 27

**Problems**

Complete the following reactions with major products.





***Text Books***

M. B. Smith, *Organic Synthesis*, 2<sup>nd</sup> Ed., McGraw Hill, Singapore, 2004.