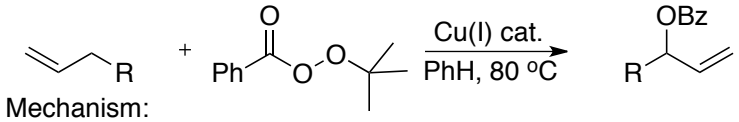
Background

- 1895–1957
- defined the "peroxide effect" anti-Markovnikov *via* radical additions
- Born Russian but migrated to the USA at age of 13.
- Obtained PhD from University of Chicago
- Trained Nobel Laureate H. C. Brown
- In 1942 (WWII), joined the American Synthetic Rubber Research Program - polymerization of styrene

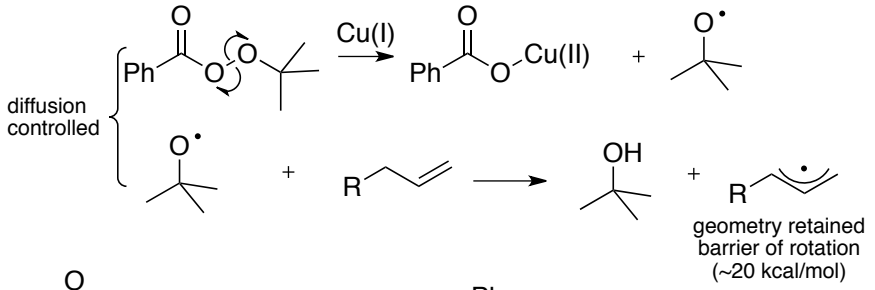
What is the Kharasch Reaction?
1) Allyic oxidation with radicals 2) The Kharasch modified Grignard rxn
3) Addition of poly-halogenated alkanes across olefin

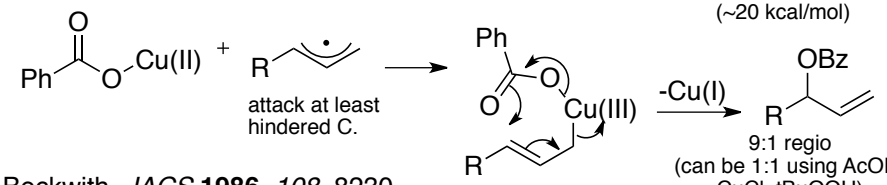
Kharasch Allylic Oxidation and its Development

- First reported in 1959 by Kharasch



Mechanism:





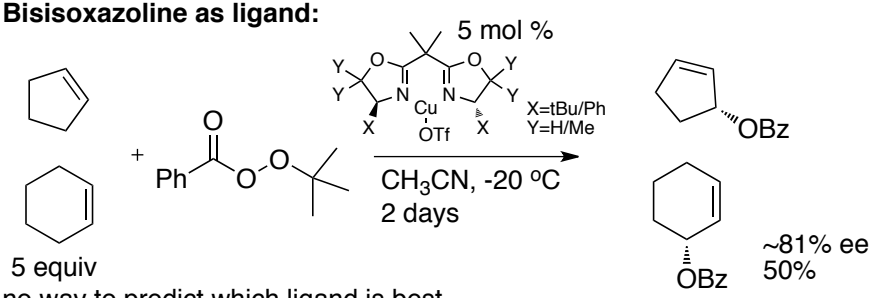
Beckwith, *JACS* **1986**, *108*, 8230.
Walling, *JACS* **1961**, *83,* 3877.
Kochi, *JACS* **1965**, *87*, 4866.

Asymmetric Development (only in 1990s)

- Main players: Andrus, Pfaltz, Katsuki
- earliest asymmetric development was diastereoselective using chiral auxiliaries.
- best result 30% ee.

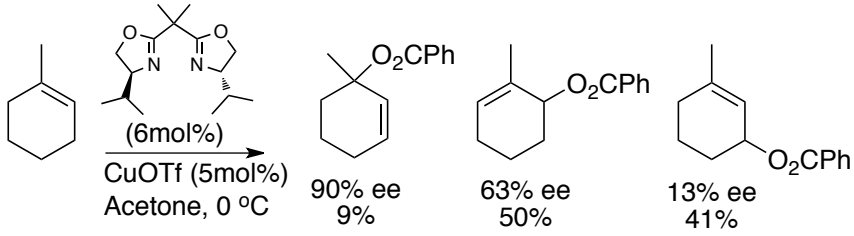
Potential for asymmetric Kharasch oxidation depends on the ability of L on Cu(III) to induce asymmetric formation of benzoate.

Bisisoxazoline as ligand:



5 equiv
no way to predict which ligand is best
require screening of X/Y
cyclooctene slow conversion/ low ee
acyclic olefins like allylbenzene and 1-octene has been done

Andrus, *TL* **1995**, *36*, 2945

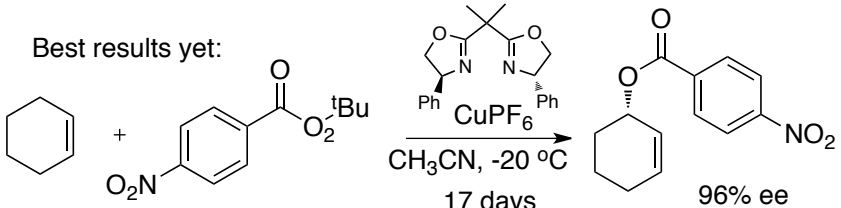


Pfaltz, *TL* **1995**, *36*, 1831

Andrus went on to show that weakening perester bond would increase homolysis and thus increase formation of Cu(II) complex. However different peresters require different Cu catalyst: CuBr to $CuPF_6(CH_3CN)_4$.

T **1997**, *53,* 6229

Best results yet:

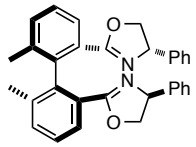


Shorter reaction time generally give lower ee (>84% ee)
Able to achieve 99% ee with cyclopentene.

Andrus, *JACS* **2002**, *124*, 8806

Biaryl atropisomeric oxazolines as ligand:

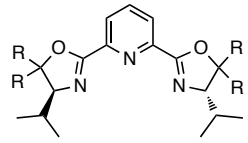
-wider bite angle between 2 nitrogens, forcing allyl radical and benzoate closer together.



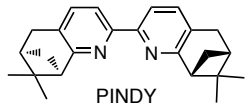
-(S,S,S) ligand shown here. Also available (S,R,S)
-recoverable by 80%
-73–78% ee for oxidation of cyclopentene and cyclohexene

Andrus, *JOC* **1997**, *62*, 9365
Andrus, *T* **2000**, *56*, 5775

Pyridine based igands:



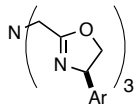
Singh, *TL* **1996**, *37*, 2633



(62–75% ee for cycloheptene)

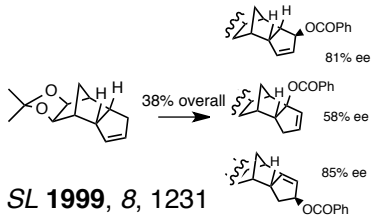
Kocovsky, *OL* **2000**, *2*, 3047

C3 Symmetric oxazole as ligand:



88% ee for cyclopentene

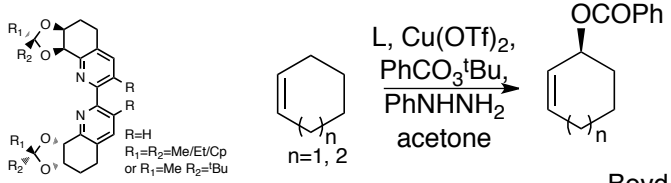
Katsuki, *SL* **1995**, 1245



SL **1999**, *8*, 1231

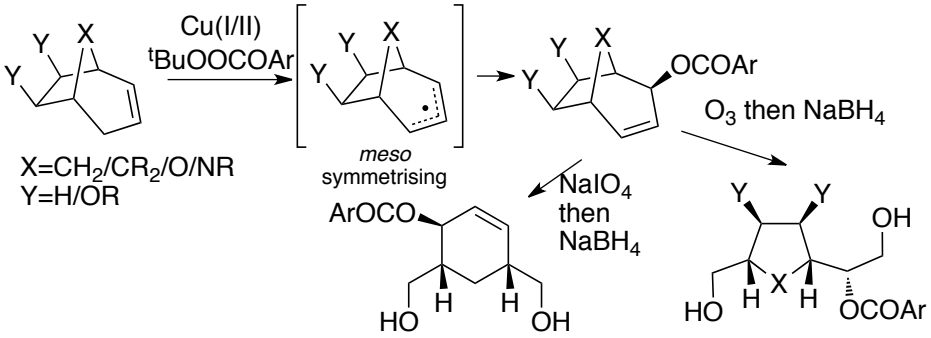
Also studied are proline derived ligands.
Observed correlation between coordinating ability of ligand to % ee
stereocontrol increases with the use of more rigid alkenes (cyclic alkenes)
Muzart, *T:A* **1995**, *6*, 147; Andrus, *T* **2002**, *58*, 845

Recent Development:



Boyd, *CC* **2008**, 5535

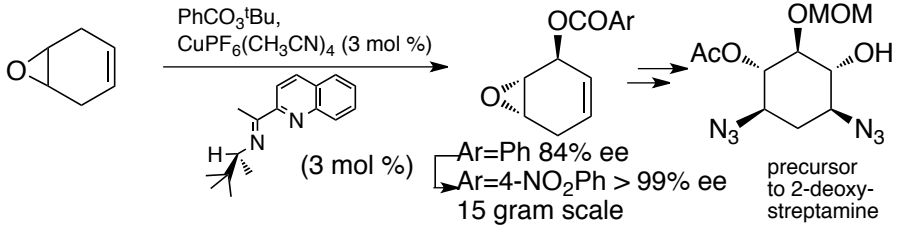
Ligand can perform asymmetric cyclopropanation of styrene (88–95% ee)



only successful for Y=H and X=CH_2 and CR_2
up to 70% ee

Clark, *TL* **2004**, *45*, 9447

Kharasch Variant (Schiff base as ligand)



Transforming to 4-NO_2Ph then recrystallizing enhances ee.

Hayashi, *OL* **2009**, *11,* 3314

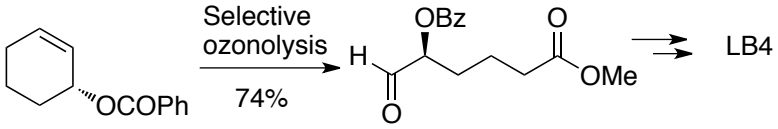
Summary:

-Asymmetric Kharasch allylic oxidation has reached >90% ee
-But is greatly hampered by the long reaction times (days)
and only applicable mostly on simple cyclic substrates.
-More complicated or acyclic olefins tend to give mixtures of regioisomers.

For detailed reviews on stereocontrol/regiocontrol/mechanistic studies see:
Andrus, *T* **2002**, *58*, 845; *C.Eur.J* **2008**, *14*, 9274.

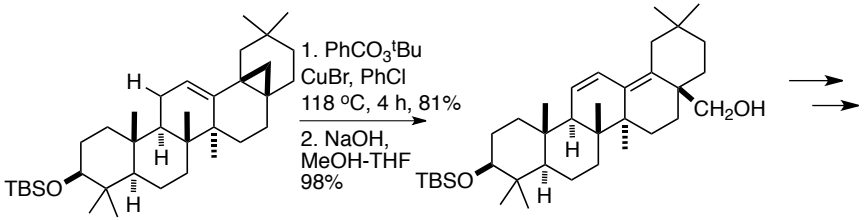
Applications of Kharasch Allylic Oxidation

1. Synthesis of Leukotriene B_4



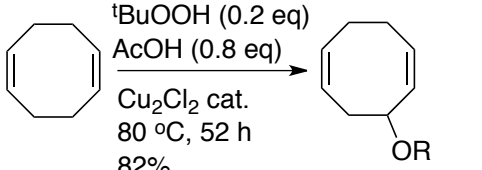
common intermediate
to 12 routes to LB4
-previously made from
6 steps from 2-deoxy-D-ribose
-or 12 steps from D-xylose

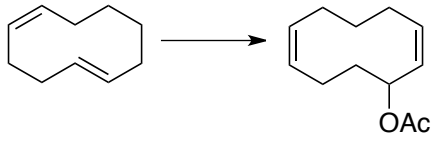
2. Synthesis of Oleanolic Acid



Corey, *JACS* **1993**, *115*, 8873

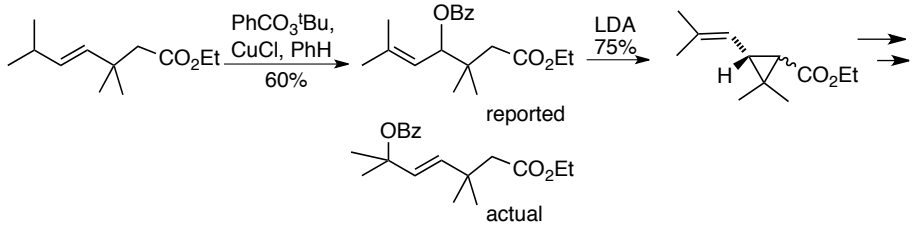
3. Synthesis of Polyether Toxin Frameworks - Brevetoxin B





Alvarez, *JOC* **1994**, *59*, 2848

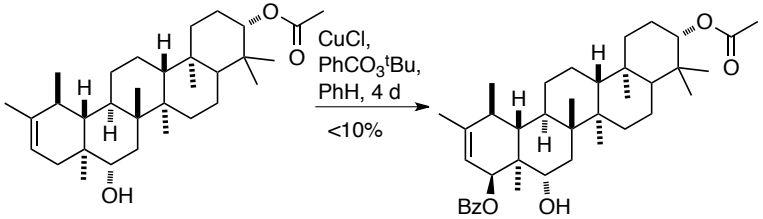
4. Synthesis of Chrysanthemic acid



-Reported regioisomer does not obey Kharasch reaction mechanism
-Found by Andrus that the other regioisomer was actually formed, but gives same products.

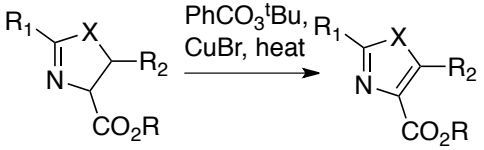
Angelo, *TL* **1976**, *28*, 2441

5.



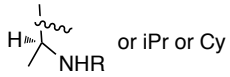
Guerriero, *C&B* **2005**, *2*, 657

6. Oxidation of oxazolines/thiazolines



Stoichiometric Cu needed
ester group crucial for reactivity

X=O or S
R_2=H or Me
R_1=no limit for Cu-mediated alkyl/aryl. Allow 2º or 3º H to remain intact if R_1=



or iPr or Cy

Meyers, *JOC* **1996**, *61*, 8207

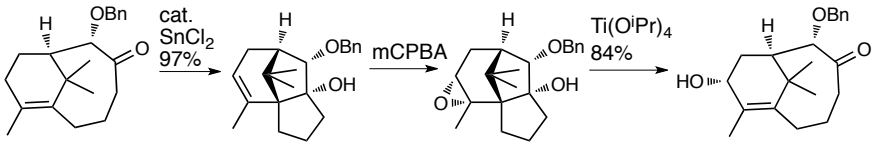
Other applications of Kharasch allylic oxidation:
Arcadi, *TL* **1997**, *38*, 2329; Bateson, *JCS PT1* **1991**, 2399; Welzel, *T* **1998**, *54*, 10753.

Not many applications of Kharasch reaction in synthesis.

Asymmetric Allylic Oxidation in Synthesis

- A field that still requires a lot of development. Many synthetic targets contain allylic alcohols, with stereocenters at the alcohol FG.
- Most commonly seen (in fact >80% of Scifinder hits on this topic) used 1,2-reduction of enone, where desired stereochem of OH is due to rigid structure of substrate - eg. steroids...

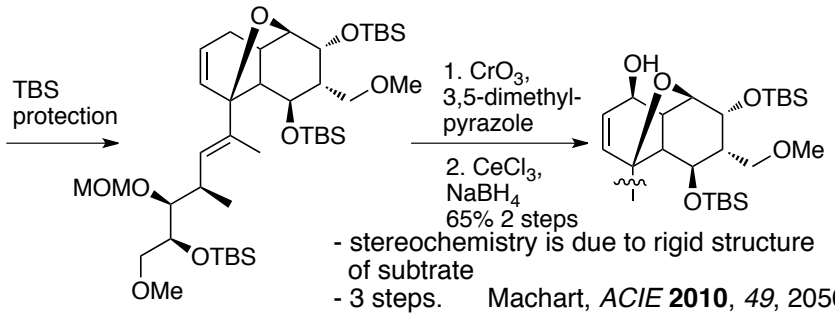
1. Routes to AB system of Taxoids (see last week's GM)



- 3 steps to allylic alcohol

SL **1998**, 897

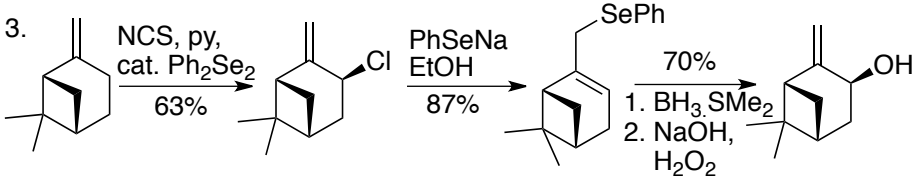
2. Total synthesis of Branimycin



- stereochemistry is due to rigid structure of subtrate
- 3 steps. Machart, *ACIE* **2010**, *49*, 2050

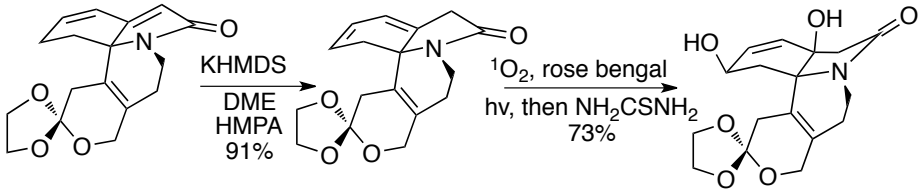
another recent and notable synthesis which employ same strategy:
Stock, *JACS*, **2009**, *131*, 11402 (Codeine and Morphine)

3.

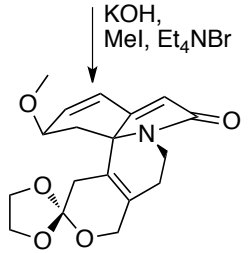


Scianowski, *T* **2009**, *65*, 10162

4. Total Synthesis of ß-Erythroidine

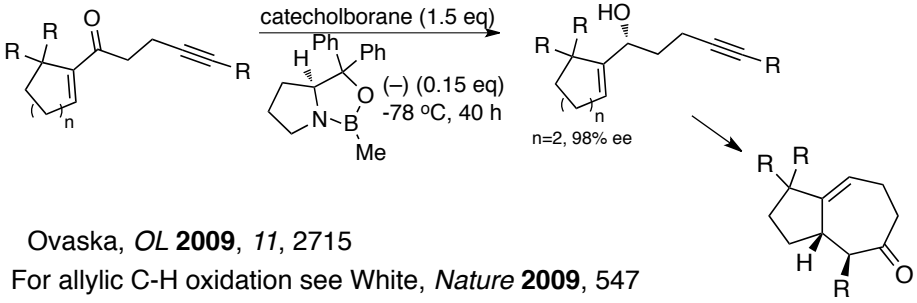


Alcohol stereochem. defined by cycloaddition of singlet oxygen.



Funk, *OL* **2006**, *8*, 3689

5. Total synthesis of Frondosin B



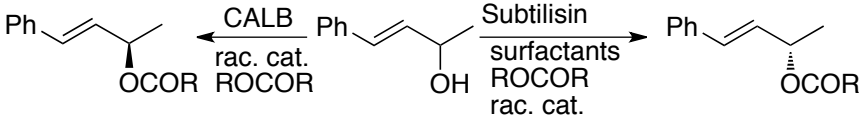
Ovaska, *OL* **2009**, *11*, 2715

For allylic C-H oxidation see White, *Nature* **2009**, 547

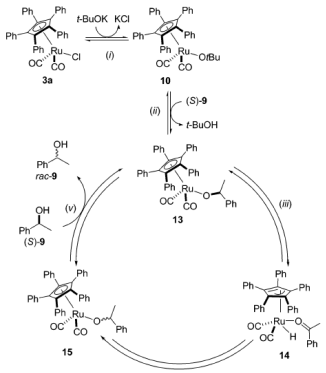
A good way to stereoselectively form allylic alcohols (late stage) in total synthesis is needed. What other methods are there anyway?

Methods to obtain chiral allylic alcohols

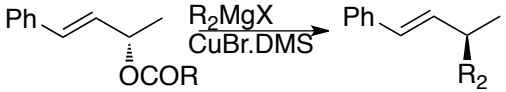
1. Enzymatic DKR Resolution



Fastest DKR of alcohols using a metal + enzyme catalysis. Previous rac. cat. either take too long to racemize or need high temp. (think enzyme). Note that small amount of base needed to activate the rac. cat.



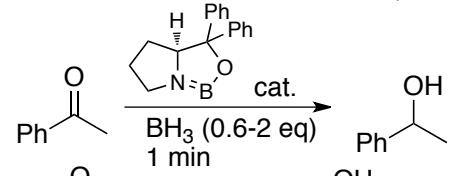
Subsequent copper-cat. allylic substitution inverts stereochemistry with small loss of optical activity (~ 75-91% ee if R_2 is aryl).

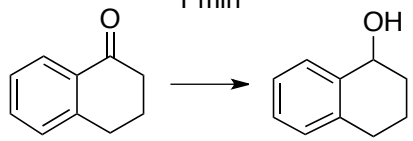


works with other enantiomer
10% of other regioisomer observed.

Backvall, *JACS* **2005**, *127*, 8817
Backvall, *JOC* **2010**, *75*, 6842

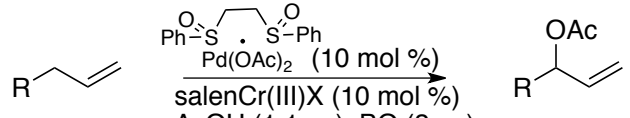
2. Enantioselective borane reduction (of enones)



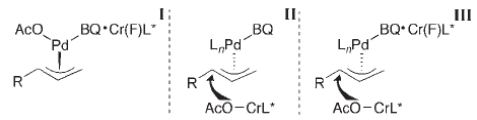


Corey, *JACS* **1987**, *109*, 5551

3. Chiral LA for enantioselective allylic oxidation



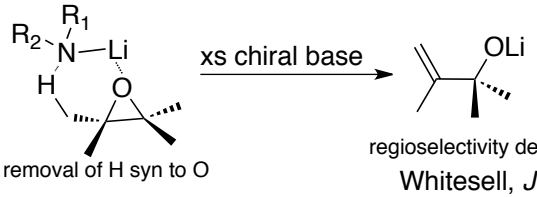
-for reactions that do not tolerate strongly coordinating ligands
-weakly coordinating bissulfoxide catalyze C-H cleavage
-BQ catalyze C-O formation
-sequential activity
-proposed 3 pathways for enantioselectivity:



White, *ACIE* **2008**, *47*, 6448

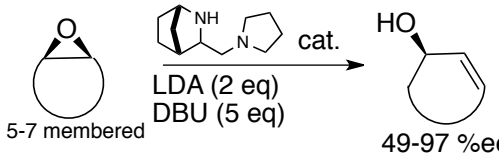
4. Rearrangement of epoxide

First development used chiral lithium base (first eg of enantioselective deprot.)

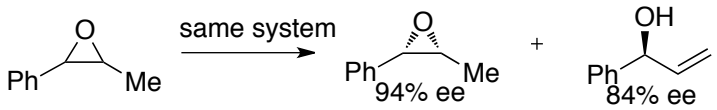


Whitesell, *JOC* **1980**, *45*, 755
Reviews: O'Brien, *JCS PT1* **1998**, 1439

Catalytic system



DBU ensures monomeric aggregate
cat. amine forms aggregate with base
2 instances where ee is poor can be improved by using stoichiometric chiral amine. Same system can perform resolution on rac-epoxide (2 examples)

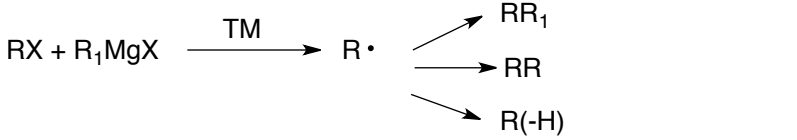


Andersson, *JACS* **2000**, *122,* 6610

Not covered in this GM includes:
General allylic oxidation methods
Ru catalyzed oxidation to enone: see Miller, *TL* **1996**, *37,* 3429; Meyer, *JACS* **2000**, *122*, 5984
Co catalyzed allylic oxidation: see Iqbal, *TL* **1995**, *36*, 159
SO_2 induced + O_2 oxidation: see Tempesti, *JOC* **1980**, *45*, 4278
Pd catalyzed allylic oxidation: see Yu, Corey, *JACS* **2003**, *125*, 3232; Yu, Corey, *OL* **2002**, *4*, 2727
Mercuric acetate allylic oxidation: see Rappoport, *JACS* **1972**, *94*, 2320
SeO_2 catalyzed allylic oxidation: see Gray, *JACS* **1977**, *99*, 5526
Mechanism for SeO_2 oxidation: see Singleton, *JOC* **2000**, *65*, 7554

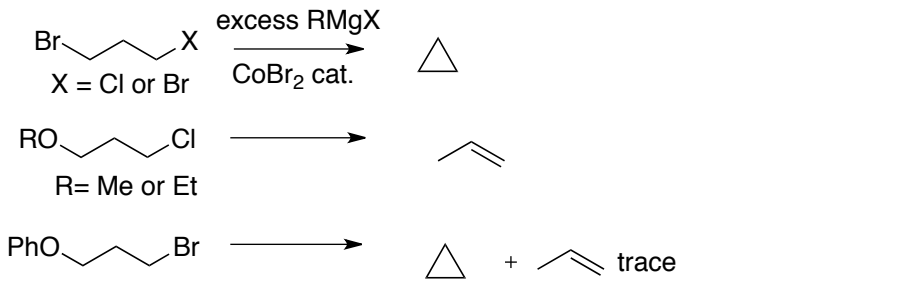
Kharasch Reactions : The Modified Grignard Reaction

Kharasch discovered that many transition metal salts, eg. $CoCl_2$, catalyzes a reaction between Grignard reagent and alkyl halide (allylic halide).



Kharasch, *JOC* **1943**, *65*, 493

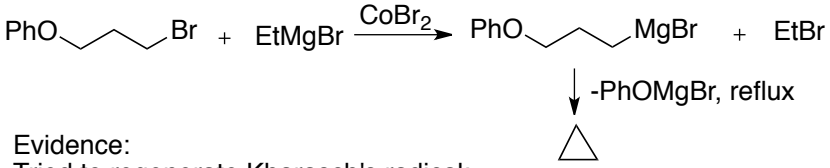
For Co catalyzed:
Mechanism: 1) $RMgX + CoX_2$ -----> $RCoX + MgX_2$
2) RCoX -----> R• + CoX
3) R'X + CoX -----> R'• + CoX_2
Kharasch suggested that alkyl radicals were formed in the reaction, which can undergo homocoupling, cross coupling or reduction to the olefin.



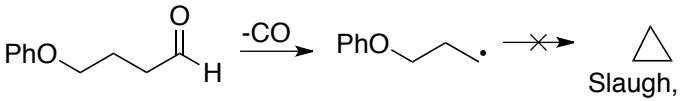
-also in this study, he found that the length of the haloalkyl chain affects the product distribution.
if n = 2, major product is PhOMgX + ethylene
if n = 3, major product is cyclopropane,
if n > 3, major product is $PhO(CH_2)_nH$ Kharasch, *JOC* **1953**, *18*, 575

"Reinterpretation of Several Kharasch Reactions"

-argues that interchange reaction occurs between alkyl halide and Grignard reagent (catalyzed by TM).
- it is a competing reaction pathway which is more likely to explain the observation of products (cyclopropane formation)
-products of the modified Grignard reaction is due to hydrolysis of interchanged Grignard reagent.



Evidence:
Tried to regenerate Kharasch's radical:

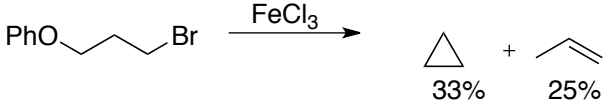


Slaugh, *JOC* **1961**, *83*, 2734

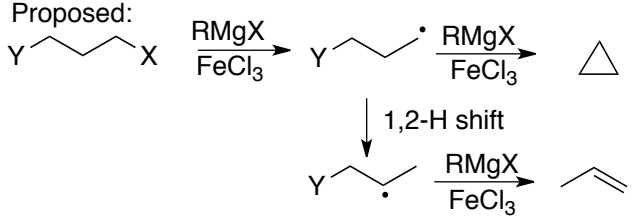
Kharasch's response with a JACS paper:

"Functional exchange does not play an important role, if at all, in these reactions"

His explanation:
3-alkoxy-1-propylmagnesium bromide cannot be a key intermediate, as it does not explain formation of propylene. It is also known to be stable under the reaction condition. Neither is it plausible for cyclopropane to isomerize into propylene

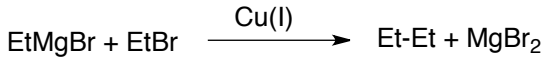


Proposed:



Kharasch, *JACS* **1961**, *83*, 3232

Yet another mechanistic input:



-addition of radical trap such as styrene, does not affect the rate of ethane formation -----> reduction of styrene should be observed.
-proposed formation of alkylcuprate intermediate.

Kochi, *JACS* **1971**, *93*, 1485

Kochi went on to do a detailed study on the interaction of transition metal salts with Grignard reagents (without alkyl halides, with or without styrene) and the same on the interaction of mixture of 2 Grignard reagent with TM salts.

Findings:

1. Radical mechanism can be neglected for homocoupling R-R (one type of GR) since styrene has no effect on rate. Instead it might proceed under bimolecular mechanism: $RMX_{n-x} + RMX_{n-x}$ --> $R\text{-}R + 2MY_{n-x}$
2. Disproportionation of GR to give alkene and alkane

2 plausible mechansims:

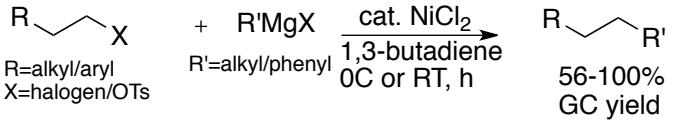
a) "Hydride" RCH_2CH_2M --> $RCH{=}CH_2 + HM$
$RCH_2CH_2M + HM$ --> $RCH_2CH_3 + 2M$

b) "Direct Hydride Migration" $RCH_2CH_2M + RCH_2CH_2M$ --> $RCH{=}CH_2 + RCH_2CH_3 + 2M$

Kochi, *BCSJ* **1971**, *44*, 3063

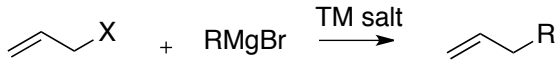
For a more recent mechanistic argument supporting the formation of alkyl radicals, see Henderson, *JCS DT* **1992**, 1259.

A similar recent example of Ni-catalyzed cross coupling:



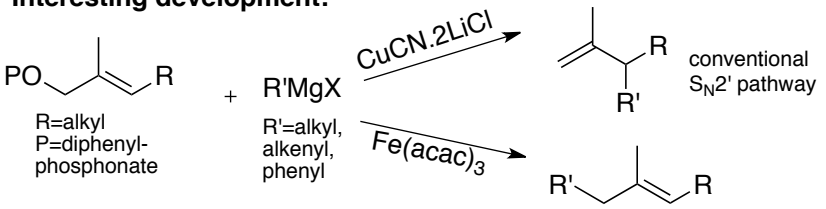
Kambe, *JACS* **2002**, *124*, 4222

Allyl halide + Grignard Reagent (cat. TM salt)



also observe homocoupling of allyl halide, or H-xfer

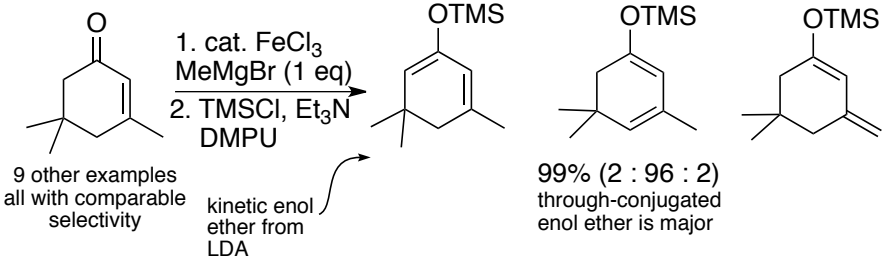
Interesting development:



Yamamoto, *SL* **1991**, 513

Application:

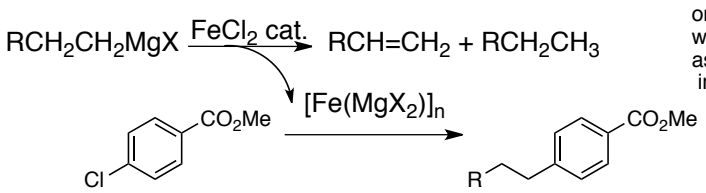
1. Regioselective Generation of Dienol Ethers from Enones:



using excess reagents will switch selectivity of *endo* for *exo*-enol ether to be major product

Holton, *JACS* **1984**, *106*, 7619

2. "Super-Ate" complex of iron:



only applicable to GR with 2 or more carbons as reduction process involves ß-H elimination

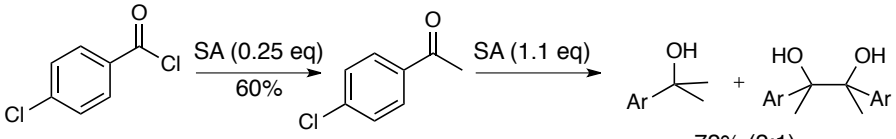
In line with this is the fact that MeMgBr fails to react with the substrate in the presence of any iron catalyst, whereas higher alkyl GR do so much easily.

Why?

Successfully made a iron "super-ate" complex for Me substitution

$MeLi(xs) + FeCl_3$ ---> $[(Me_4Fe)(MeLi)][Li(OEt_2)]_2 + 3LiCl$

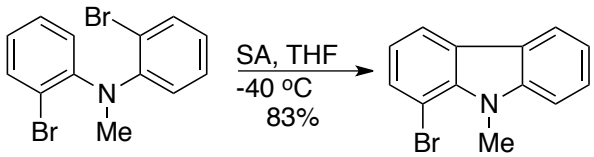
This "super-ate" (SA) complex does not react with pX-C_6H_4COOMe or normal alkenyl halides. It only reacts with activated enol triflates, acid chlorides or electron deficient heteroarene.



72% (2:1)

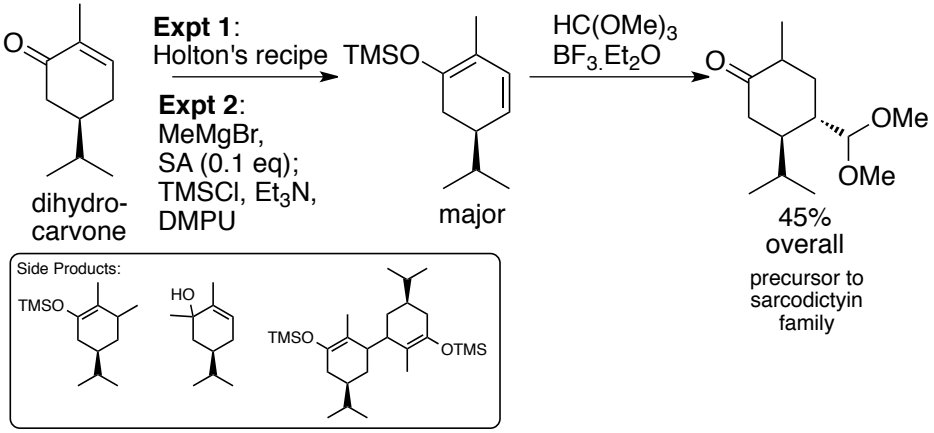
excess SA complex gives carbonyl addition product and pinacol product. pinacol product suggests some form of SET mechanism on the ketone.

Another example of the SET:



"Ulmann coupling" (ish)

He decided to try his "super-ate" complex on a similar Holton problem:



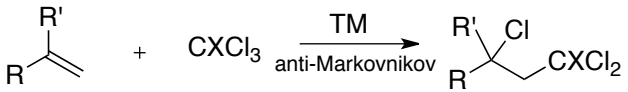
Crude product spectrum after quench is *virtually identical* in both cases. The dimer side prdt suggests a SET event.

do we have an actual "Kharasch reagent"?

Furstner, *ACIE* **2006**, *45*, 450

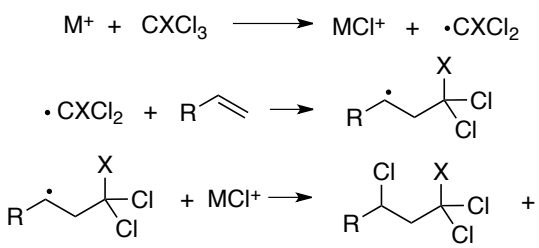
Addition of Per-haloalkanes to olefins

Overview



-Discovered by Kharasch, *Science* **1945**, *102*, 128
-A radical mechanism is proposed, see *JOC* **1938**, *2,* 288.
-Drawbacks include 1. limited scope of polyhalogenated substrates
2. harsh reaction conditions (high T and time)
-Ways to improve: 1. New transition metal complexes (Ru found to be most efficient (>40 °C)
2. adding Lewis acids as cocatalysts to activate C-X bond
-It is noted that different mechanisms exist for each TM catalyst

General Mechanism for TM-catalyzed Kharasch addition:

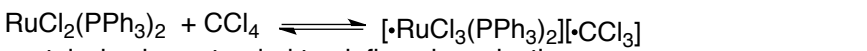


-"redox-chain" process
-MCl^+ has a larger chain xfer constant

Minisci, *ACR* **1975**, *8*, 165

Ru

-the same Grubb's ruthenium benzylidene complex used for olefin metathesis is employed here.
-ligands on ruthenium can also be changed to minimize olefin metathesis or other side reactions that might occur.
-reaction can be done at temperatures as low as 40 °C in a few hours.
-a different mechanism from the "redox-chain" has been proposed to rationalize the markedly different reactivity and selectivity
-"radical reaction in cooridination sphere" - radicals generated remain under the influence of the metal center



-Ru catalysis also extended to olefin polymerization

Matsumoto, *J. Organomet. C* **1979**, *174*, 157

Rh

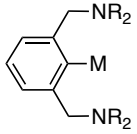
-chiral Rh catalyst allows enantioselective addition to olefin.
-White tried to rationalize Rh stereoselectivity (over Cu(I)/Fe(II)/Ru(II) by proposing that an oxidative addition first step occurs (analogous to hydrogenation of alkene
-isolated oxidative addition adduct

-However, his proposed mechanism is not well received, and others argue that an oxidative addition does not rule out radicals, because there is precedence that oxidative addition of Ir and Pt complexes undergo radical mechanisms.

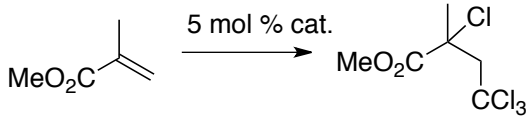
White, *JCS CC* **1991**, 165; Koten, *ACR*, **1998**, *31*, 423

Ni

-Cu cat. Kharasch addition shows a low redox potential is needed.
-Ni(NCN) has a super low potential of +0.14 to +0.57 V (Ni(II)/Ni(III)) (cf. normal +0.7 to +1.2 V)
-addition of carbon tetrachloride to methyl methacrylate is complete in 15 min at RT over 90% conversion ---> mildest and fastest condition yet.



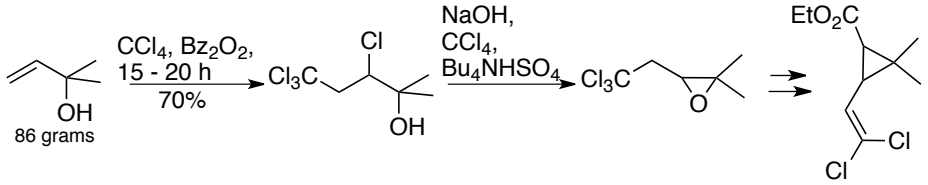
NCN ligand ("pincer")



Koten, *ACR*, **1998**, *31*, 423

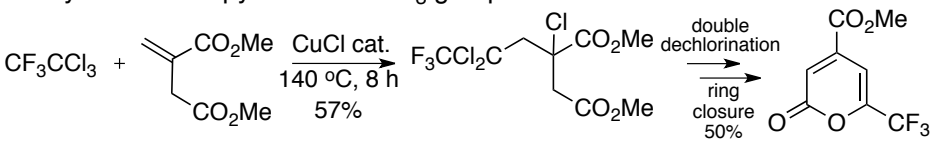
Applications of the Kharasch addition

1. Synthesis of Permethrin (NRDC143) moiety

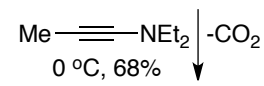


Svendsen, *JOC* **1979**, *44*, 416

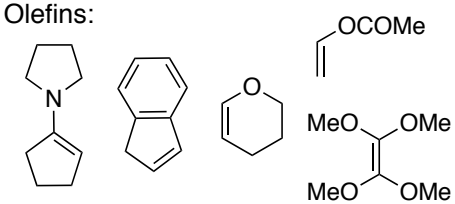
2. Synthesis of 2-pyrones with CF_3 groups

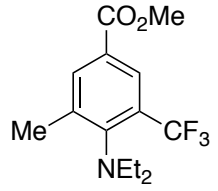


-2-pyrones undergo inverse e- demand DA with acetylenes, spontaneously losing CO_2.
less e- rich acetylenes require higher temp.
-also undergo DA with olefins, but no loss CO_2.



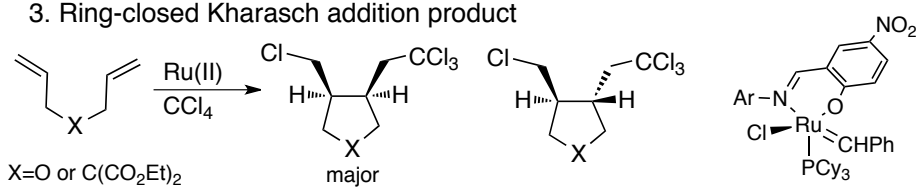
Olefins:





Martin, *TL* **1985**, *26*, 3947

3. Ring-closed Kharasch addition product

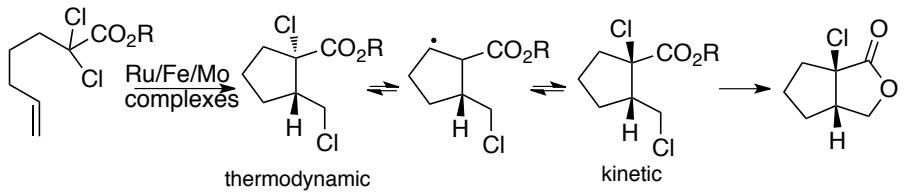


no 6-endo trig closure observed. >54% yield in all cases.

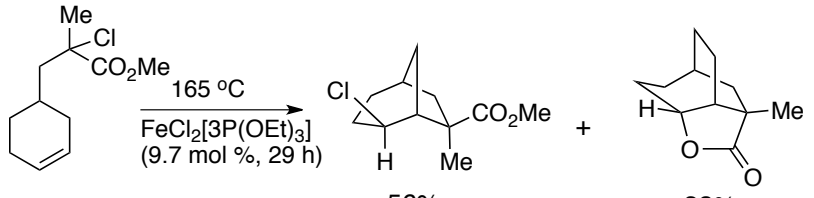
Verpoort, *CatL* **2002**, *83*, 9

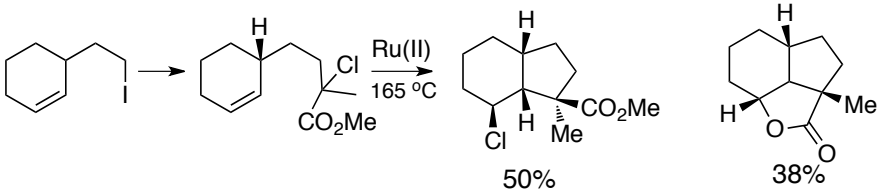
4. More Intramolecular Kharasch Cyclization

Dihaloesters:



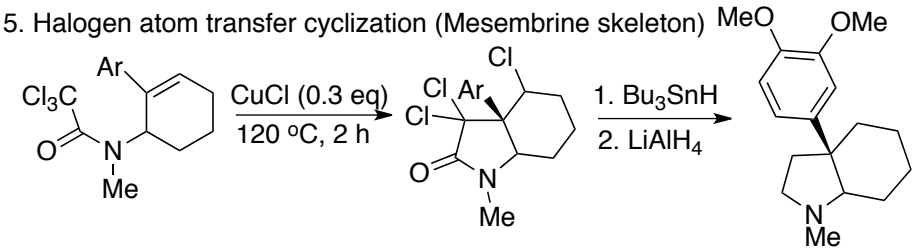
Haloesters:





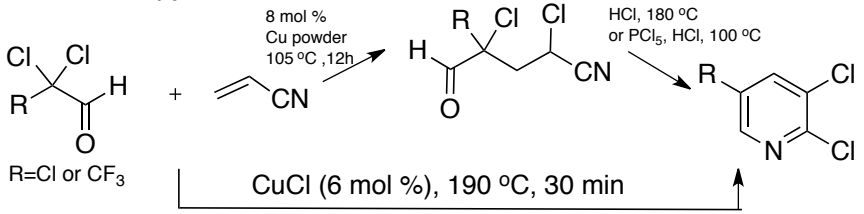
Weinreb, *T* **1988**, *44*, 4671

5. Halogen atom transfer cyclization (Mesembrine skeleton)



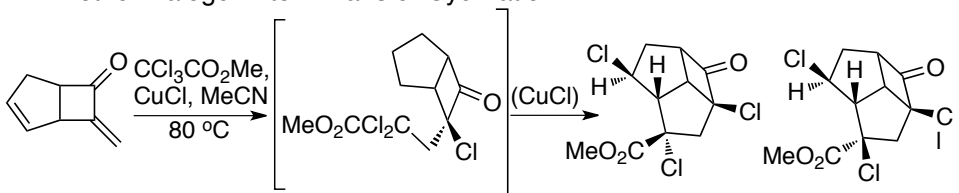
Itoh, *JCS CC* **1985**, 518

6. Chlorinated pyridines



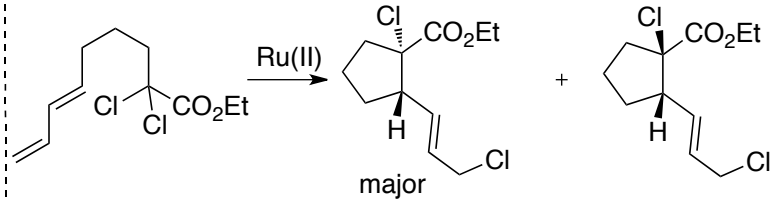
Bellus, *Pure Appl. Chem.* **1985**, *57*, 1827

7. Another Halogen Atom Transfer Cyclization



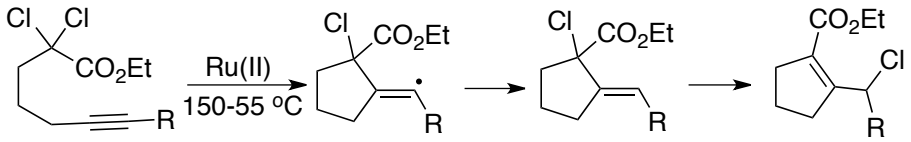
Bellus, *Pure Appl. Chem.* **1985**, *57*, 1827

8. Ru cat. Intramolecular Addition to 1,3-diene

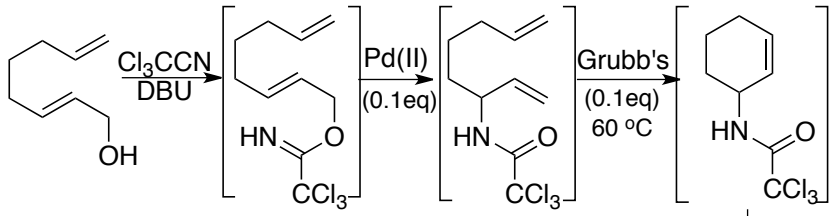


solely 1,4-addition product. *E*-selective

Chem. Rev. **1994**, *94*, 559



9. Synthesis of bicyclic γ-lactams

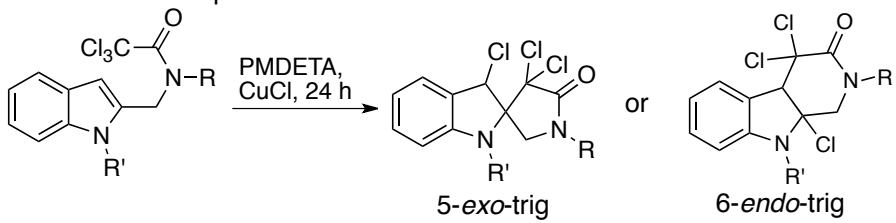


87%

-3-step tandem process
-Overman arrangement of allylic trichloroacetimidates, Grubb's ring closing metathesis and lastly Kharasch cyclization (atom transfer).

Sutherland, *OBC* **2010**, *8*, 3418

10. Formation of Spiroindoles

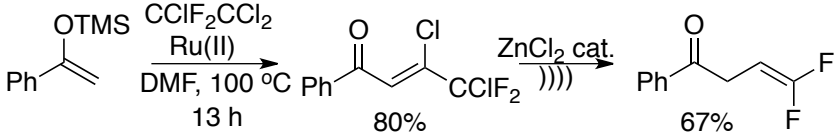


5-*exo*-trig 6-*endo*-trig

-spiroindole formation verified by HMBC analysis

Stevens, *E. JOC* **2010**, 5444

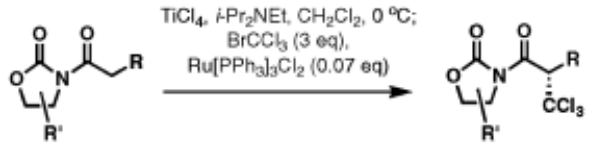
11. (Extension) Synthesis of (γ,γ–difluoroallyl)carbonyl compounds



-good way to make fluorine containing olefins.
-modified addition product due to loss of TMS group and subsequent loss of HCl (g).

Okano, *JOC* **1993**, *58*, 5164

12. (Extension) Radical Trichloromethylation



Zakarian, *JACS* **2010**, *132*, 1482

Not covered in this meeting:
1) Kharasch addition extension to controlled polymerization
2) Any other "Kharasch reaction" missing

Conclusion

- The mechanisms of all 3 Kharasch reactions are not fully elucidated.
- Synthetic applications of each of the 3 reactions covered here are unfortunately limited.
- Good asymmetric allylic oxidations have to be developed.