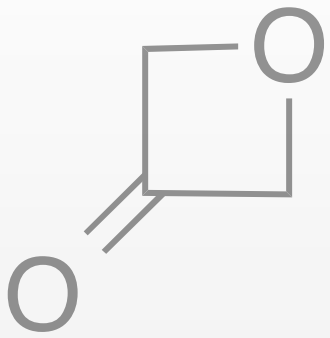
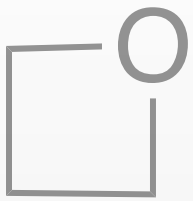
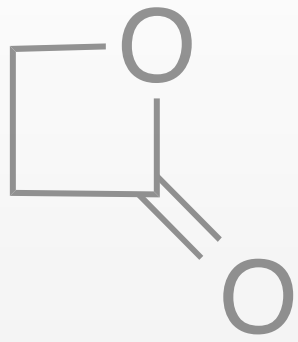




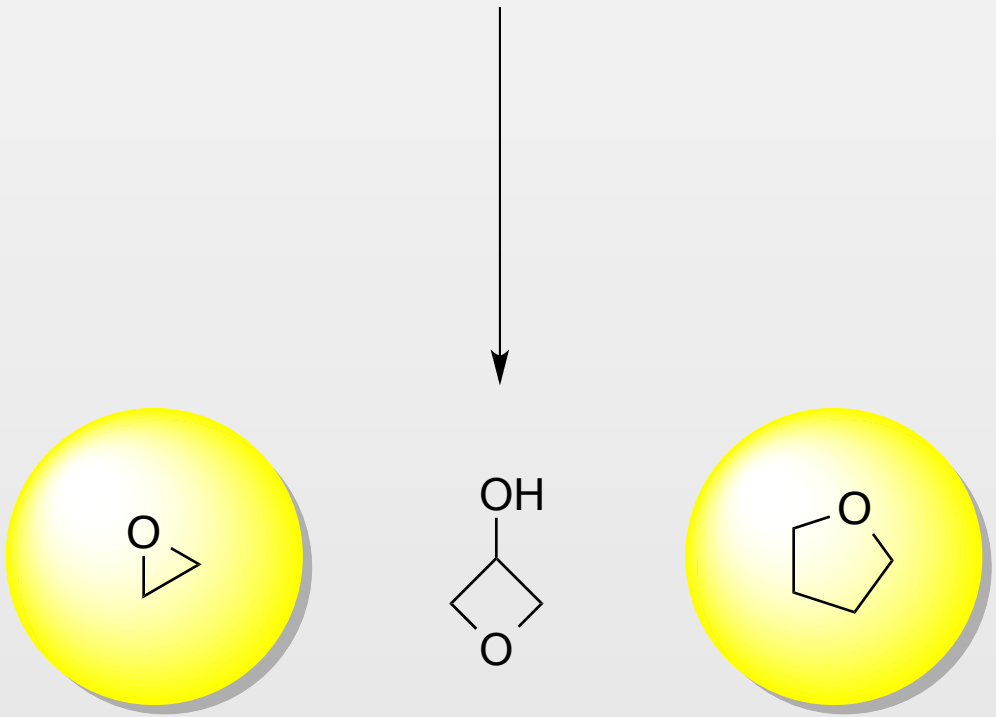
Oxetane

Drug Development, Synthesis & Applications

John Thompson

Dong Group Literature Seminar

September 24th, 2014


O
OH
O
O

Overview

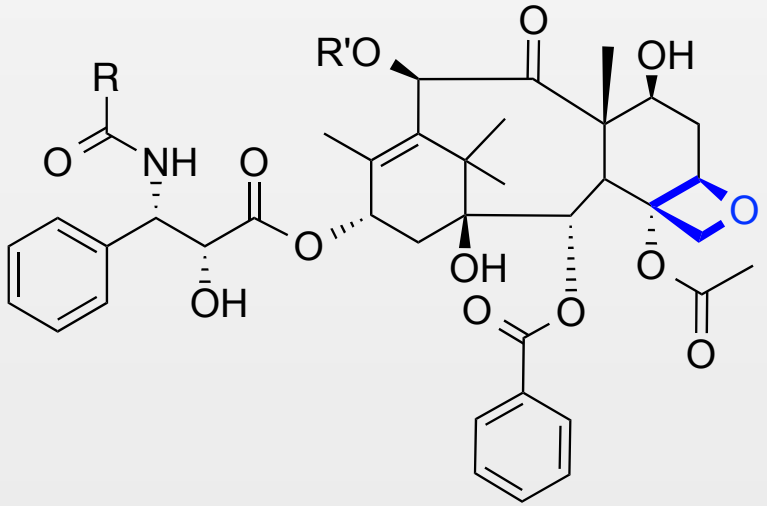
1. Drug Discovery & Pharmaceutical Interest

2. Chemical Properties & Synthesis of Oxetane Rings

3. Applications of Oxetane Rings

    i. Ring Opening for Complex Molecule Synthesis

    ii. Organometallic Chemistry



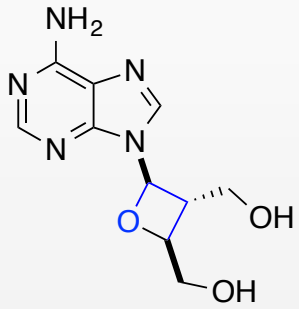
R = Ph, R' = Ac, Paclitaxel (Taxol)
R = O^{t}Bu, R' = H, Taxotere (Docetaxel)

All marketed drugs containing the **oxetane** ring come from the Taxane family of natural products

Computational studies show the oxetane moiety providing:
(1) rigidification of the overall structure
(2) H-Bond acceptor for a threonine-OH group in binding pocket

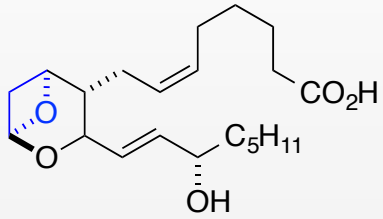
The full extent of the oxetane biological role is still unclear

Other Oxetanes in Natural Products



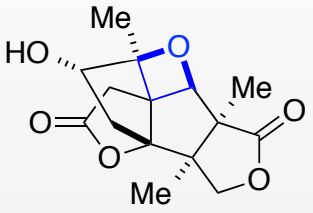
Oxetanocin A

HIV Inhibitor



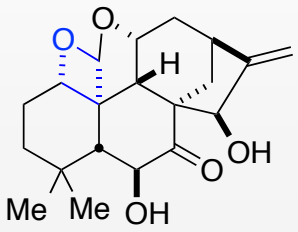
Thromboxane A_2

promotes vasoconstriction/ platelet aggregation



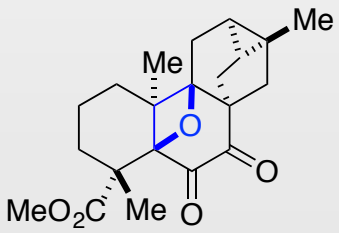
Merrilactone A

stimulates rat neuron growth



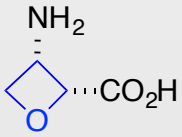
Maoyecrystal I

anti-cancer



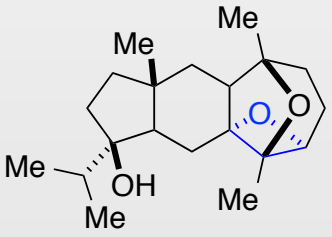
Mitrephorone A

high cytotoxicity



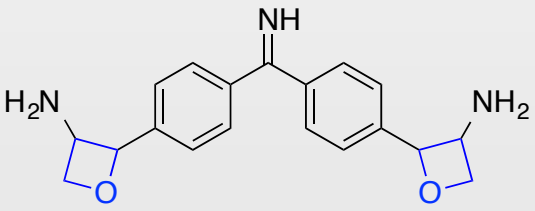
Oxetin

herbicidal / antibacterial



Dictyoxetane

polycyclic diterpenoid



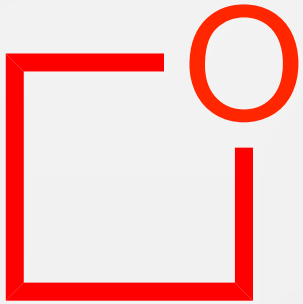
Bradyoxetin

gene regulation in soybean

Angew. Chem. Int. Ed. **2010**, *49*, 9052.

Medicinal Chemistry

- Compound property optimization is a major hurdle for drug discovery
- Small molecules that can be easily added onto and change compound properties in predictable ways are highly valued
- The oxetane ring is a very small molecule whose properties in the past decade have shown far reaching advantages for biological modulation
  - This compound has been neglected due to difficult synthetic access and concerns about chemical and metabolic stability



Key Figures

Erick M. Carreira

ETH Zürich

Klaus Müller

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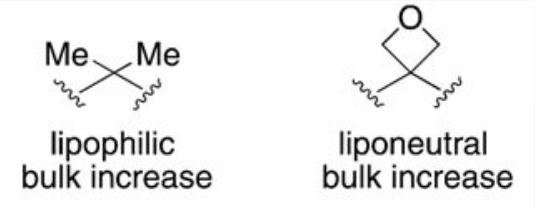
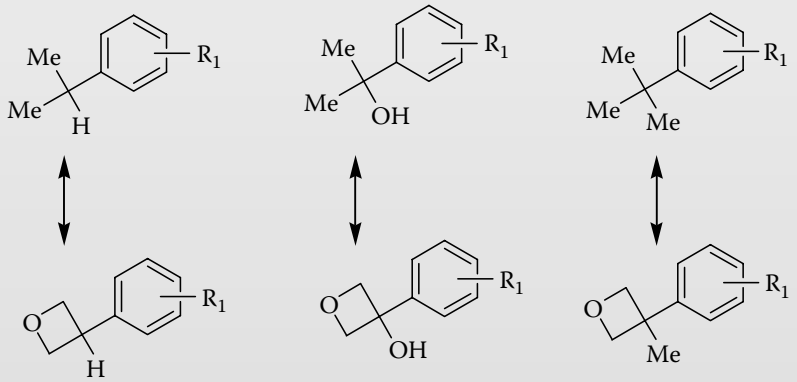
Oxetanes to Replace Common Functionalities

- Replacement of gem-dimethyl groups (t-butyl = methyl substituted gem-dimethyl group)



  - **Why are these groups so common in drugs?** Steric hindrance prevents chemical or metabolic liabilities of nearby functional groups
    - More than 10% of all launched drugs contain at least one gem-dimethyl group
  - However, replacing **H** for **Me** increases lipophilicity (may have adverse effects)

- Oxetane & gem-dimethyl groups have near equivalent partial molar volumes in water
  - Leads to geometrically similar structures with markedly different pharmacokinetic properties
  - World Drug Index (2008)
    - 714 molecules with t-butyl groups
    - 69 in market



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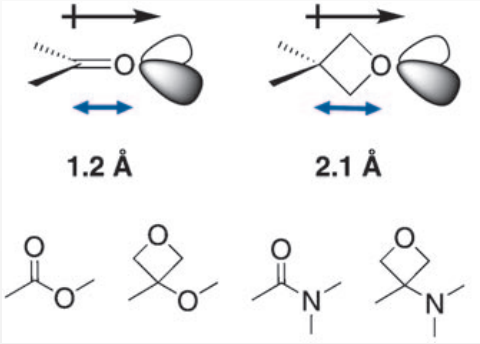
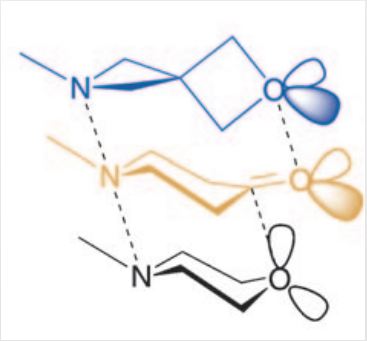
Oxetanes to Replace Common Functionalities

- **Carbonyl Surrogate**
  - Aldehydes (sterically accessible Michael acceptors) or acyl halides are precluded from drug discovery



- More stable groups: esters, ketones, and amides have liabilities related
  - many enzymes can hydrolyze
- Alpha-carbonyl compounds ease of deprotonation can destroy stereocenters.



- **Exchange spirocyclic oxetane for morpholine**
  - 17 marketed drugs with morpholine units
  - Majority all degrade

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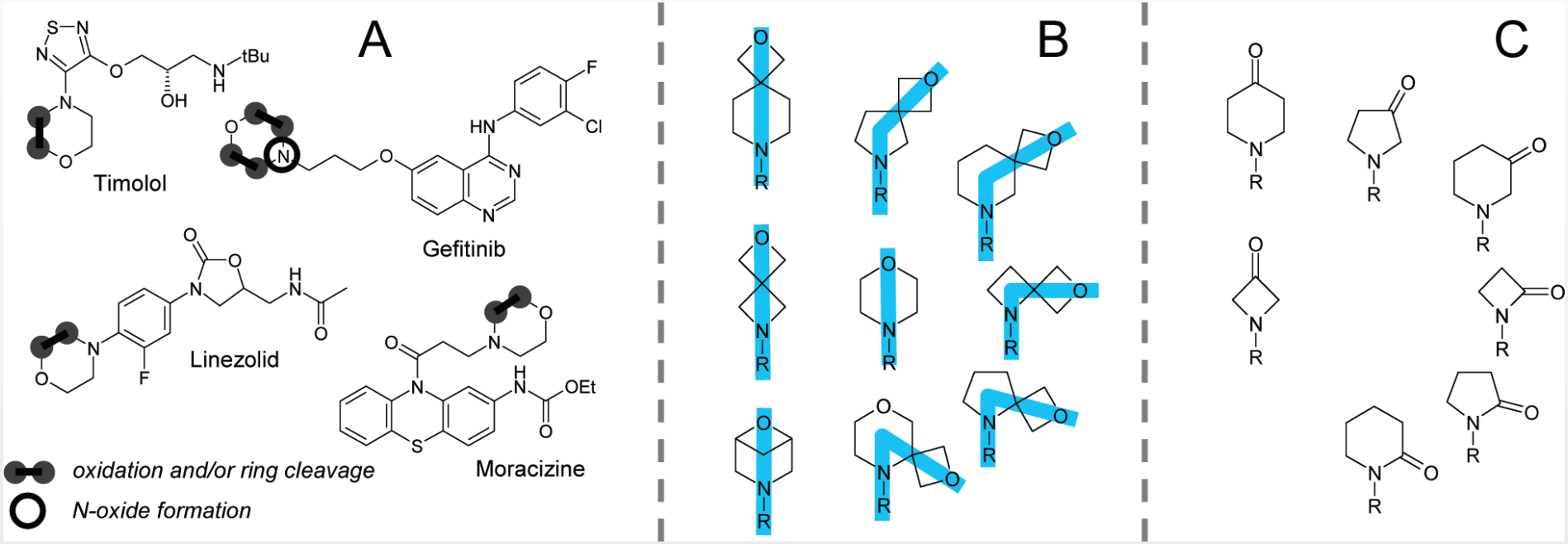
Oxetanes to Replace Morpholine

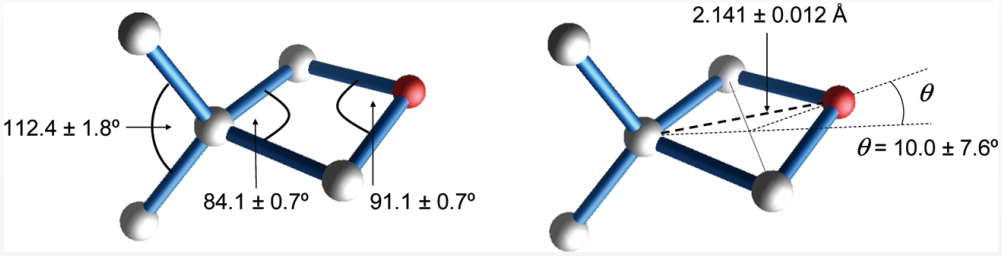


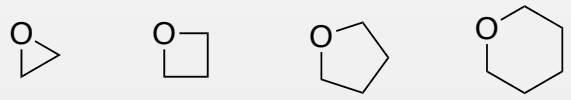
Replacement of gem-dimethyls, carbonyls, and morpholine units for oxetane derivatives in several tests all show higher metabolic stability

J. Med. Chem. **2010**, *53*, 3227.

Chemical Properties

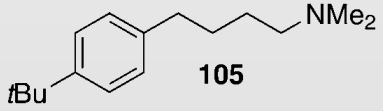
- Structure
  - Wider C-C-C bond
  - Slight puckering
  - Gas phase suggests planar
  - 3-substitution increases puckering (due to eclipsing interactions
  - Strain energy is 107 kcal/mol





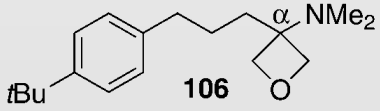
Ring Strain (kJ/mol)	114	107	23	5

- *Achiral when substituted on 3-position*
- **Solubility**
  - Increases soluble up to 4000x than a gem-dimethyl derivative
  - Changes polarity of molecules



105

Sol. <1



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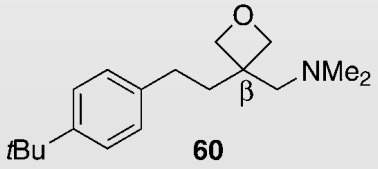
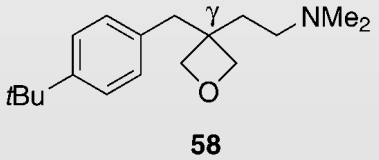
57



60

Sol. 25



58

4100

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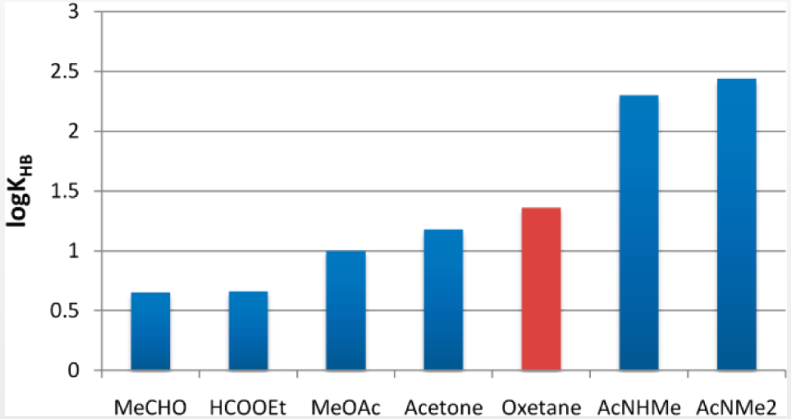
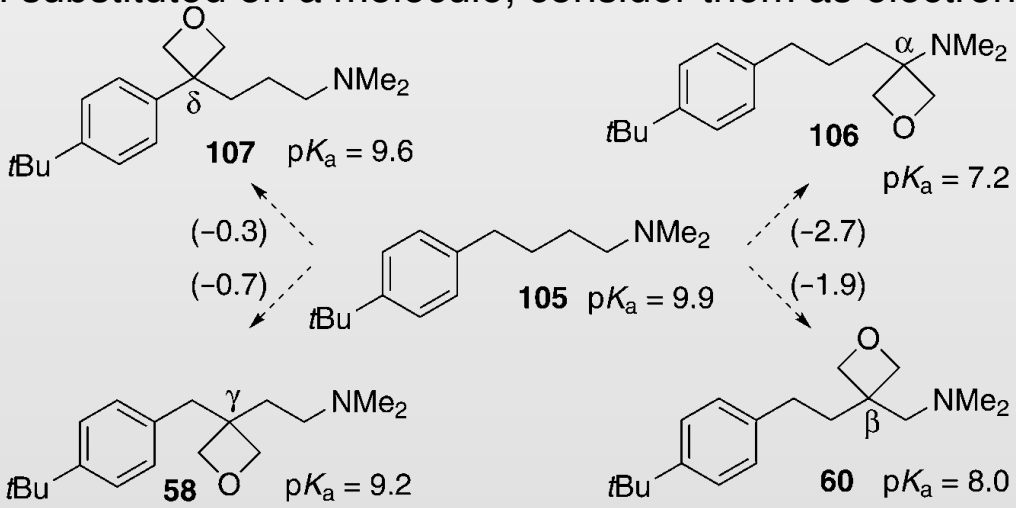
Chemical Properties

- Oxetanes have most lewis basic oxygen of cyclic ethers (pKa = 2-4)
- H-bond acceptor
  - Compete with aldehydes/ketones/esters



- When substituted on a molecule, consider them as electron withdrawing groups



Angew. Chem. Int. Ed. **2010**, *49*, 9052.

Stability under Common Chemical Practices

- **Stable under basic conditions**
  - Ring opening very slow
  - LAH requires high temperatures and long reaction times to reduce ring
  - Organolithium/grignards require elevated temperatures and lewis acids to open

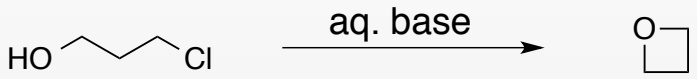
- **Acidic conditions**
  - Non-disubstituted oxetanes are stable above pH 1
  - 3,3-disubstituted oxetanes stable even at pH 1
  - Concentrated acid is problematic
    - Acid-cat ring opening in dioxane with H_2SO_4 or $HClO_4$ as fast as ethylene oxide
  - Strong Lewis acids coordinate well to promote transformations

- *Alkaline and weak acid stability allows oxetanes to be introduced early on in synthetic routes*

J. Med. Chem. **2010**, *53*, 3227.

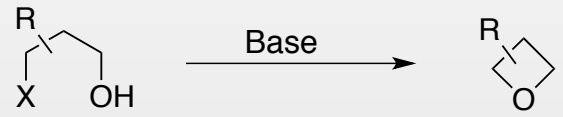
Synthetic Routes to Oxetanes

- First discovered in 1878 by Reboul

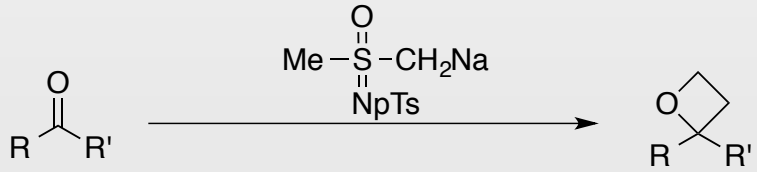


Ann. Chim. **1878**, *14*, 496.

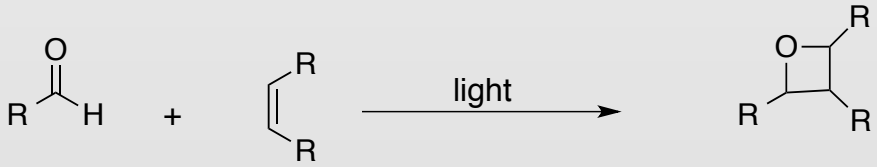
- Most Common Routes:
  1. Intramolecular Williamson-Ether synthesis



  2. Sulfonium ylides to aldehydes

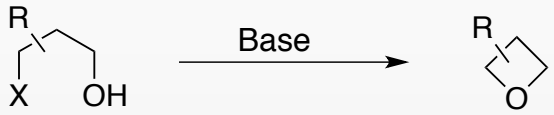


  3. Paternó-Büchi cycloaddition

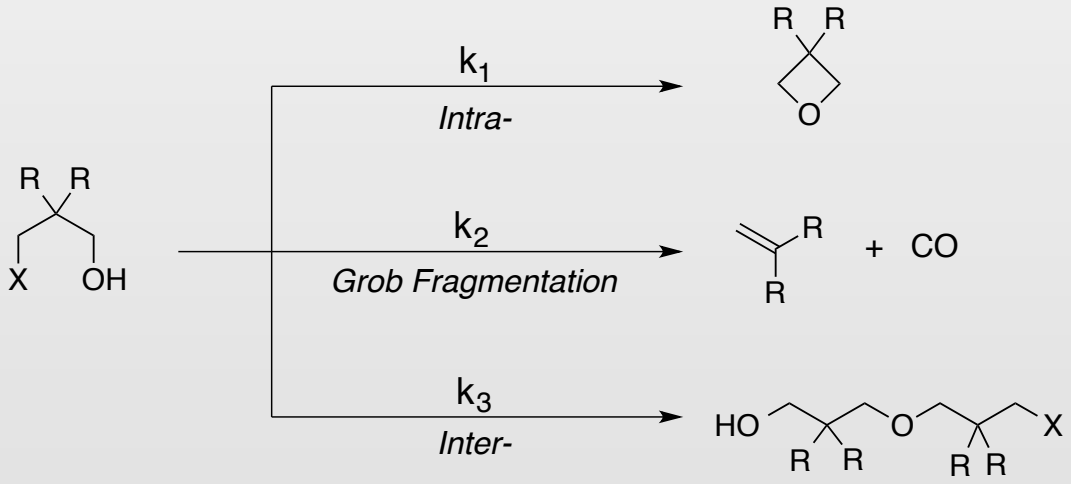


Angew. Chem. Int. Ed. **2010**, *49*, 9052.

1. Intramolecular Williamson-Ether synthesis



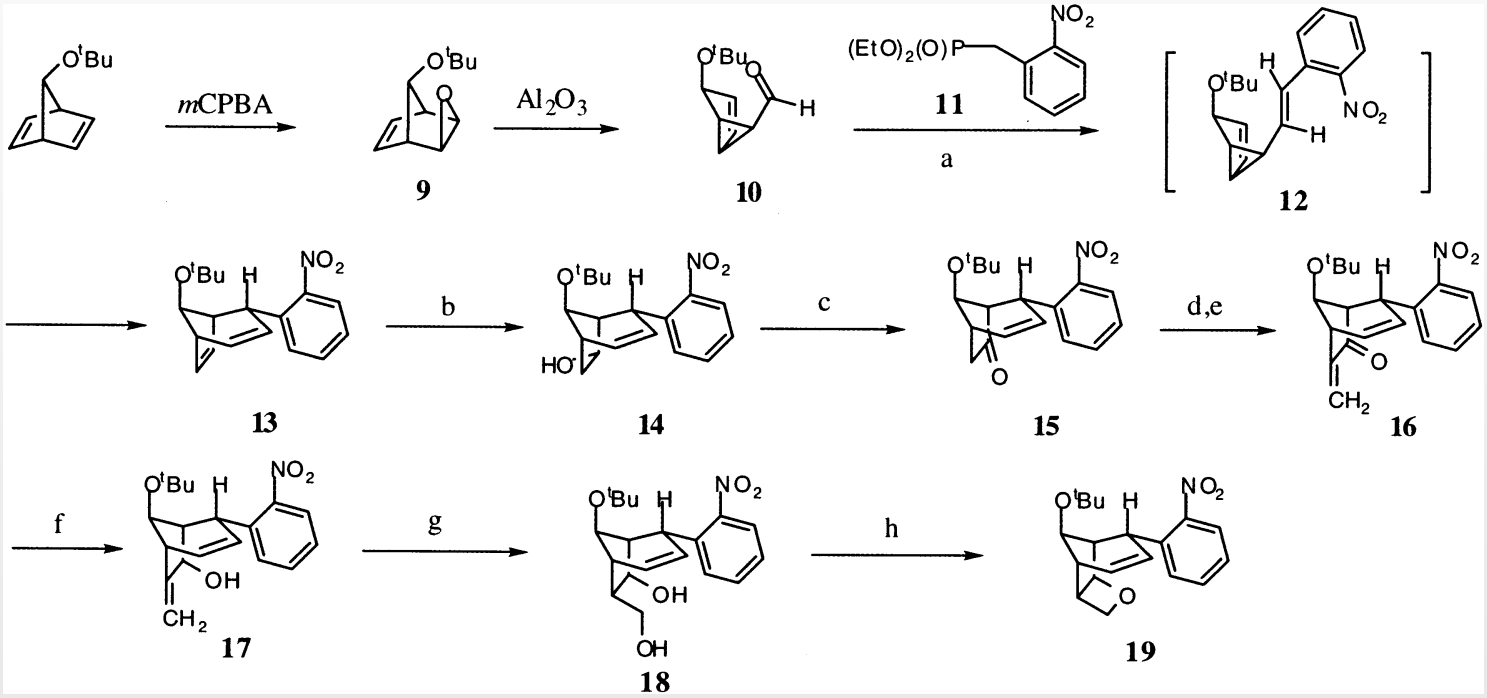
- Most general approach
  - Most widely used and applicable
- Difficult to predict substrate success
  - Chloro/bromo substrates can differ greatly
- By-product formation is plentiful and hard to inhibit

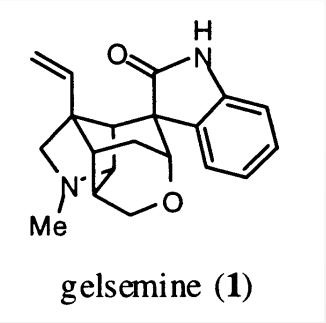


J. Med. Chem. **2010**, *53*, 3227.

1. Intramolecular Williamson-Ether synthesis

- Danishefsky Total Synthesis of Gelsemine



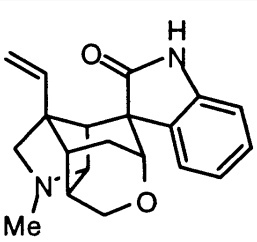


Scheme 2. Synthesis of the oxetane ring. *Reagents and conditions*: (a) **11**, NaOMe, DMF, 0°C, 74%; (b) $BH_2Cl{\cdot}DMS$, Et_2O, 0°C; $NaOH/H_2O_2$, 77%, +7% regioisomer;[8] (c) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, 98.7%; (d) LiHMDS, TESCl, Et_3N, THF, −78 to 0°C; Eschenmoser's salt, CH_2Cl_2, 91%; (e) MeI, CH_2Cl_2/Et_2O; Al_2O_3, CH_2Cl_2, 95%; (f) $NaBH_4$, $CeCl_3{\cdot}7H_2O$, MeOH, 99%; (g) 9-BBN dimer, THF; $NaOH/H_2O_2$, 88%; (h) MsCl, Et_3N, CH_2Cl_2, −78°C; NaHMDS, THF, −78°C, 91%. DMS = dimethyl sulfide; HMDS = hexamethyldisilazane; TESCl = chlorotriethylsilane; Eschenmoser's salt = $(CH_3)_2N{=}CH_2I$; 9-BBN = 9-borabicyclo[3.3.1]-nonane.

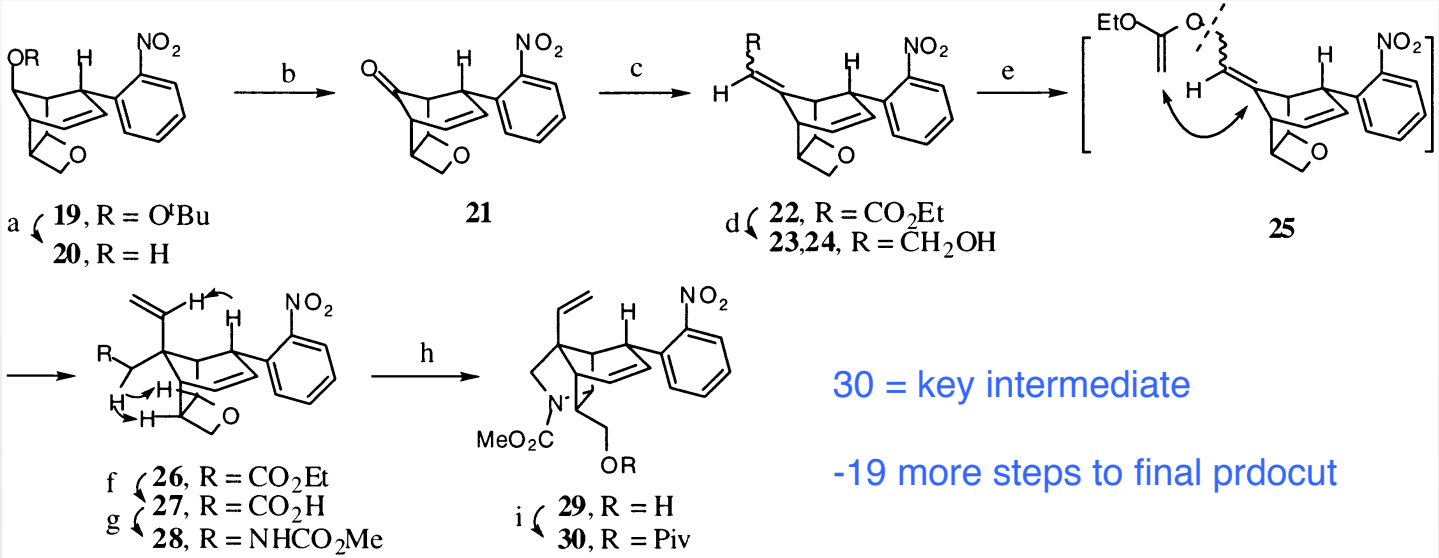
Danishefsky. *Tett. Lett.* **2002**, *43*, 545.

1. Intramolecular Williamson-Ether synthesis

- Oxetane moiety used to store molecular functionality



gelsemine (**1**)



30 = key intermediate

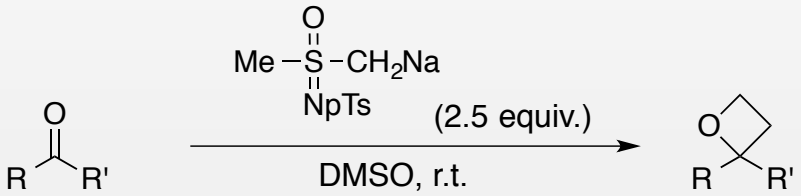
-19 more steps to final prdocut

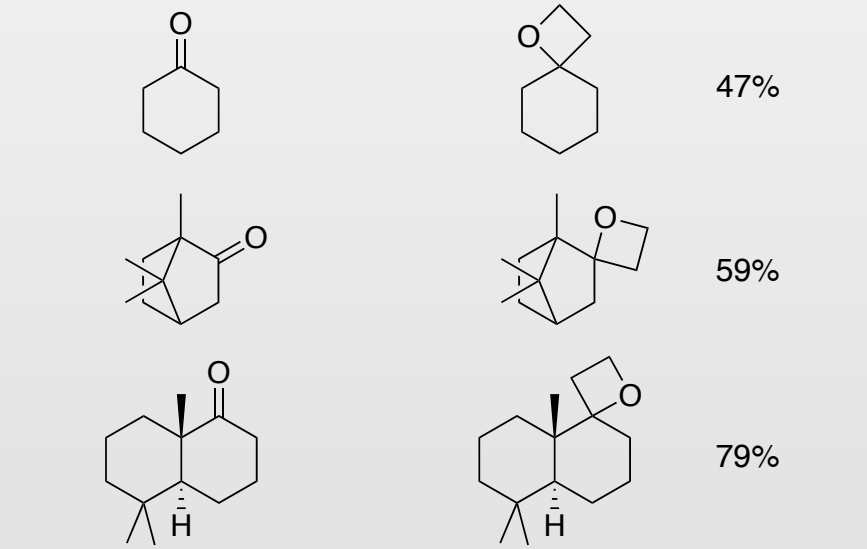
Scheme 3. Construction of quaternary C7 and the pyrollidine ring. *Reagents and conditions*: (a) TFA/CH_2Cl_2, 0°C, 81%; (b) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, −78°C, 81%; (c) triethylphosphonoacetate, NaH, THF, 0°C, 3:2, 92%; (d) DIBAL, CH_2Cl_2, −78°C, 88%; (e) cat. propionic acid, $H_3CC(OEt)_3$, toluene, reflux, 64%; (f) NaOH/THF/EtOH, 86%; (g) diphenylphosphoryl azide, Et_3N, benzene, 25°C, reflux; MeOH, reflux; 89%; (h) $BF_3{\cdot}Et_2O$, CH_2Cl_2, −78 to 12°C, 64%; (i) PivCl, Et_3N, DMAP, CH_2Cl_2, 0–25°C, 92%. DIBAL = diisobutylaluminum hydride; PivCl = 2,2,2-trimethylacetyl chloride; DMAP = *N*,*N*-dimethylaminopyridine.

Danishefsky. *Tett. Lett.* **2002**, *43*, 545.

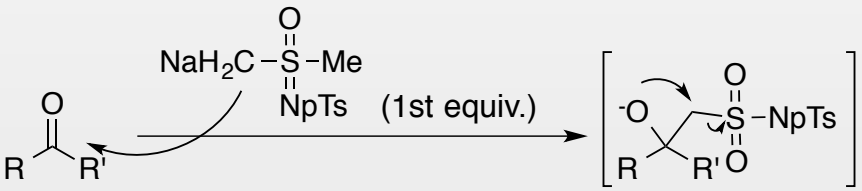
2. Sulfonium Ylides

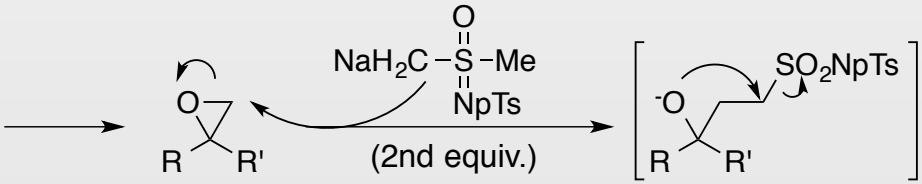
- One-pot conversion of aldehydes/ketones to 2-substited oxetanes
- Variant of Corey-Chaykovsky Reaction

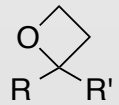




Proposed Mechanism



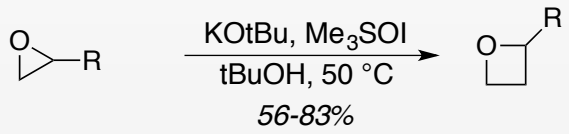




Welch. Rao. *JACS* **1979**, *101*, 6135.

2. Sulfonium Ylides

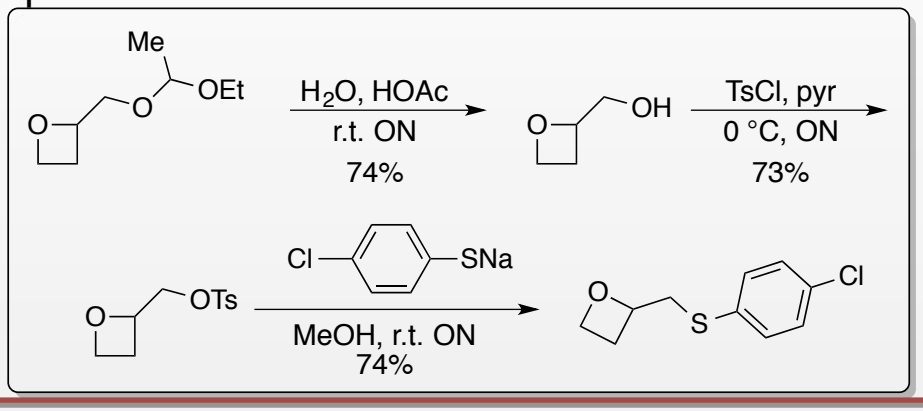
- Start with epoxides to form more complicated oxetanes

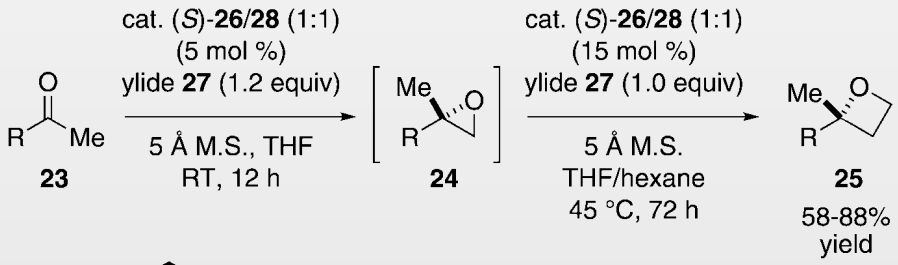


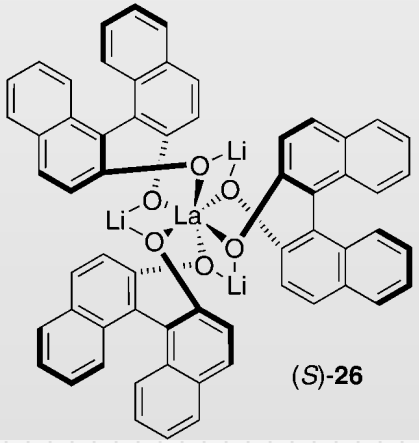
R = CH_2OH, $C_2H_4CH{=}CH_2$

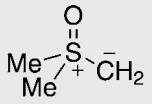
very tolerant

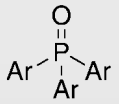
Fitton. *Synthesis* **1987**, *12*, 1140.

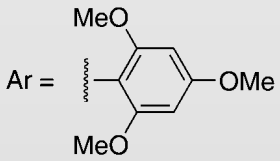







27


28



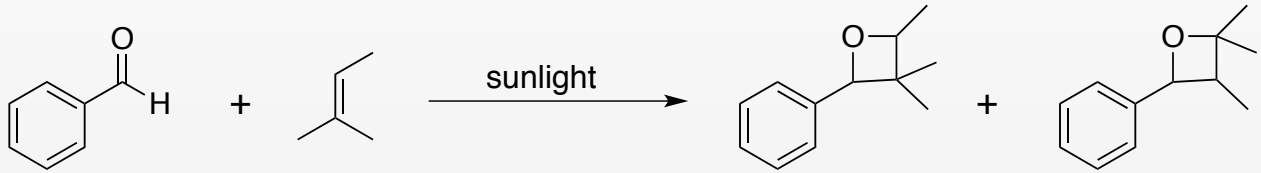
Chiral Version

- Can work by direct conversion but lower yields
- 2 steps: increases rate of epoxide opening reaction
- 99.5% ee (2nd step works as resolution process)

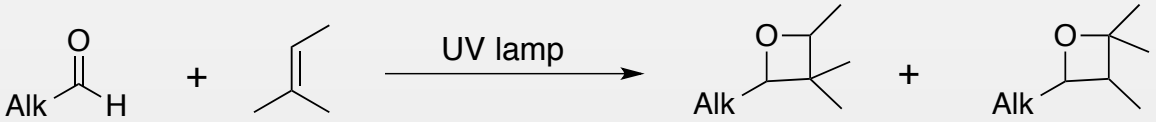
Shibasaki. *Angew. Chem. Int. Ed.* **2009**, *48*, 1677.

3. Paternó-Büchi Cycloaddition

- Reaction first discovered by Emanuele Paternò in 1909 – Structure unconfirmed



- Re-examined in 1954 by George Büchi – extended reaction



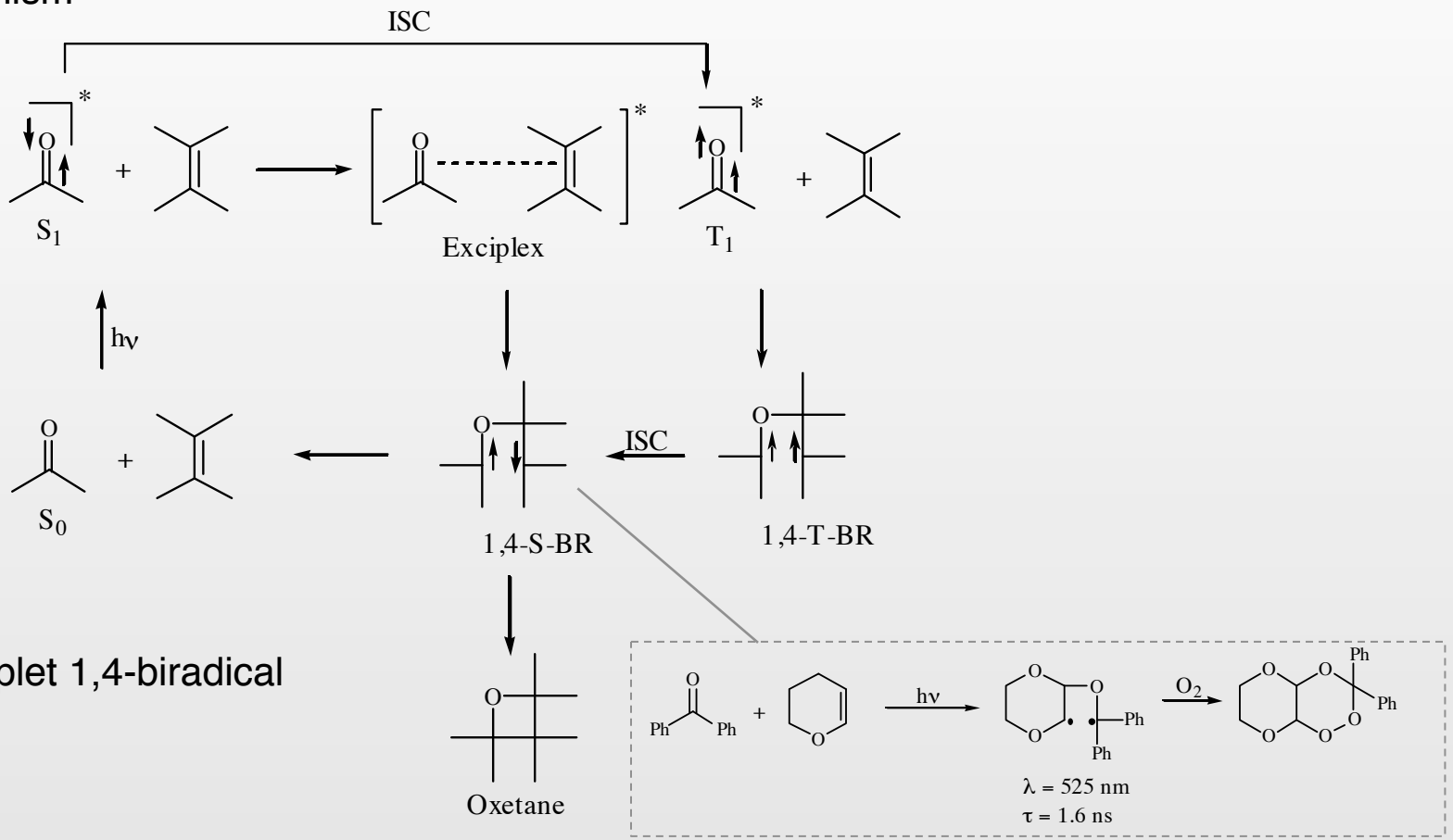
- Reaction promoted by UV light
  - Carbonyl species is usually the light absorbing species

- Access to substituted oxetanes

Paterno *Gazz. Chim. Ital.* **1909**, *39*, 341
Büchi. *JACS* **1954**, *76*, 4327.

3. Paternó-Büchi Cycloaddition

- Mechanism

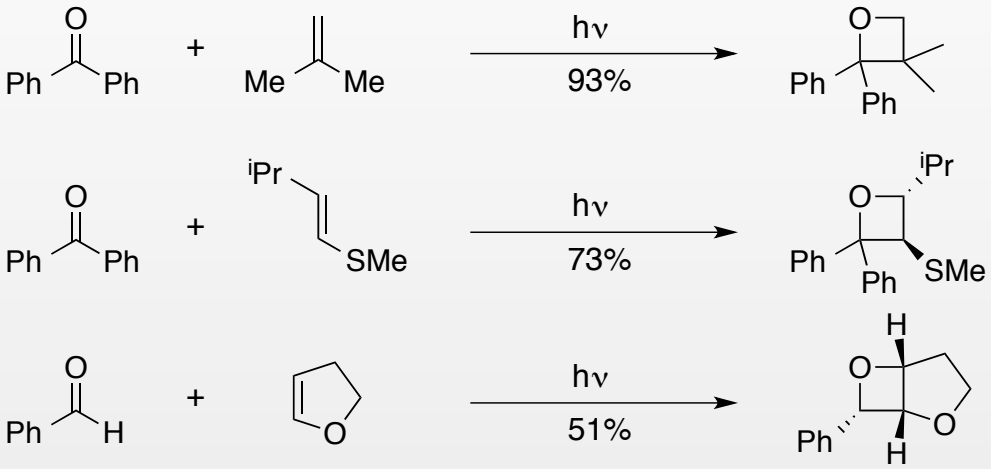


  - Triplet 1,4-biradical

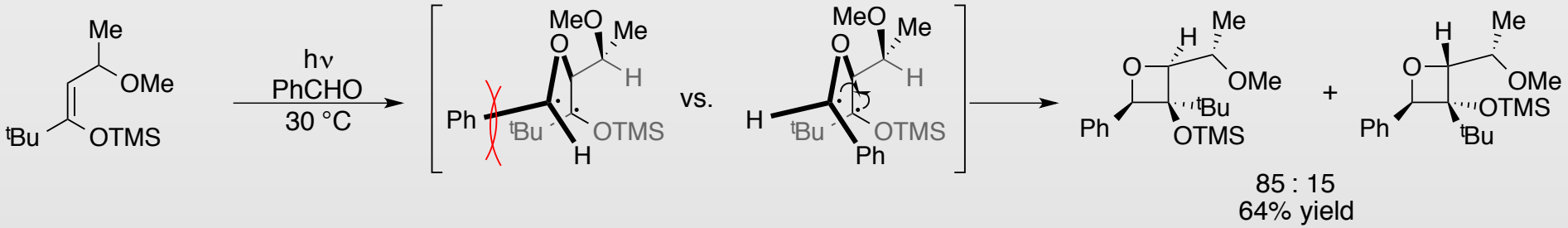
Koecky. *Organic Photochemistry, A Visual Approach.* VCH Publishers, New York **1992**, *126.*

3. Paternó-Büchi Cycloaddition

- Most stable diradicals favored, as well as stereochemical approach of radicals



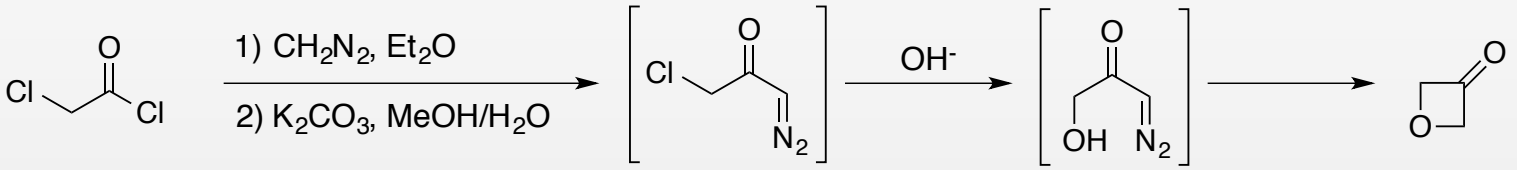
- Reaction commonly employed for chiral product synthesis



Bach. *Angew. Chem. Int. Ed.* **1995**, *34*, 2271.
Bach. *JACS* **1997**, *119*, 2437.

Most Targeted Oxetane

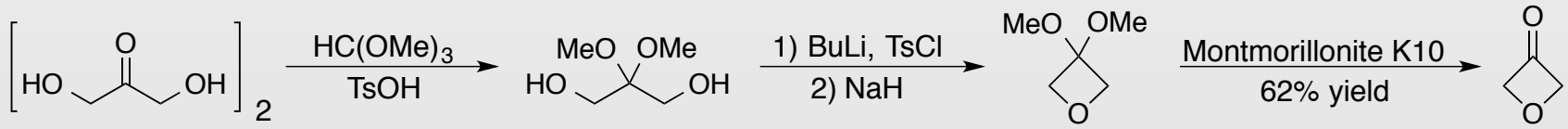
- Functionalization of oxetanes is difficult, therefore oxetan-3-one is common starting point
- First synthesis by Marshall in 1952



  - Converted to hydrazone for isolation

Marshall. *J. Chem. Soc.* **1952**, 467.

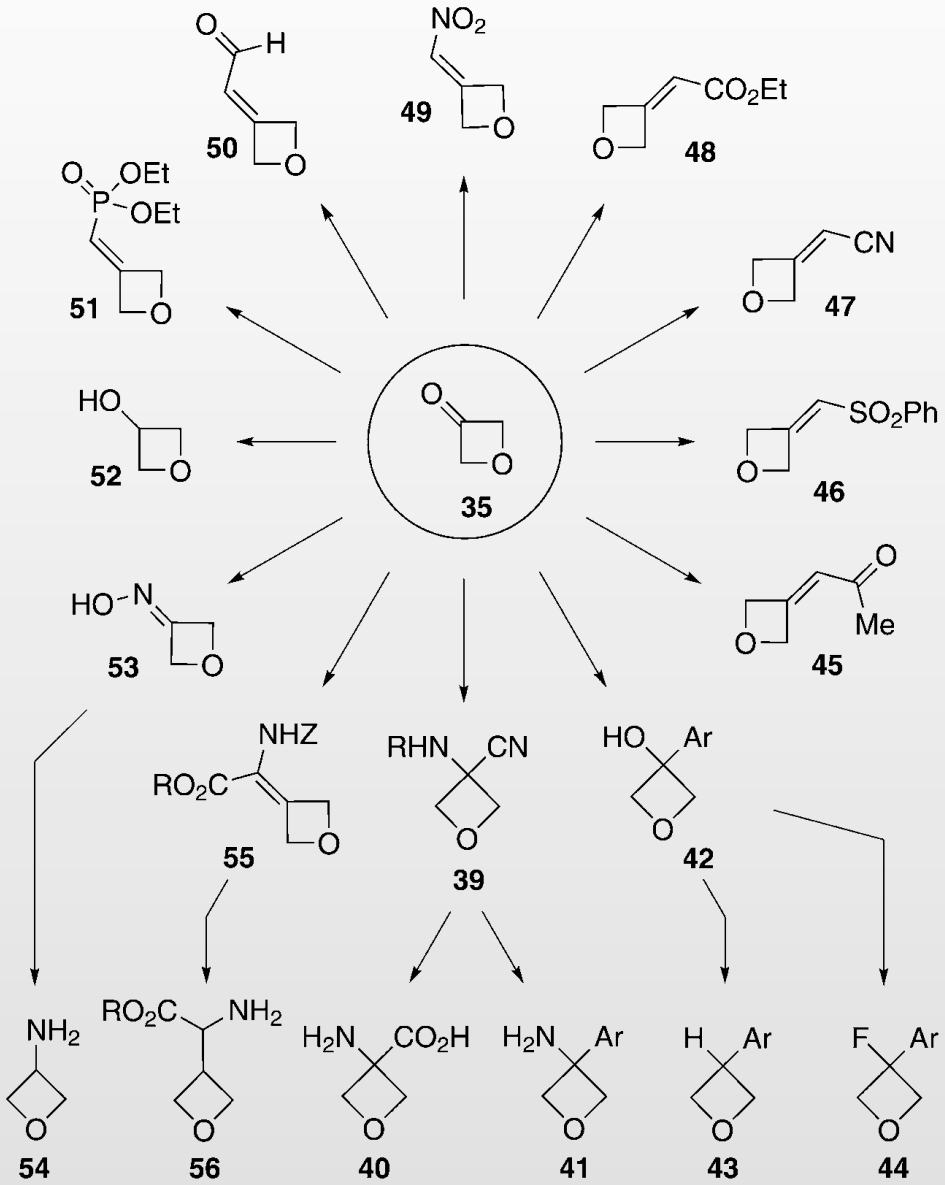
- Many procedures require prep GC to isolate pure
- General route established by Carreira



3 steps: 33% yield

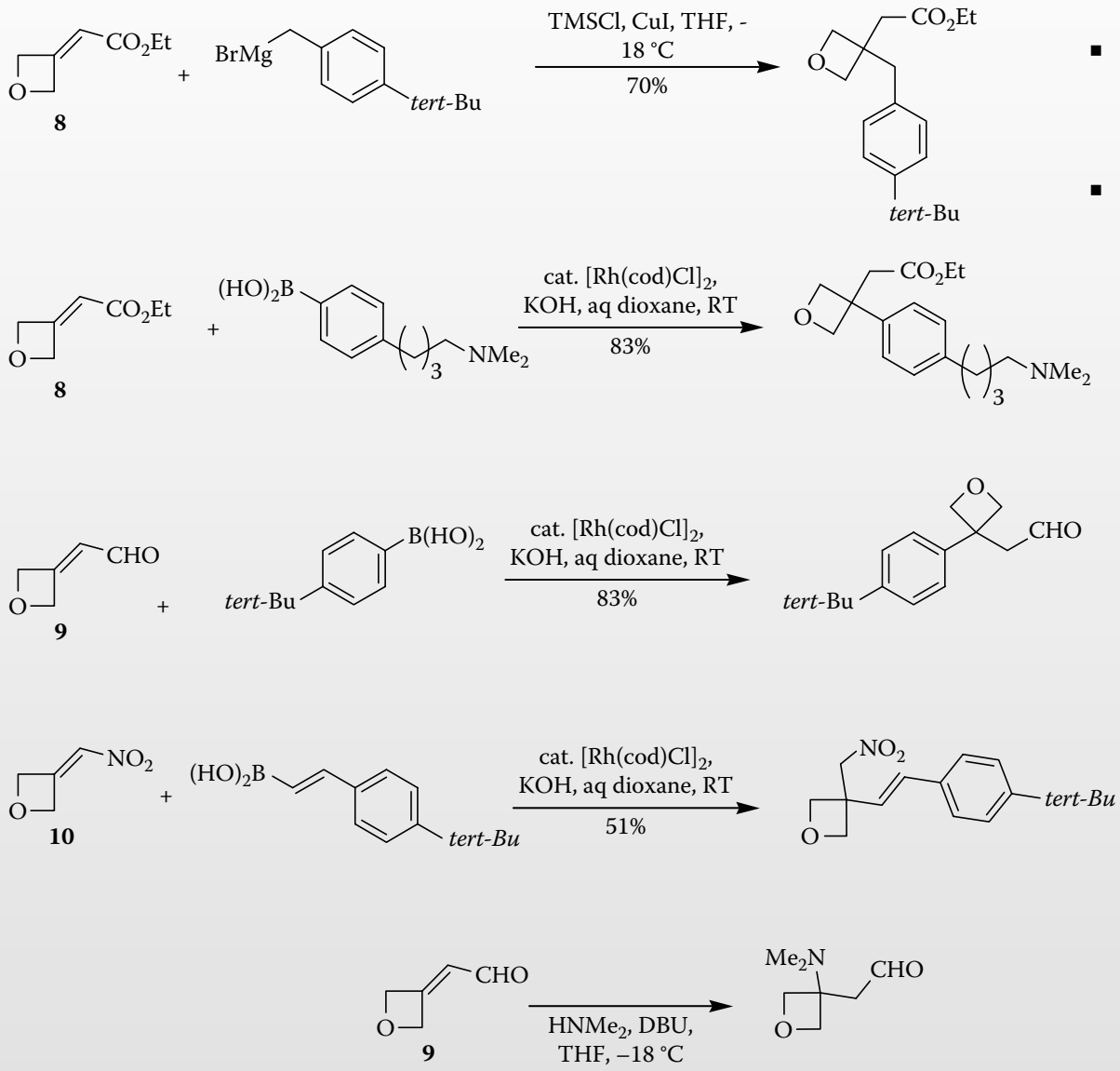
Muller, K.; Carreira, E.. *Angew. Chem. Int. Ed.* **2006**, *118*, 7900.

Oxetan-3-one Applications



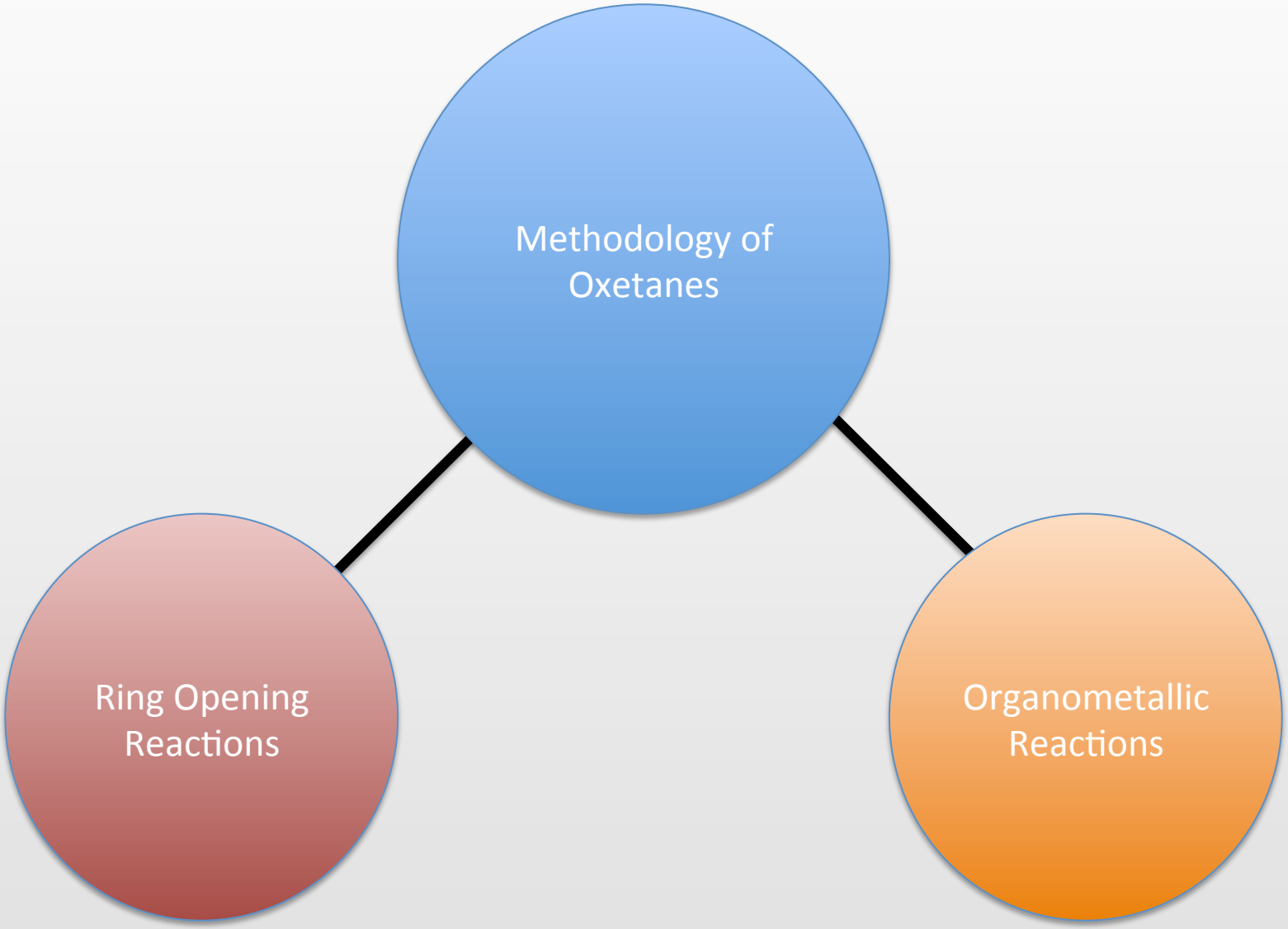
Angew. Chem. Int. Ed. **2010**, *49*, 9052.

Oxetan-3-one Applications

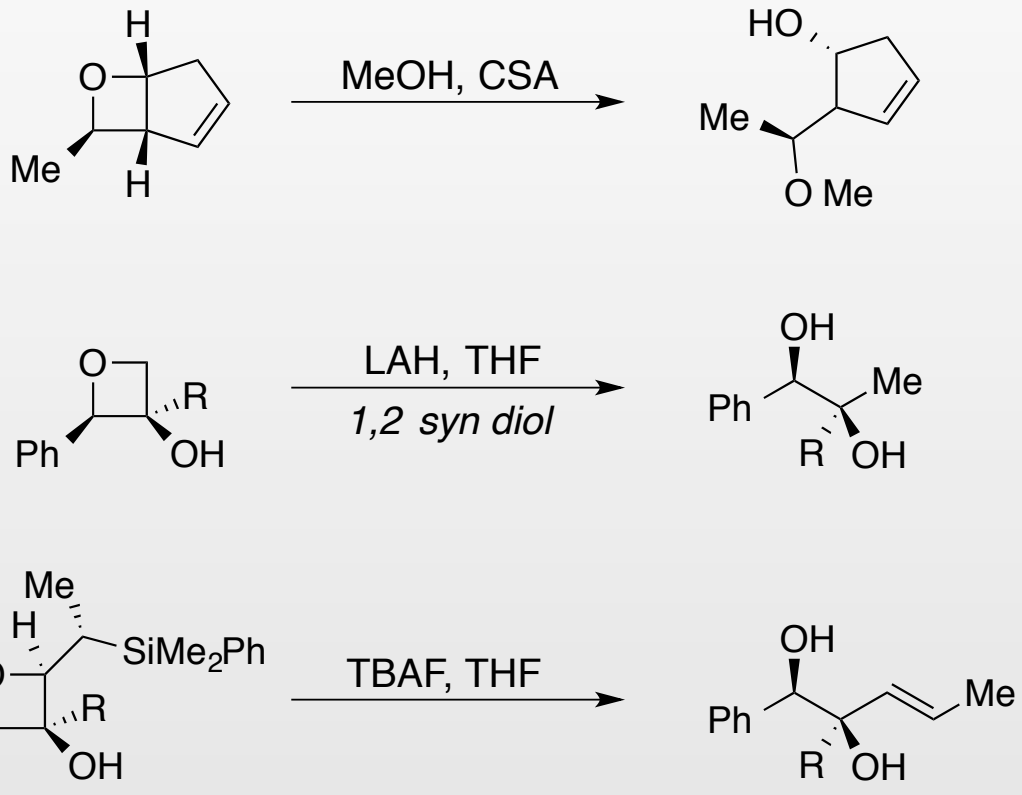


- Methylene compounds seem very stable
- Applicable to add in late-stage functionalization of molecules

Gadamasetti and Braish. *Process Chemistry in the Pharmaceutical Industry* **2008**, Vol 2, CRC Press.


Methodology of Oxetanes
Ring Opening Reactions
Organometallic Reactions

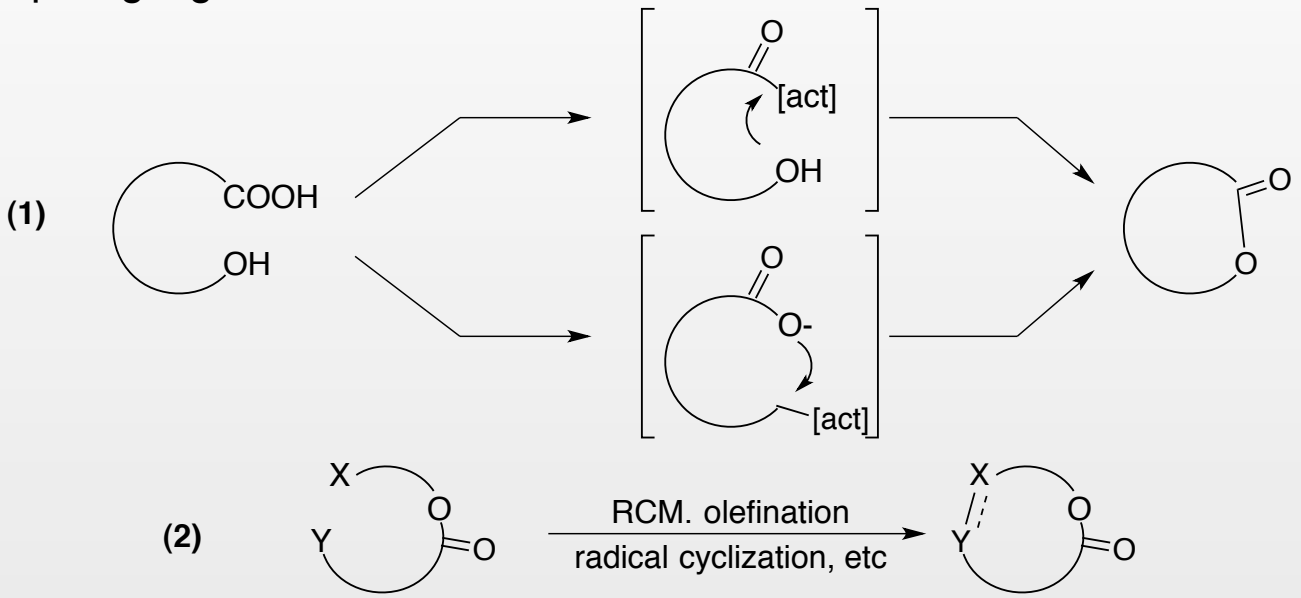
Simple Acid and Base Ring Opening



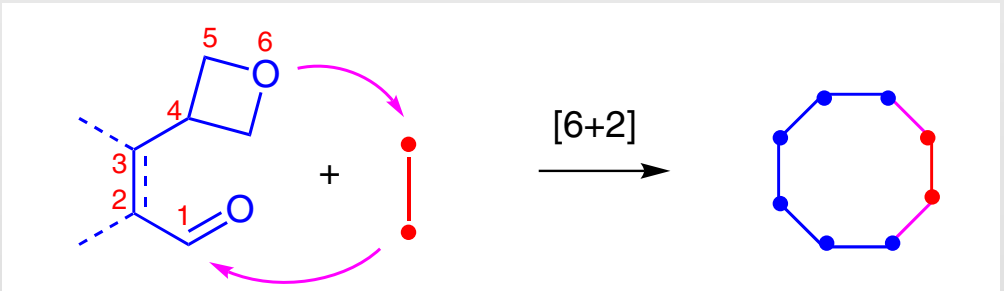
Bach. *Liebigs Ann.* **1997**, 1627.
Bach. *Synthesis* **1998**, 683.

Expansion to Medium Sized Lactone Rings

- Most approaches start from linear substrate and must overcome unfavorable ring closing
  - Requiring high dilution and slow addition

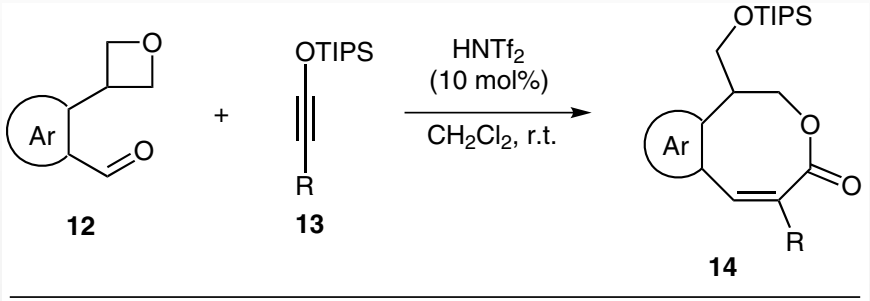


- Amphoteric molecule could cyclize with dipolarophiles
  - (electrophilic and nucleophilic moieties)

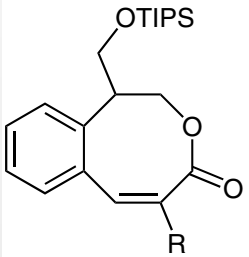


Sun, J. *Angew. Chem. Int. Ed.* **2012**, *51*, 6209.

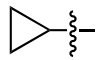
Expansion to Medium Sized Lactone Rings



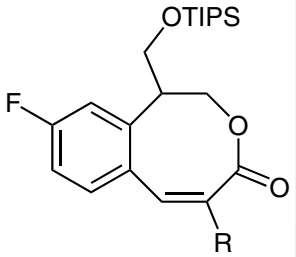
12 **13** **14**



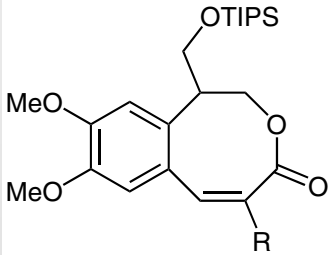
R:
n-Bu (**14a**), 71%
t-Bu (**14b**), 60%
n-Oct (**14c**), 64%
Ph (**14d**), 47%



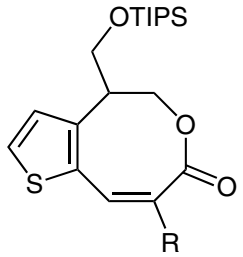
(**14e**), 62%



R:
n-Bu (**14f**), 70%
t-Bu (**14g**), 87%
n-Oct (**14h**), 74%
$Ph(CH_2)_3$ (**14i**), 51%
$TIPSO(CH_2)_3$ (**14j**), 71%

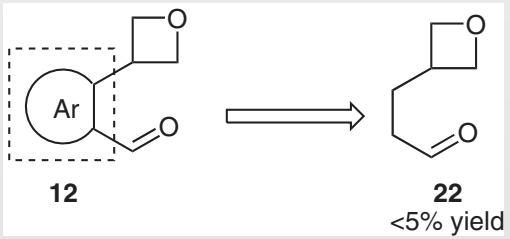


R:
n-Bu (**14k**), 47%
t-Bu (**14l**), 52%



R:
n-Bu (**14m**), 49%
t-Bu (**14n**), 53%
Ph (**14o**), 48%

- One of the first intermolecular medium ring
- Acid catalyst screening:
  - $HNTf_2$ was best
  - TfOH / AuOTf / $AuCl_3$ / $AgNTf_2$ worked in lower yields
  - TsOH / MsOH / TFA trace yields
- One large limitation
  - Requires aryl backbone



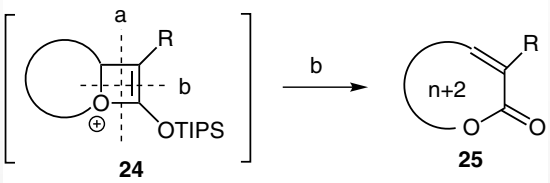
12 **22**
<5% yield

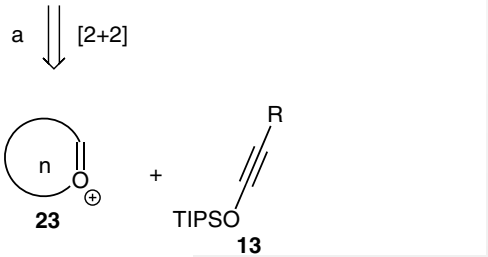
- **Mechanism is question!**

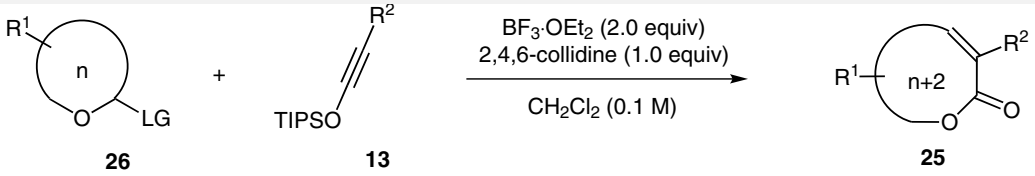
Sun, J. *Angew. Chem. Int. Ed.* **2012**, *51*, 6209.

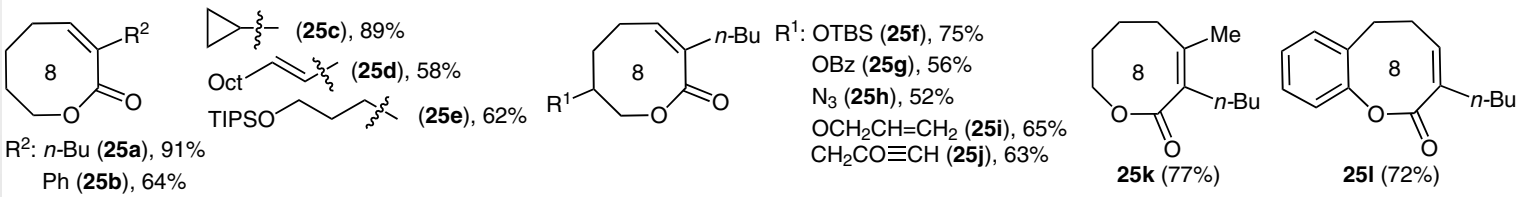
Improved Access to Large Lactones

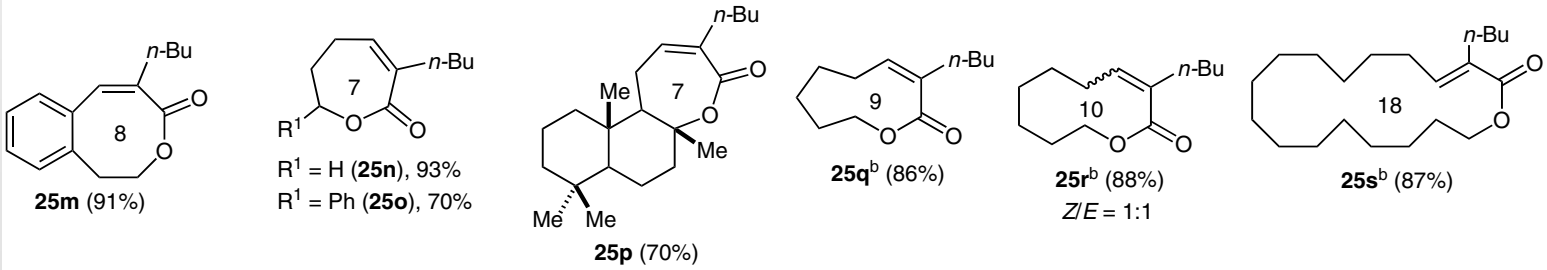
- Needed to fix aryl linker substrate limitation
  - Form various sizes of rings both large and small
  - Does not need any forced configuration







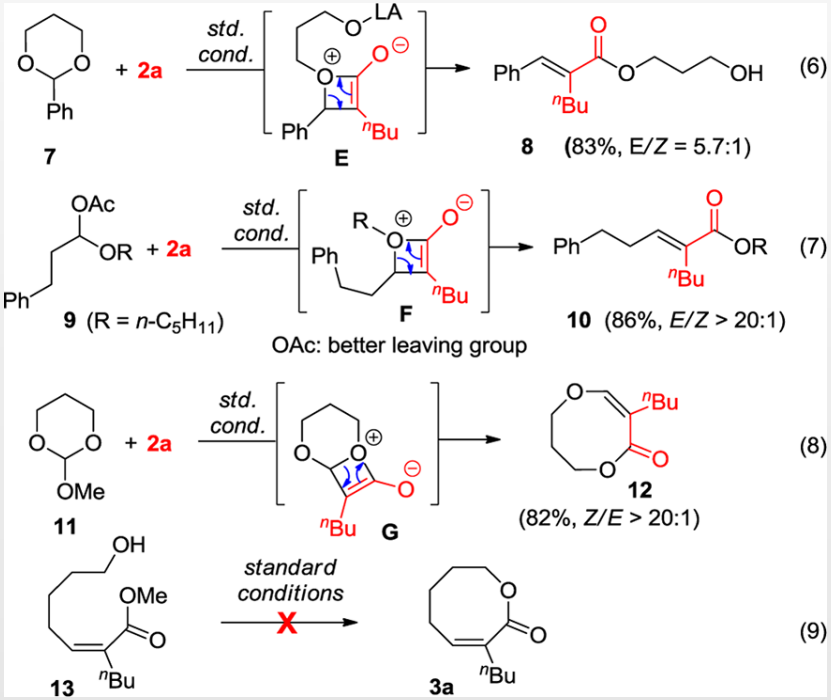




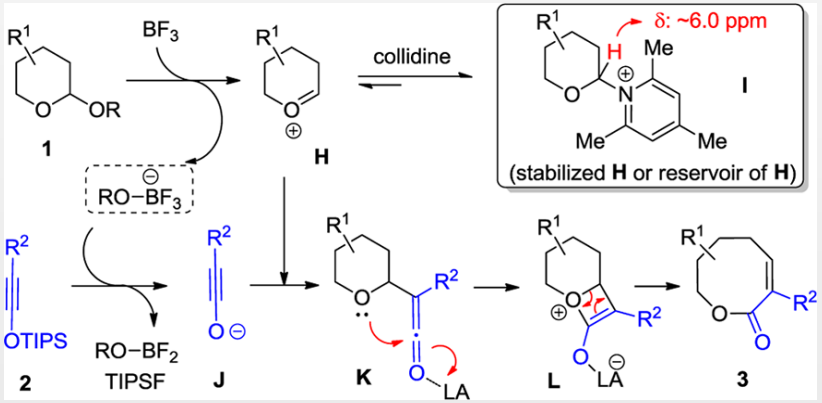
Sun, J. *JACS* **2013**, *135*, 4680.

Improved Access to Large Lactones

- Utilized linear & cyclic control experiments to unravel the mechanism
- Key intermediate is oxetenium species



Scheme 3. Proposed Mechanism



- [2+2] may be through stepwise ketene species
- Collidine is proposed to stabilize the highly unstable oxocarbenium

Sun, J. *JACS* **2013**, *135*, 4680.

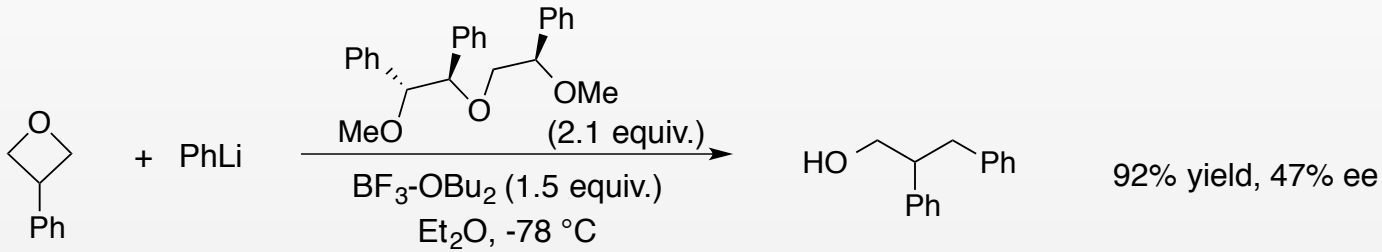
Catalytic Asymmetric Ring Opening

- **3-Substituted oxetanes are prochiral**
  - Ring opening can lead to chiral products (desymmetrization)
  - Form chiral, high substituted 3 carbon building blocks

- **Challenges**:
  - Alcohol product is competing nucleophile – limiting strong nucleophiles for opening or internal nucleophiles
  - Chiral lewis acid coordination is remote to the generated chiral center

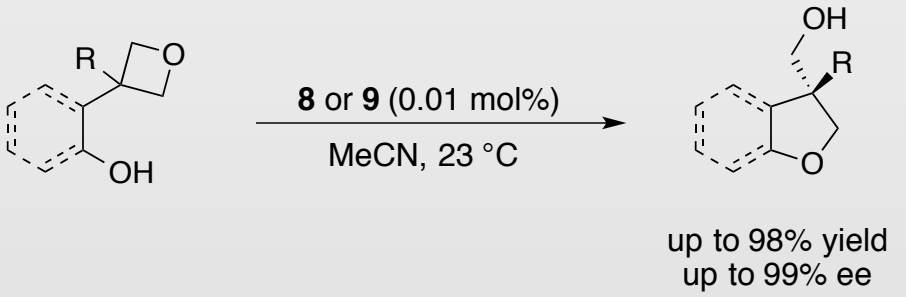
Catalytic Asymmetric Ring Opening

- 1996: Tomioka first intermolecular nucleophilic desymmetrization

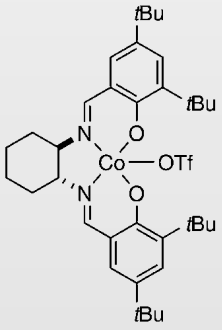


Tomoika, K. *Tetrahedron: Asymmetry* **1996**, *7*, 2483.
Tomioka, K. *Tetrahderon* **1997**, *53*, 10699.

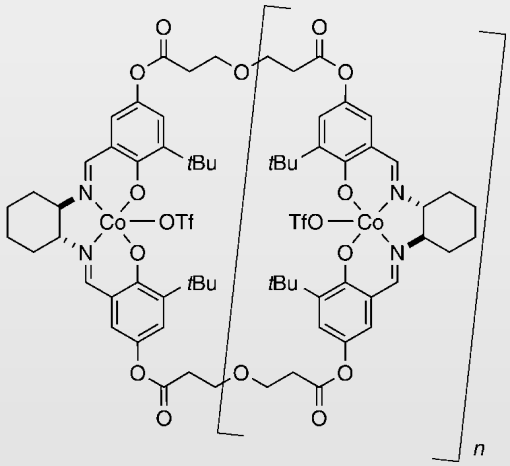
- 2009: Loy and Jacobsen accomplish intramolecular approach
  - Oligomeric catalyst extends chiral backbone for remote induction
  - Failed for intermolecular reactions



up to 98% yield
up to 99% ee



96

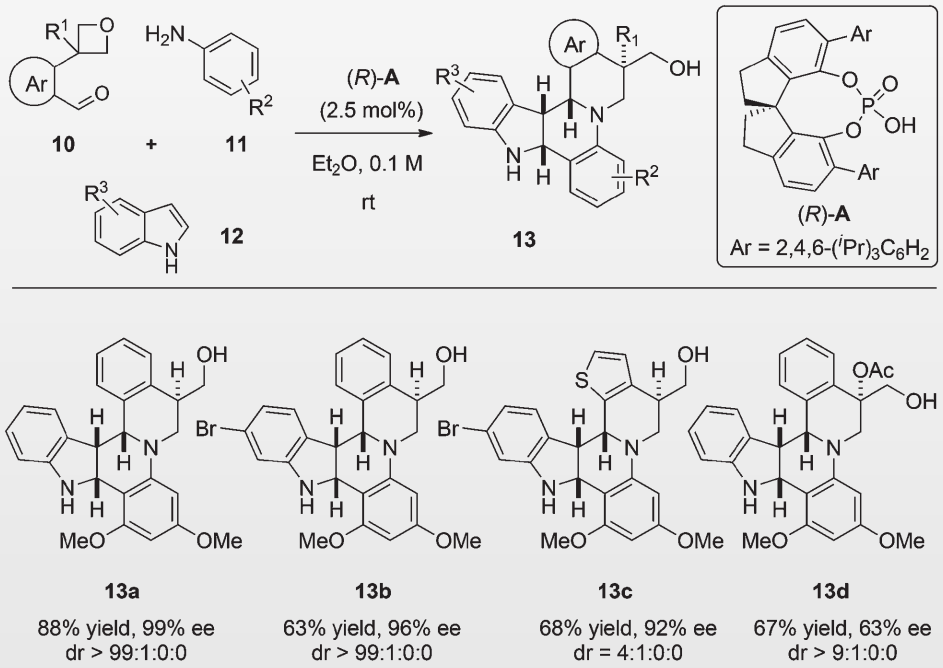


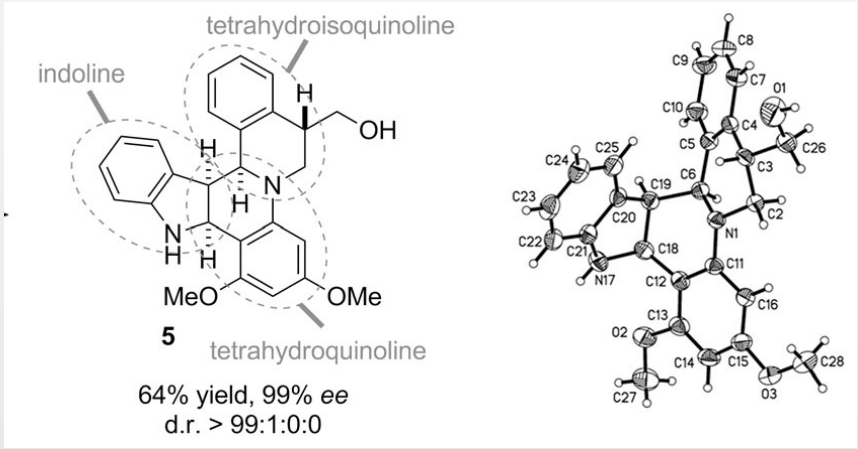
97 (*n* = 1–4)

Jacobsen, E. *JACS* **2009**, *131*, 2786.

Catalytic Asymmetric Ring Opening

- Basicity of oxetanes is higher than epoxides and ethers
  - Activation by chiral phosphoric acids (relatively weak acidity) requires strong/internal nucleophiles



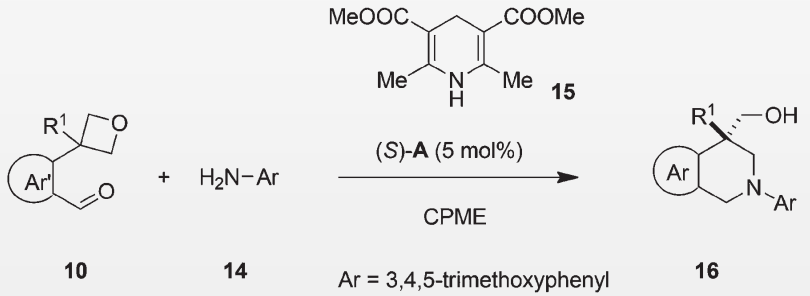


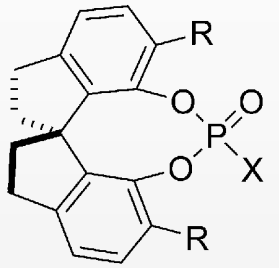
- Generates 2 new C-C and 2 new C-N bonds
  - Chiral product from 3 achiral compounds
  - *First example with nitrogen nucleophiles*

Sun, J. *Angew. Chem. Int. Ed.* **2013**, *52*, 2027.

Catalytic Asymmetric Ring Opening

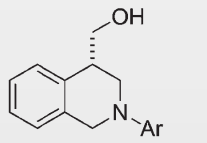
- Chiral Tetrahydroisoquinoline synthesis at C4 position (rare)
  - Hantzsch ester as reductant
  - Quant centers lower ee





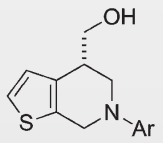
R = 2,4,6-(*i*Pr)$_3$C$_6$H$_2$

C1: X = OH



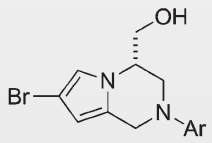
16a

90% yield, 94% ee



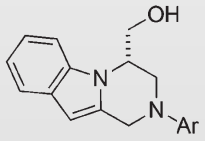
16b

96% yield, 84% ee



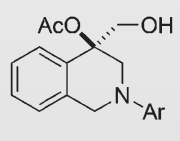
16c

88% yield, 90% ee



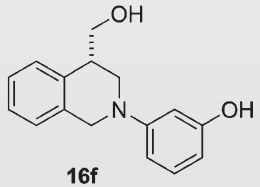
16d

91% yield, 88% ee



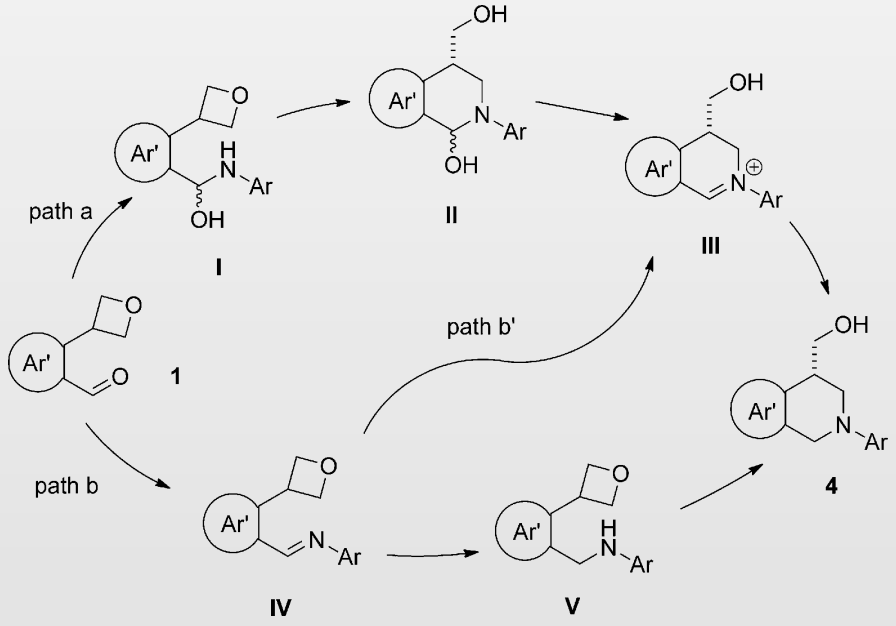
16e

94% yield, 56% ee



16f

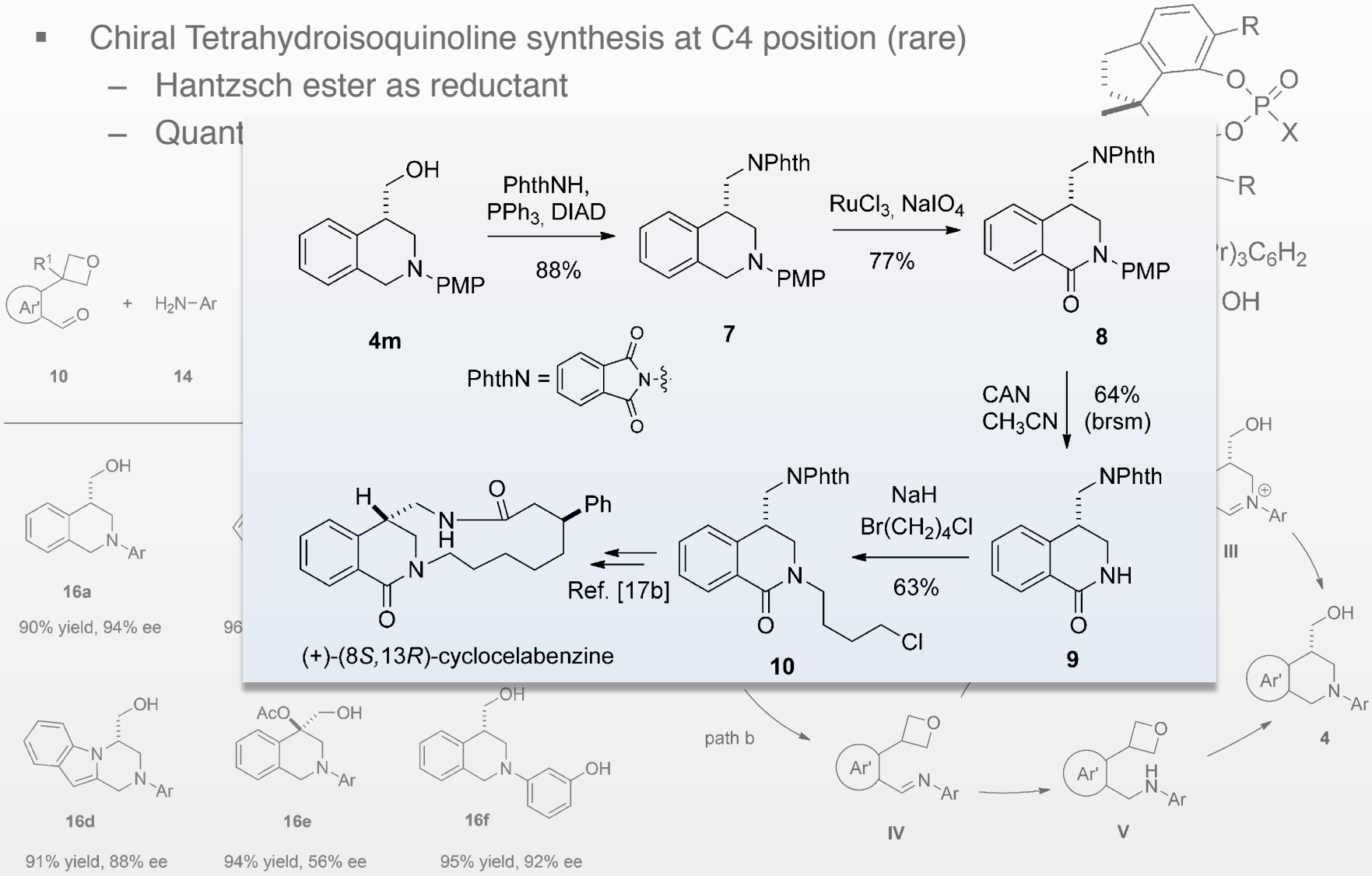
95% yield, 92% ee



Sun, J. *Chem. Eur. J.* **2013**, *19*, 8426.

Catalytic Asymmetric Ring Opening

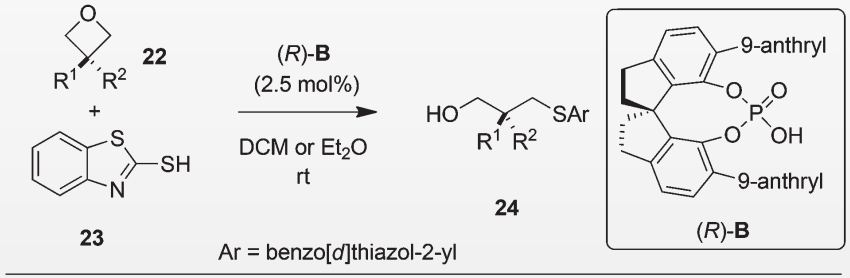
- Chiral Tetrahydroisoquinoline synthesis at C4 position (rare)
  - Hantzsch ester as reductant
  - Quant



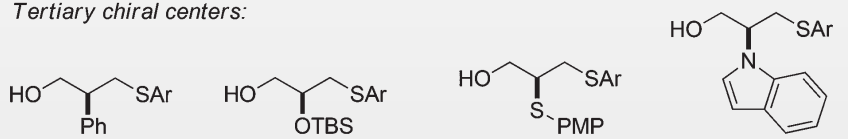
Sun, J. *Chem. Eur. J.* **2013**, *19*, 8426.

Catalytic Asymmetric Ring Opening

- **Intermolecular Nuc opening of oxetanes with common nucleophiles is challenging**
  - Alcohols, amines, and thiols result in mostly no reaction



Tertiary chiral centers:



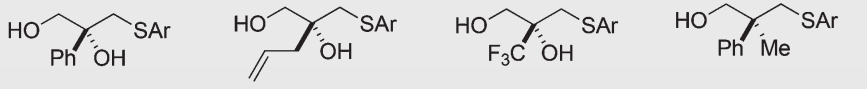
24a 91% yield, 92% ee

24b 90% yield, 93% ee

24c 94% yield, 92% ee

24d 94% yield, 96% ee

Quaternary chiral centers:

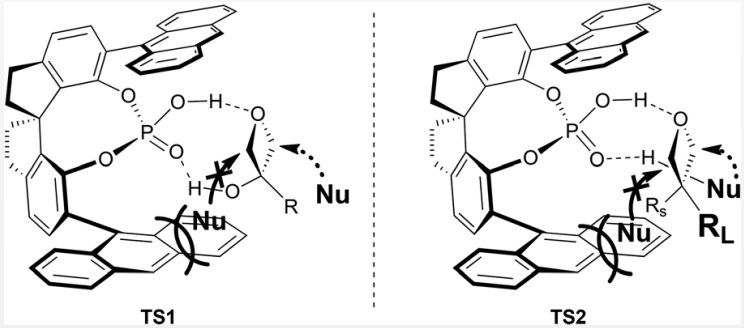


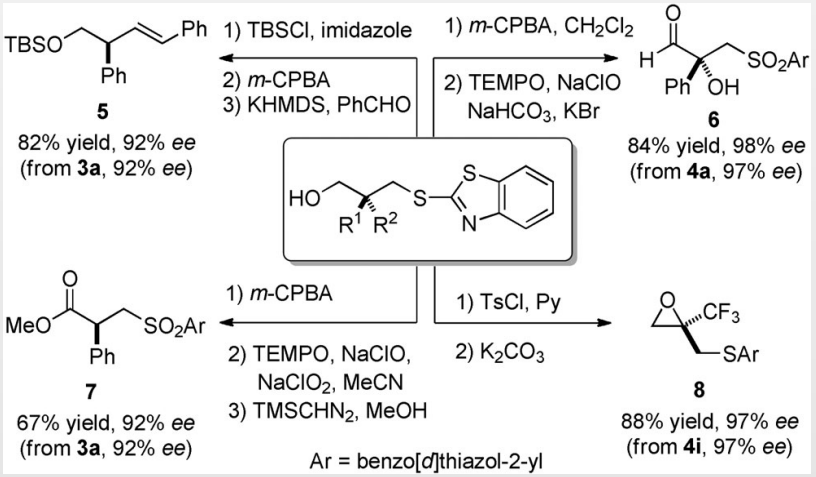
24e 91% yield, 97% ee

24f 93% yield, 94% ee

24g 93% yield, 97% ee

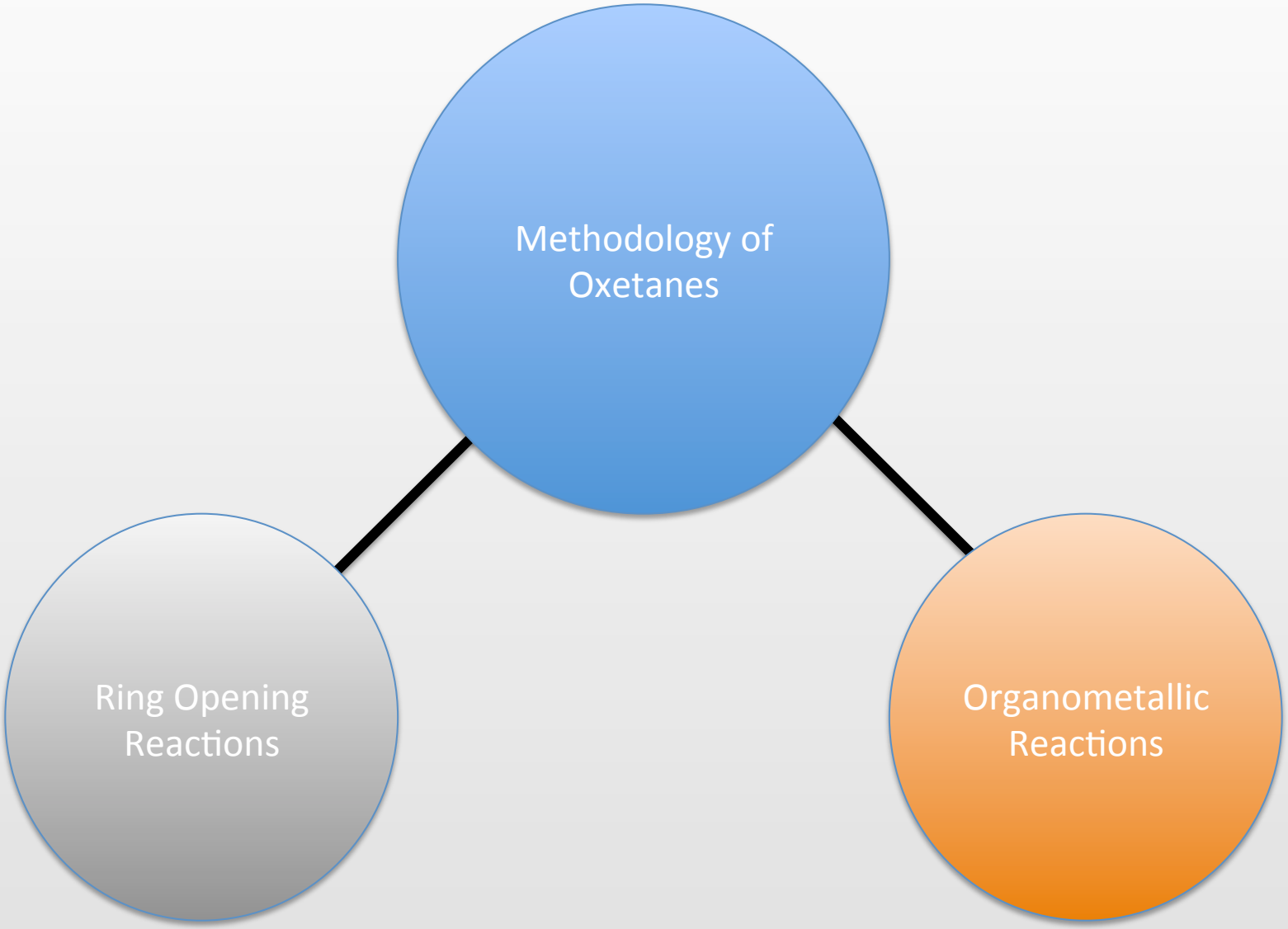
24h 93% yield, 77% ee





- Although nucleophiles were limited, they are still practical
  - Convert to other products (i.e. Julia Olefination, etc)

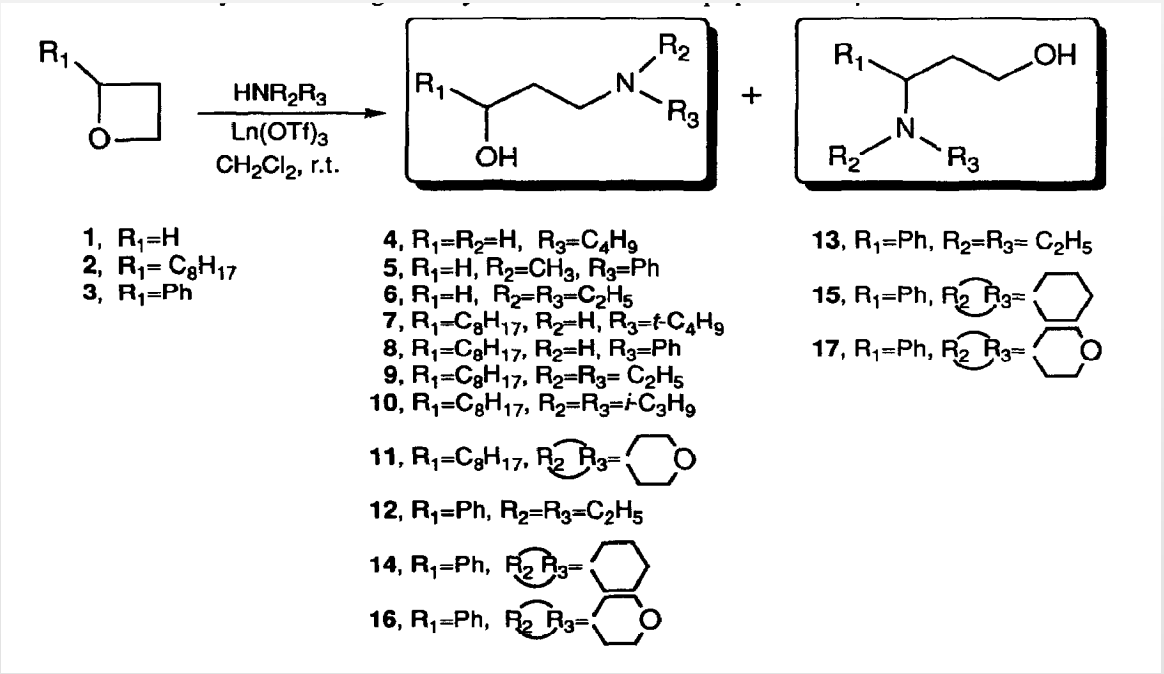
Sun, J. *Angew. Chem. Int. Ed.* **2013**, *52*, 6685.


Methodology of Oxetanes
Ring Opening Reactions
Organometallic Reactions

Lanthanide Catalyzed Ring Opening

- Ring opening is similar to oxiranes
- Strong nucleophiles under basic conditions do not normally open oxetanes
  - Very difficult to react amines with oxetanes

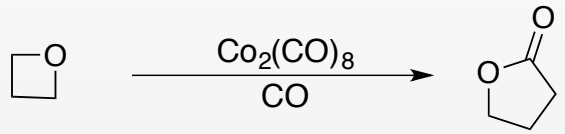
- $Ln(OTf)_3$ are great promoters: Yb, Nd, Gd
  - Reaction times of 2h, r.t.
  - Yields between 75-99% (highly regioselective)



Crotti, C. *Tet. Lett.* **1994**, *35*, 7089.

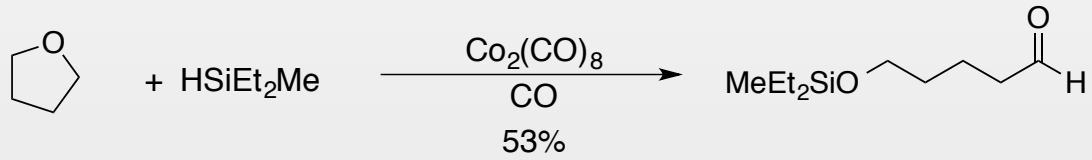
Cobalt Catalyzed C-O Bond Cleavage

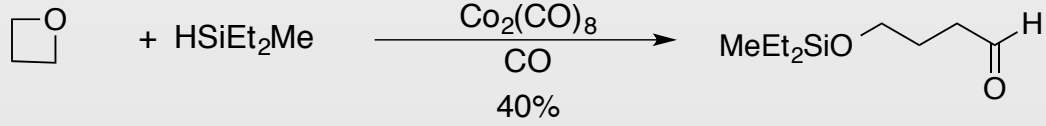
- Hydroformylation of cyclic ethers

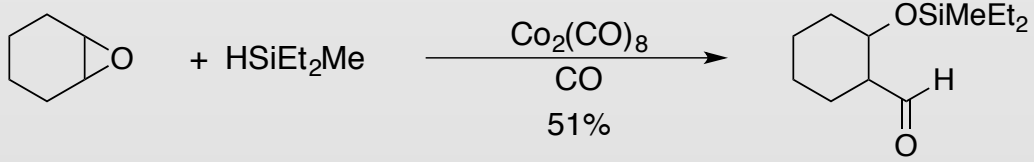


Eisenmann, J. *J. Org. Chem.* **1962**, *27*, 2706.

- Tandem hydroformylation with silanes



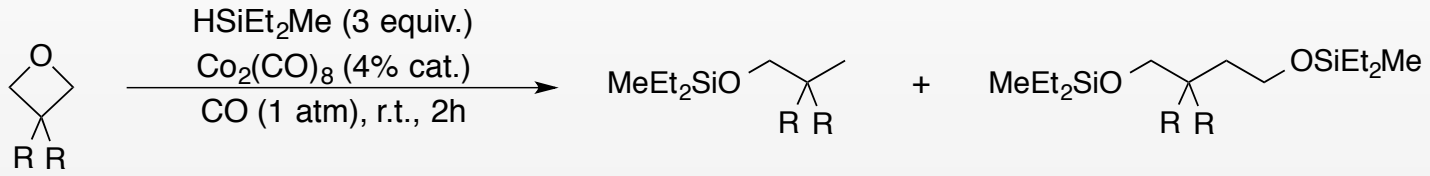




Dalcanale, E. *Synthesis* **1986**, 492.

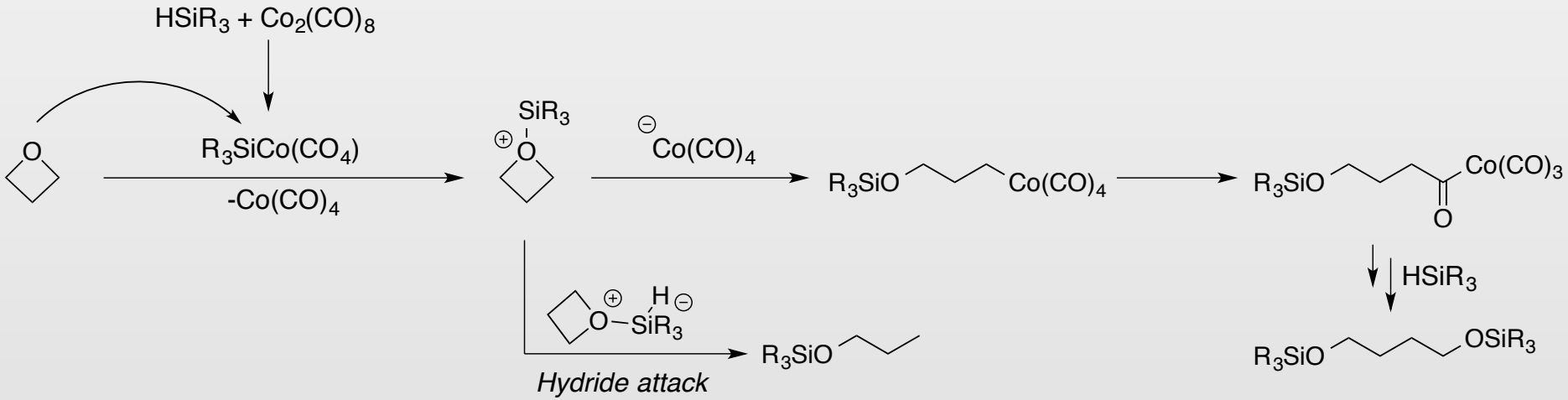
Cobalt Catalyzed C-O Bond Cleavage

- Murai: First catalytic report with oxetanes, previously shown for oxiranes



DCM	83	16
Benzene	17	63
n-hexanes	trace	96

Proposed Mechanism

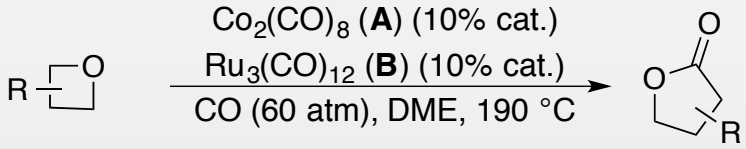


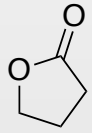
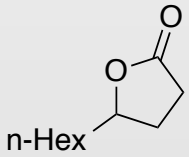
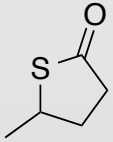
Murai, T. *J. Organomet. Chem.* **1986**, *302*, 249.

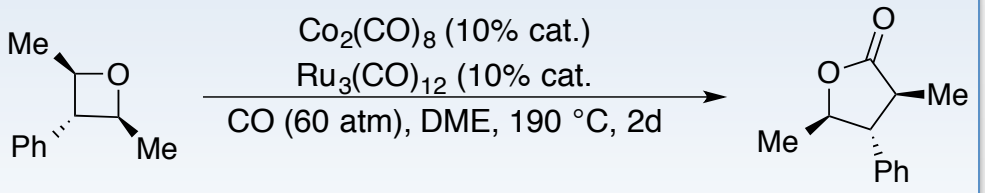
Cobalt/Ruthenium Carbonylation

- Oxetane to 5-membered ring carbonylation (harsh conditions)
  - Carbonylation is regiospecific to least hindered side

- Cobalt better catalyst for oxetane, ruthenium better for thietane
  - Thietanes are more reactive
  - Thietane required both catalysts



	catalyst	yield
	A	50
	B	20
	A+B	**70**
	A	40
	B	80
	A+B	**89**
	A	0
	B	0
	A+B	**95**

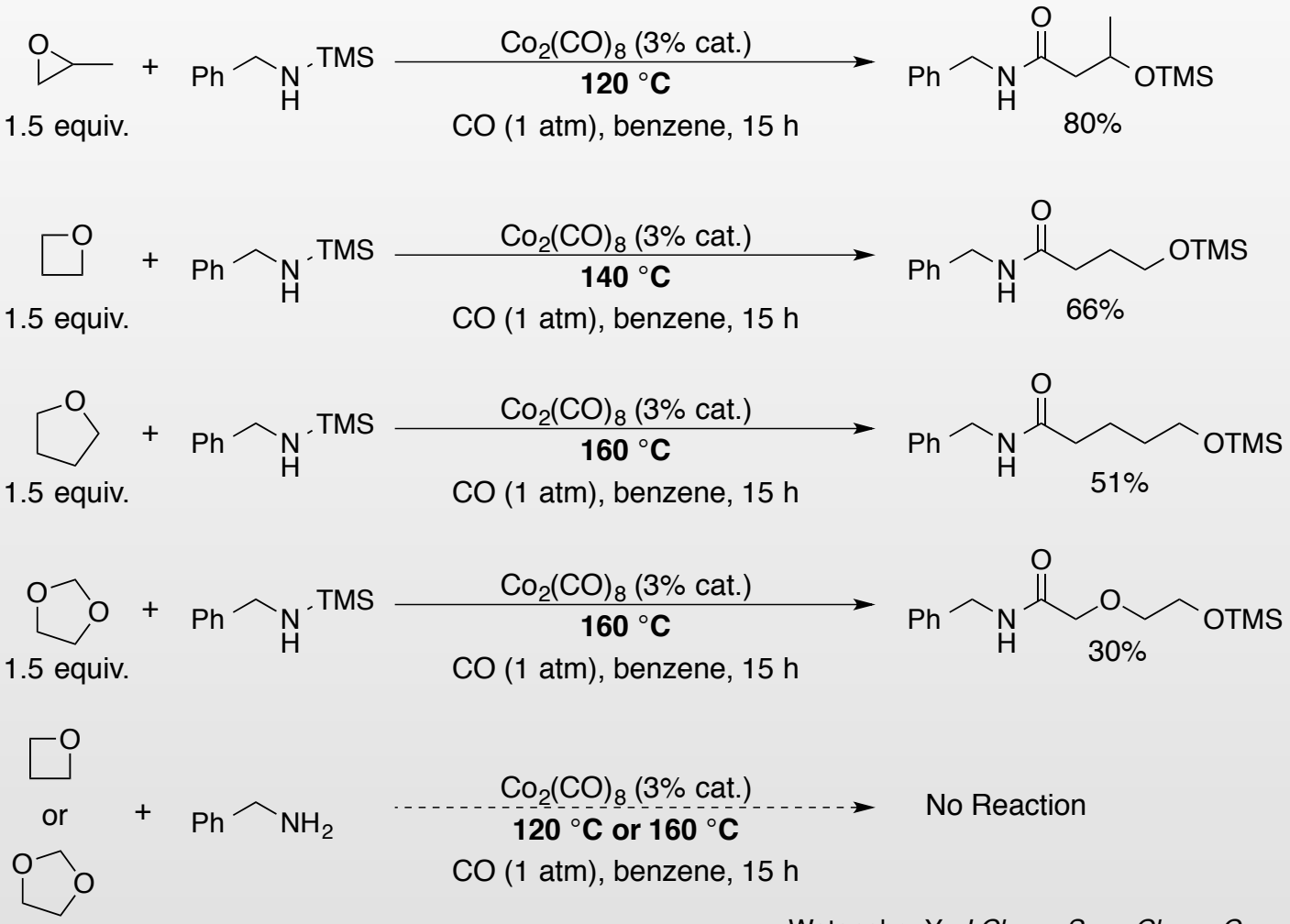


Insertion takes place with retention of substituent stereochemistry

Alper, H. *J. Org. Chem.* **1989**, *54*, 21.

Cobalt Carbonylation with *N*-TMS amines

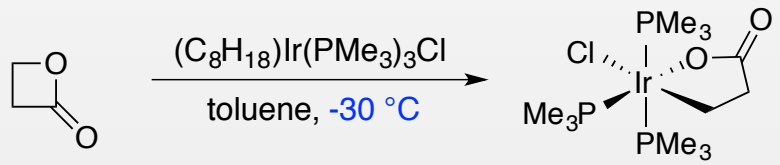
- Re / Re / Mn / Fe / Ru / Mo based carbonyl catalysts all failed for this transformation
  - Amines induce disproportionation of $Co(CO)_8$



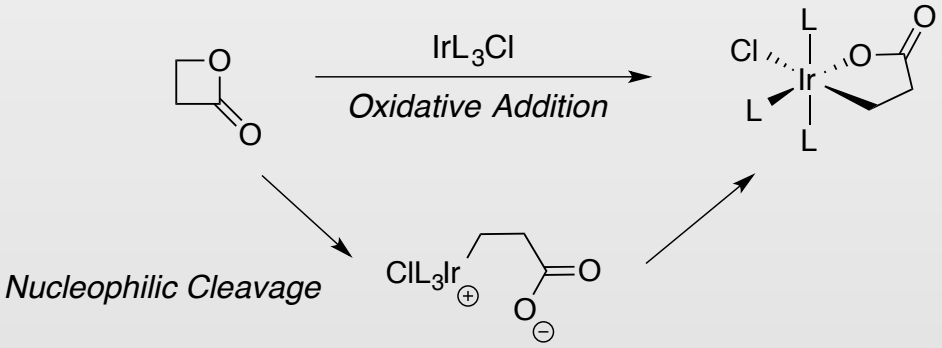
Watanabe, Y. *J Chem. Soc., Chem. Commun.* **1989**, 1253.

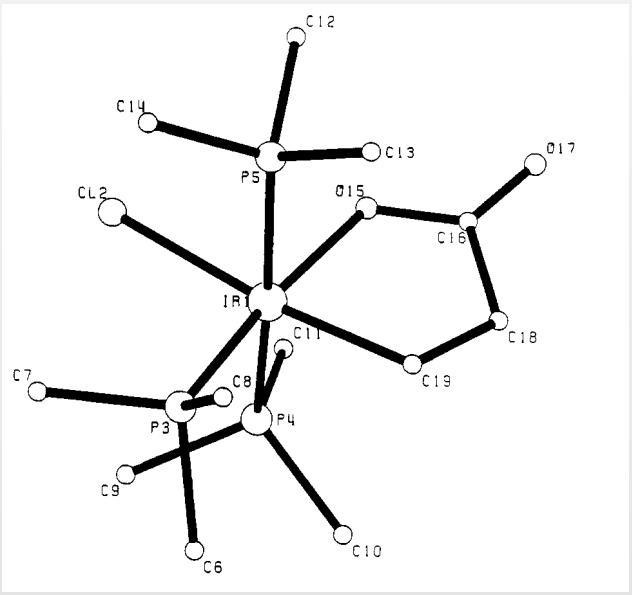
C-O Insertion with Iridium

- Iridium complex known to C-O insert into epoxides
  - Inserts with β-propiolactone
  - No O-C-O bond cleavage
  - Pt(II) and Ni(0) also result in C-O bond cleavage but no metallocycles were obtained



- Mechanism

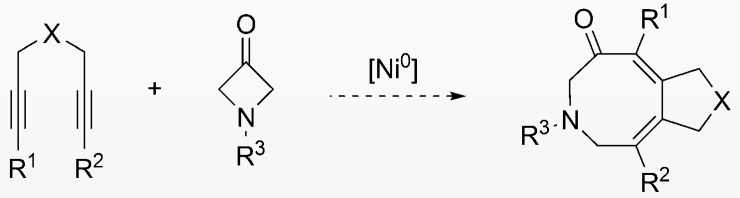


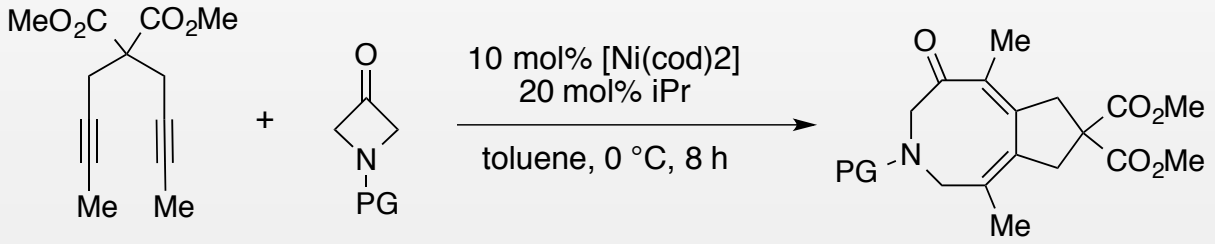


Milstein, D. *Organometallics* **1990**, *9*, 1300.

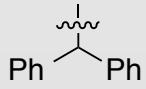
Low Temp C-C Bond Cleavage with Nickel

- Used protected amine to prevent self condensation
- Conditions similar to Murakami with cyclobutanones
- Reaction run at room temp!



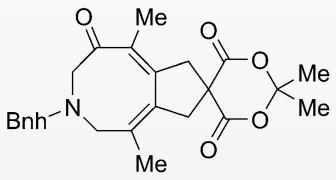


Entry	PG	Temp (°C)	Conc. (M)	Yield (%)
1	Boc	r.t.	0.1	70
2	Boc	60	0.1	35
3	Boc	100	0.1	21
4	Boc	0	0.1	84
5	Boc	0	0.05	88
6	Ts	0	0.05	25
7	Bnh	0	0.05	92

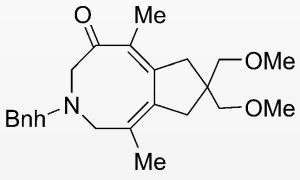
Bnh = 

Louie, J. *Angew. Chem. Int. Ed.* **2012**, *51*, 8602.

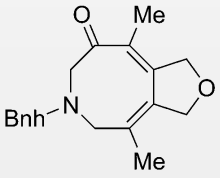
Low Temp C-C Bond Cleavage



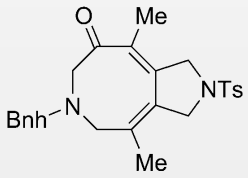
3bd, 78 %



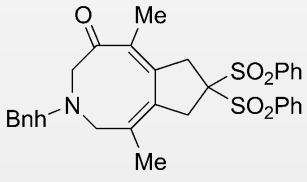
3cd, 48 %



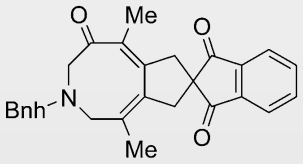
3dd, 91 %



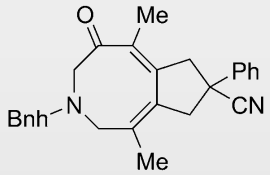
3ed, 79 %



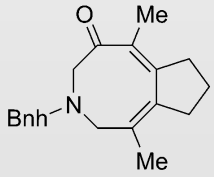
3fd, 59 %



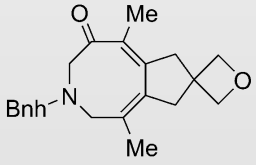
3gd, 88 %



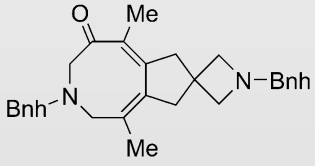
3hd, 64 %



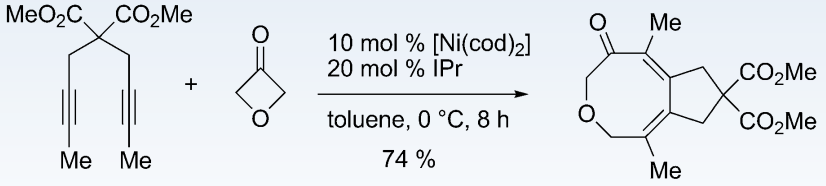
3id, 68 %

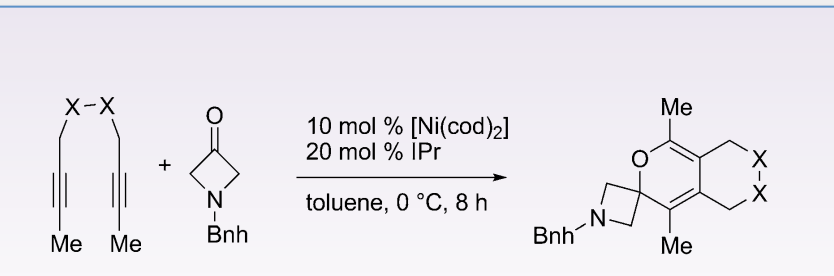


3jd, 87 %



3kd, 71 %





1n X = CH_2 **2d**
1o X = $C(CO_2Et)_2$

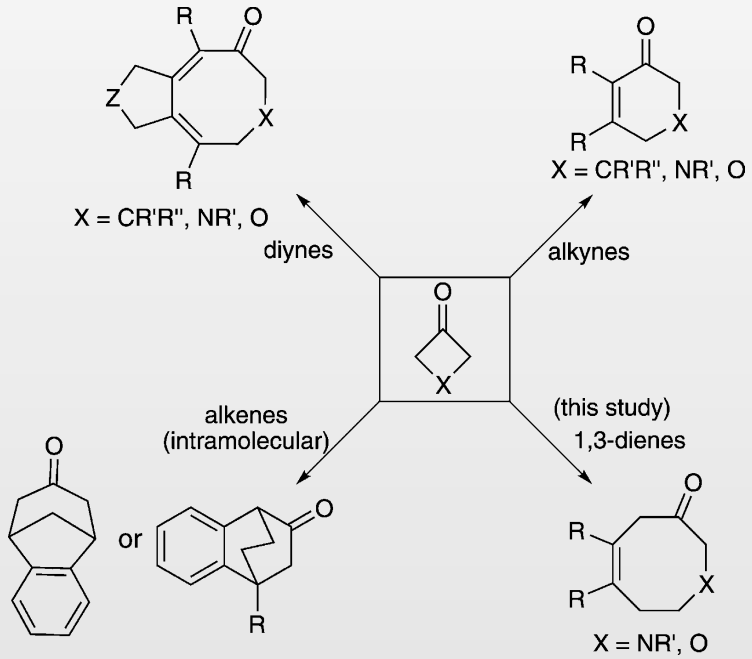
3nd X = CH_2, 82 %
3od X = $C(CO_2Et)_2$, 80 %

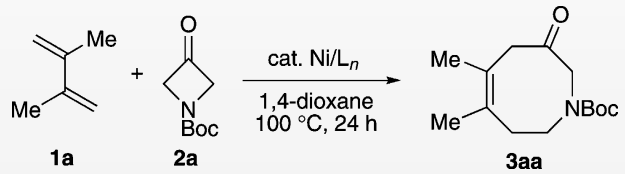
Mechanism is a question

Louie, J. *Angew. Chem. Int. Ed.* **2012**, *51*, 8602.

C-C bond activation

- Further extension with dienes





1a **2a** **3aa**

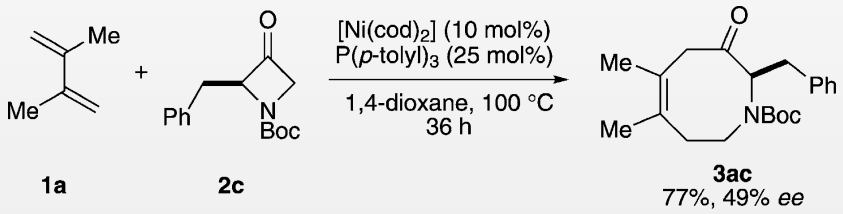
Entry	Ligand	Conversion [%][b]	Yield [%][c]
1	IPr	83	–
2	SIPr	42	–
3	IMes	89	–
4	dppf	34	n.d.
5	dppp	–	–
6	dppb	> **99**	**79**
7	PCy_3	25	n.d.
8	PPh_3	> 99	75
9	$P(p\text{-}CF_3C_6H_4)_3$	59	n.d.
10	$P(p\text{-}OMeC_6H_4)_3$	70	n.d.
11	$P(p\text{-tolyl})_3$	> **99**	**79**

[a] Reaction conditions: diene **1a** (2 equiv), azetidinone (1 equiv, 0.4 M), $[Ni(cod)_2]$ (10 mol%), ligand (20 mol% for entries 1–3; 12 mol% for entries 4–6; 25 mol% for entries 7–11). [b] The conversion of **1a** was determined by GC with naphthalene as an internal standard. [c] Yield of isolated **3aa**. Boc = *tert*-butoxycarbonyl, cod = 1,5-cyclooctadiene, Cy = cyclohexyl, dppb = 1,4-bis(diphenylphosphanyl)butane, dppf = 1,1′-bis(diphenylphosphanyl)ferrocene, dppp = 1,3-bis(diphenylphosphanyl)propane, IMes = *N*,*N*′-bis(2,4,6-trimethylphenyl)imidazol-2-ylidene, IPr = *N*,*N*′-bis(2,6-diisopropylphenyl)imidazol-2-ylidene, SIPr = *N*,*N*′-bis(2,6-diisopropylphenyl)-4,5-dihydroimidazol-2-ylidene; n.d. = not determined.

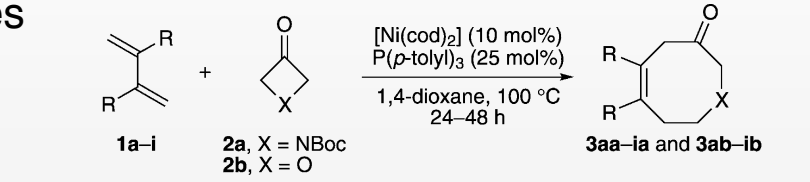
Louie, J. *Angew. Chem. Int. Ed.* **2013**, *52*, 12161.

C-C bond activation

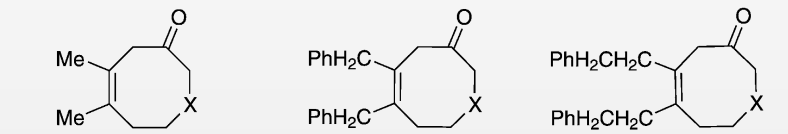
- Ogoshi showed Ni(0) catalysts can do C-C activation of cyclobutanones and couple with dienes but resulted in very stable metallocycles
- Can form large fuzed heterocycles



1a **2c** **3ac** 77%, 49% *ee*



1a–i **2a**, X = NBoc **2b**, X = O **3aa–ia** and **3ab–ib**

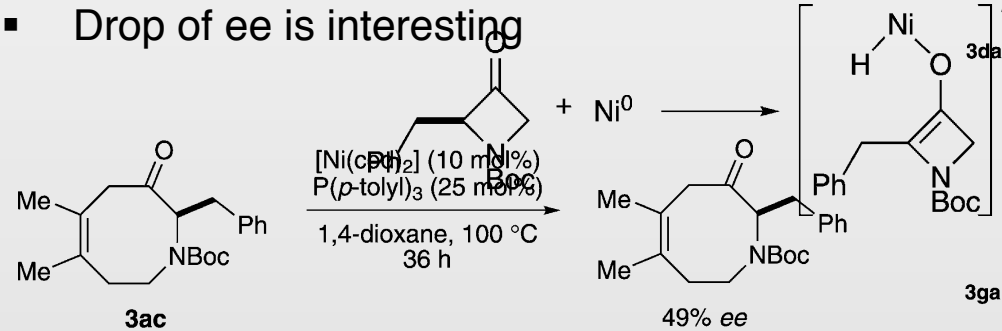


3aa, X = NBoc, 24 h, 79%
3ab, X = O, 24 h, 40%

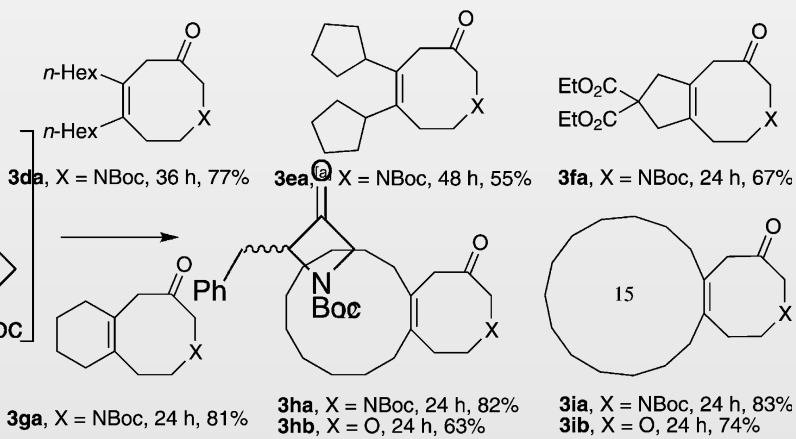
3ba, X = NBoc, 36 h, 80%
3bb, X = O, 36 h, 60%

3ca, X = NBoc, 36 h, 82%
3cb, X = O, 36 h, 63%

- Regioselectivity (selective)
- Drop of ee is interesting



3ac 49% *ee* 49% *ee*



3da, X = NBoc, 36 h, 77%
3ea[a], X = NBoc, 48 h, 55%
3fa, X = NBoc, 24 h, 67%
3ga, X = NBoc, 24 h, 81%
3ha, X = NBoc, 24 h, 82%
3hb, X = O, 24 h, 63%
3ia, X = NBoc, 24 h, 83%
3ib, X = O, 24 h, 74%

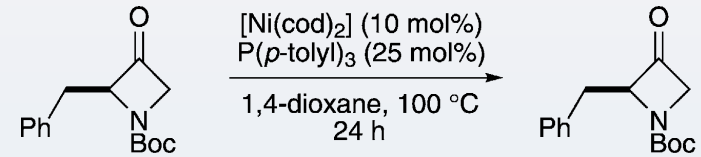
Scheme 2. Nickel-catalyzed cycloaddition of 1,3-dienes with azetidinone **2a** and oxetanone **2b**. Reaction conditions: diene **1** (2 equiv), **2a** (1 equiv, 0.4 M) or **2b** (1 equiv, 0.2 M), $[Ni(cod)_2]$ (10 mol%), P(*p*-tolyl)$_3$ (25 mol%), 1,4-dioxane, 100 °C. [a] A catalyst loading of 15 mol% was required.

Louie, J. *Angew. Chem. Int. Ed.* **2013**, *52*, 12161.

C-C bond activation

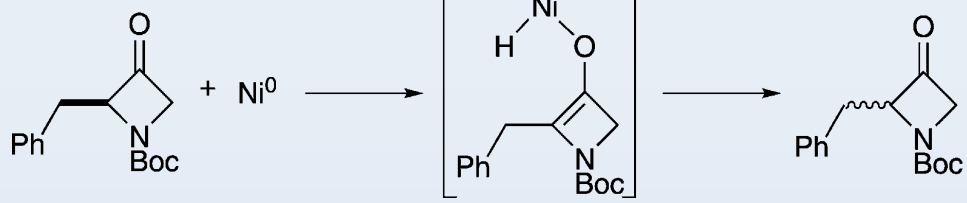
- Ogoshi showed Ni(0) catalysts can do C-C activation of cyclobutanones and couple with dienes but resulted in very stable metallocycles
- Can form

Loss of ee due to Ni C-H Activation!

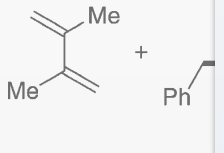


2c
> 99% *ee*

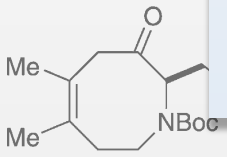
20% *ee*



- Reg
  - –
- Drop of



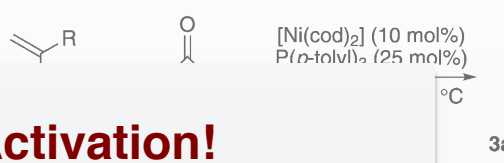
1a



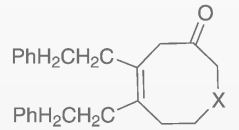
3ac
49% *ee*

36 h

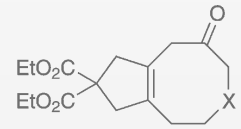
49% *ee*



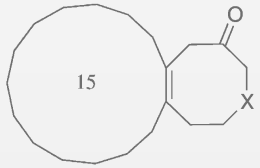
3aa–ia and **3ab–ib**



3ca, X = NBoc, 36 h, 82%
3cb, X = O, 36 h, 63%



3fa, X = NBoc, 24 h, 67%



3ga, X = NBoc, 24 h, 81%

3ha, X = NBoc, 24 h, 82%
3hb, X = O, 24 h, 63%

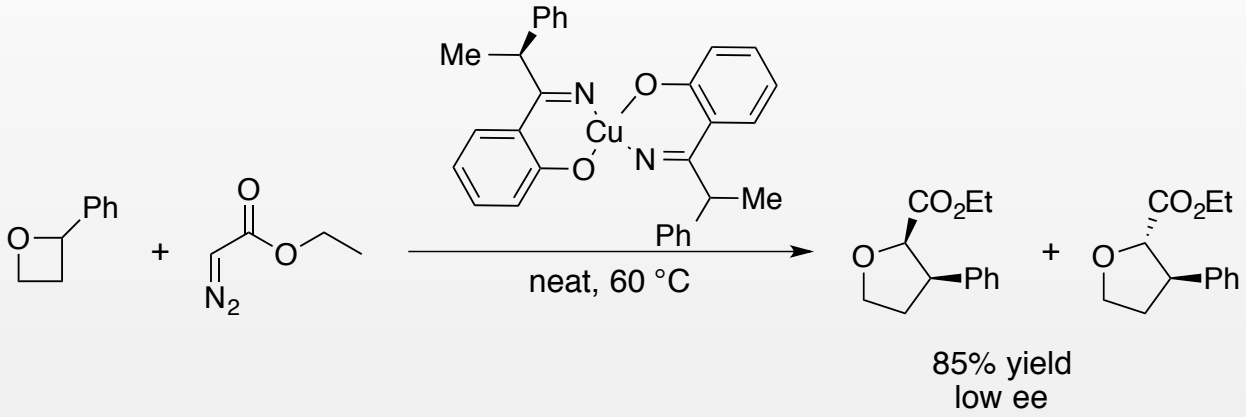
3ia, X = NBoc, 24 h, 83%
3ib, X = O, 24 h, 74%

Scheme 2. Nickel-catalyzed cycloaddition of 1,3-dienes with azetidinone **2a** and oxetanone **2b**. Reaction conditions: diene **1** (2 equiv), **2a** (1 equiv, 0.4 M) or **2b** (1 equiv, 0.2 M), $[Ni(cod)_2]$ (10 mol%), $P(p\text{-tolyl})_3$ (25 mol%), 1,4-dioxane, 100 °C. [a] A catalyst loading of 15 mol% was required.

Louie, J. *Angew. Chem. Int. Ed.* **2013**, *52*, 12161.

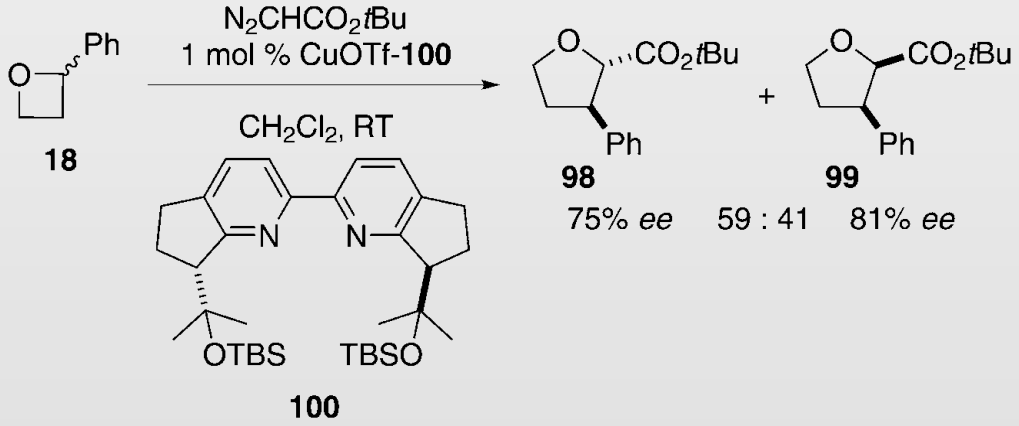
Copper Catalyzed Ring Expansions to THF

- First discovered by Noyori in 1966



Noyori, R. *Tet. Lett.* **1966**, *7*, 5239.

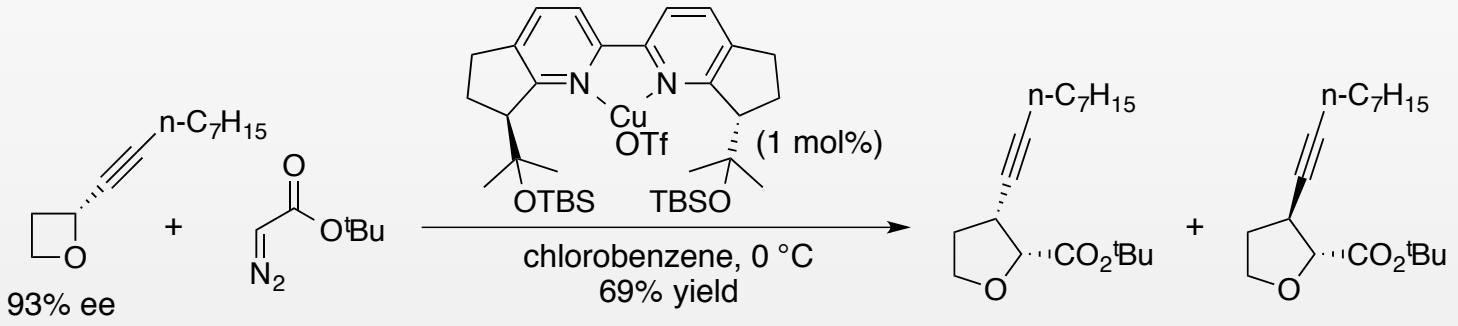
- Katsuki switched to bipyridine ligands to enhance ee



Katsuki, T. *Chem. Lett.* **1994**, 1857.

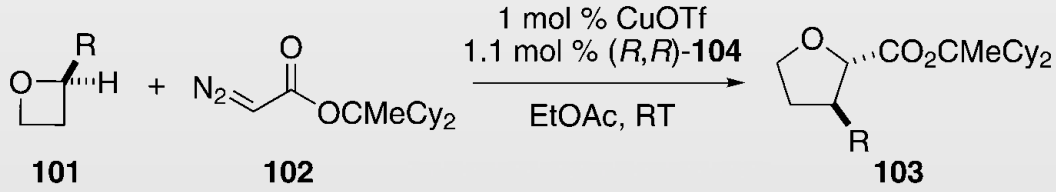
Copper Catalyzed Ring Expansions to THF

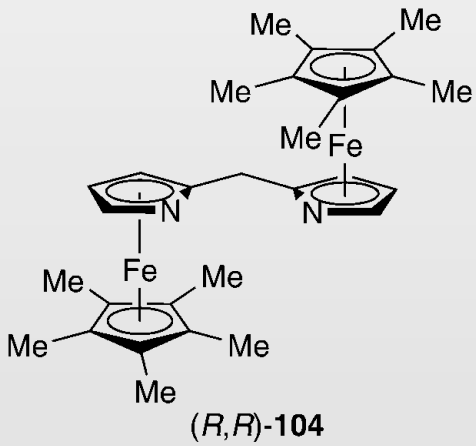
- Transformation applied total synthesis of *trans*-Whisky lactone and formal total synthesis of (–)-avenaciolide and (–)-isoavenaciolide



Katsuki, T. *Syn. Lett.* **1997**, 387.

- Best expansion to date is from Fu's lab in 2001





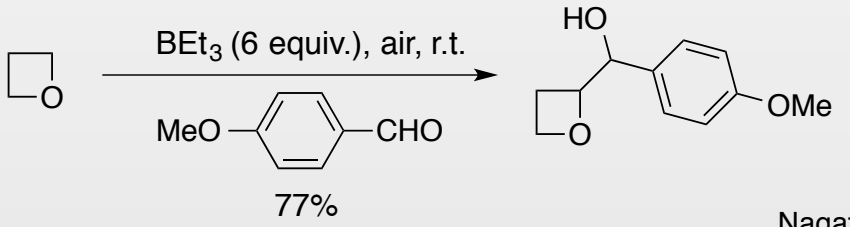
Fu, G.c. *Tetrahedron* **2001**, *57*, 2621.

C-H Functionalization with Oxetanes

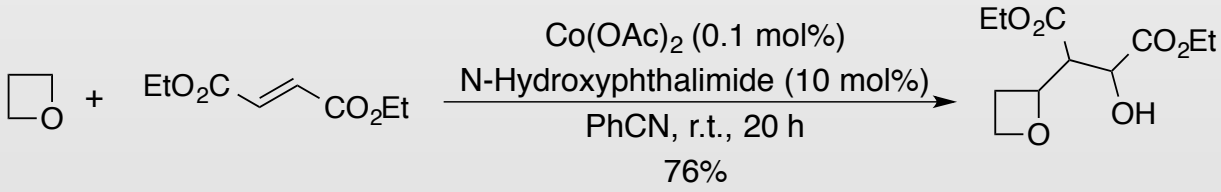
- C-H bonds α to an oxygen make possible selective radical-mediated transformations
- Oxetanyl radical at α-carbon decreases puckering of 4-membered ring
  - BDE = 92.6 kcal/mol
  - Cyclobutane = 97.1 kcal/mol

Huie, R.*;* Kafafi, S. *J. Phys. Chem.* **1991**, *95*, 9340.

- C-H Functionalization approach is favorable because acid/base alkylations will not work



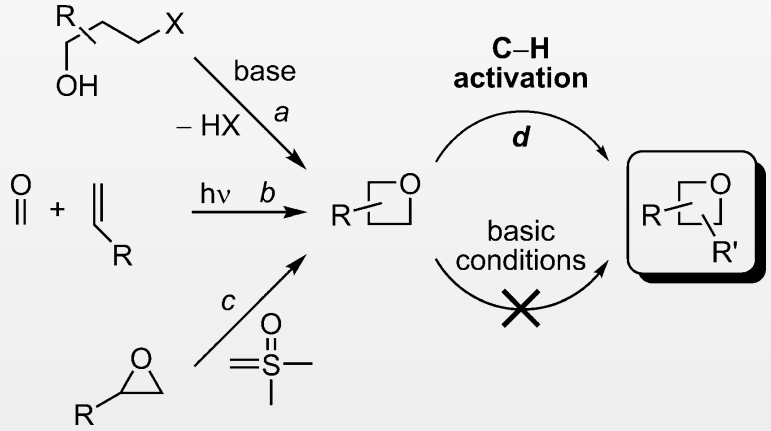
Nagato, H. *J. Org. Chem.* **2005**, *70*, 2342.



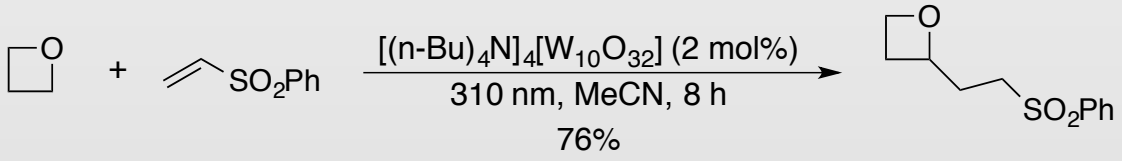
Ishii, Y. *Tet. Lett.* **2002**, *43*, 3617.

C-H Activation with Oxetanes

- C-H activation on could be intriguing for late stage functionalization of natural products and drug targets containing oxetanes



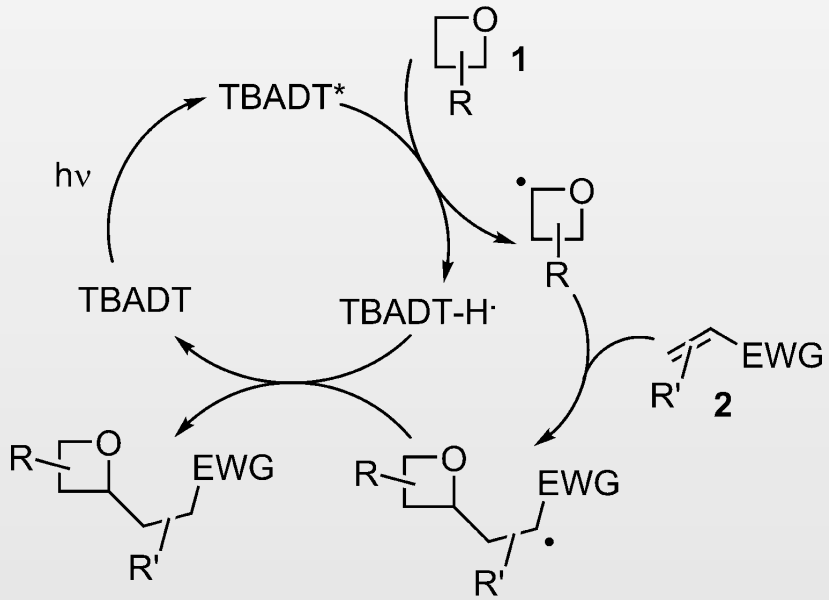
- Decatungstate anion photocatalysis has been done on THF ehters
  - C_2-H bond BDE = 92.6 kcal/mol vs THF = 92.8 kcal/mol

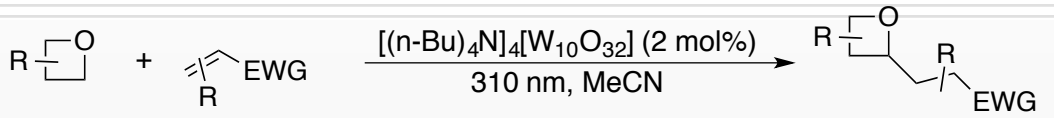


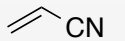
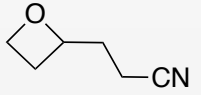
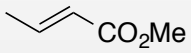
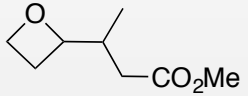
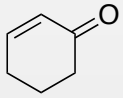
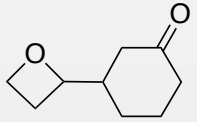
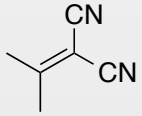
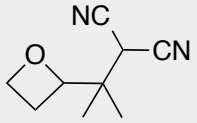
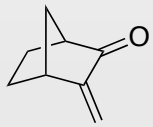
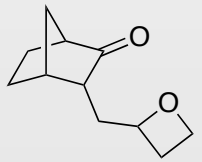
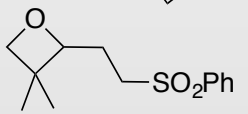
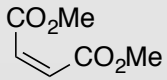
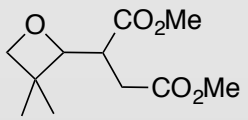
Fagnoni, M. *Adv. Synth. Catal.* **2014**, *356*, 2781.

C-H Activation with Oxetanes

- Reaction requires both light and photocatalyst
  - Requires electron deficient olefins



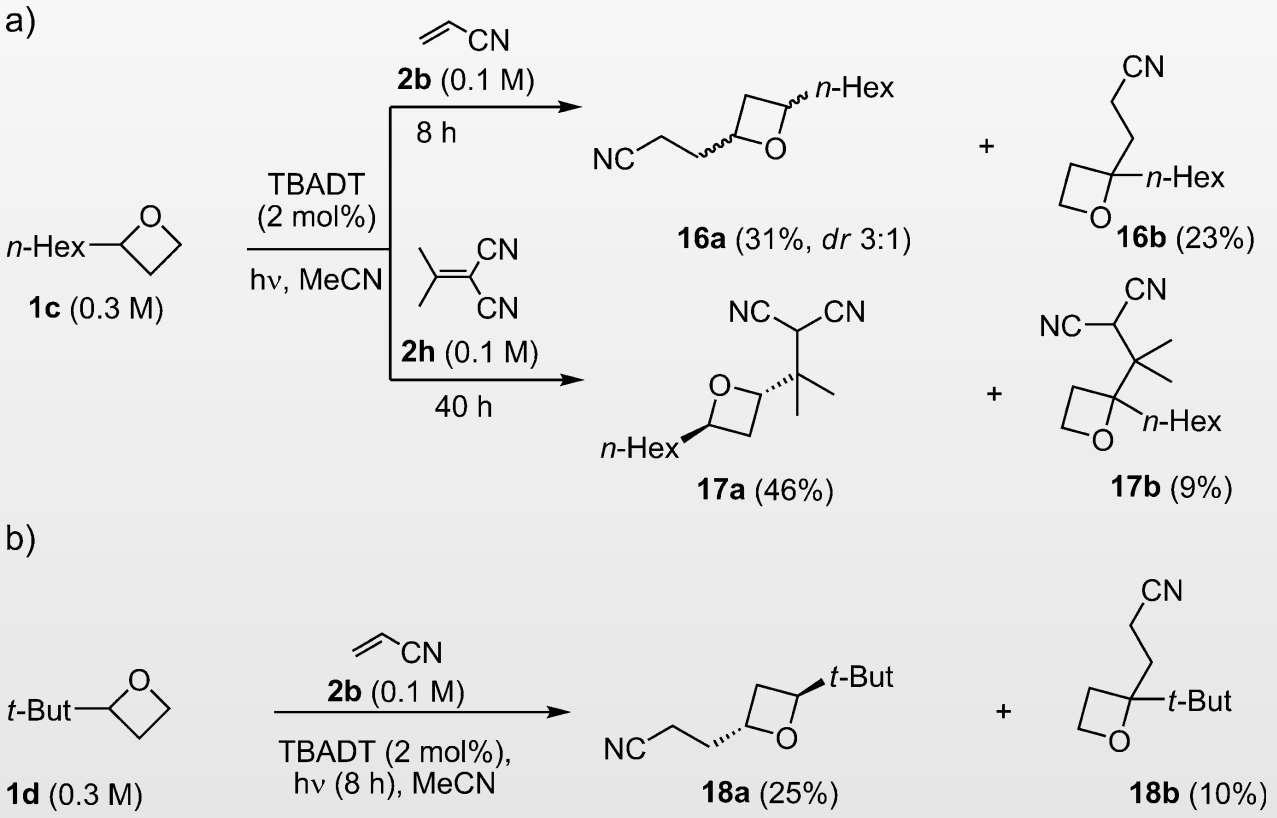


Oxetane	Olefin	Product	Yield (%)
			70
			60
			62
			64
			50
			52
			69

Fagnoni, M. *Adv. Synth. Catal.* **2014**, *356*, 2781.

C-H Activation with Oxetanes

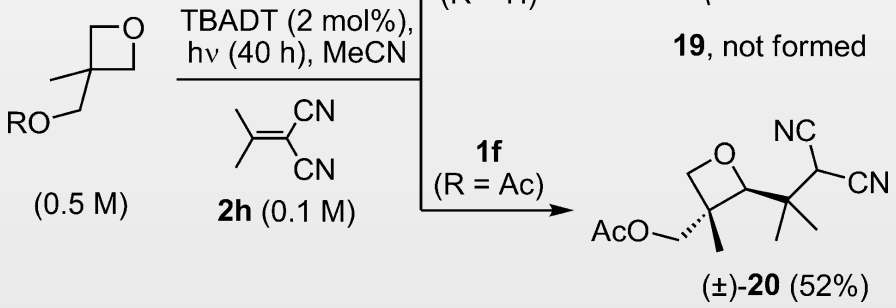
- Selectivity slightly favors methine activation
  - H-abstraction is reversible, sterics hinder coupling in formation of tertiary radical



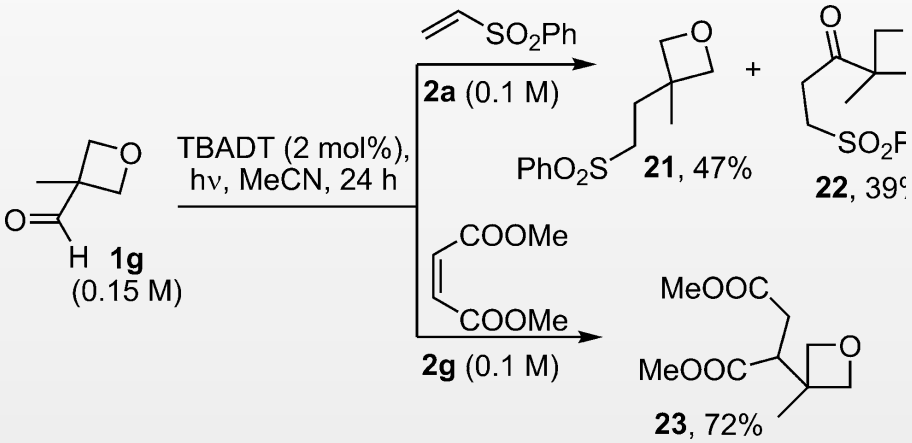
Fagnoni, M. *Adv. Synth. Catal.* **2014**, *356*, 2781.

C-H Activation with Oxetanes

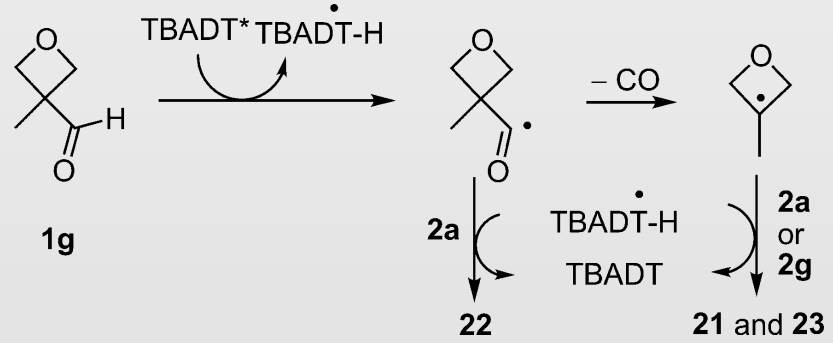
- Competetion between 2-position of oxetanes and other potential hydrogen donors



- R=H, product formed was aldehyde
- Aceylation inhibited competing pathway



Scheme 5.



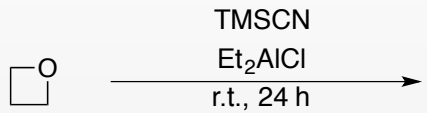
Fagnoni, M. *Adv. Synth. Catal.* **2014**, *356*, 2781.

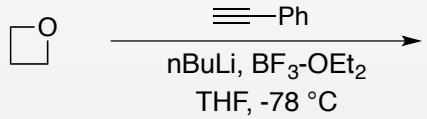
Wrap Up

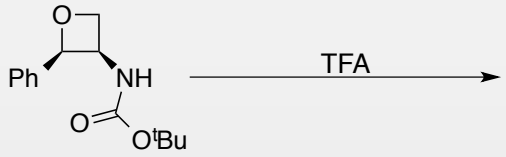
- The use of oxetane containing molecules for drug discovery will likely increase greatly in the coming years
    - Either from chemists push to use this new exciting molecule
    - Or from physiochemical changes induced by replacing previous functionalities
- The added polarity effect of oxetane incorporation and lack of reactivity could be utilized widely for complex molecule synthesis and polymer formation for solubility increase
- Transition metal reactions with oxetanes have mainly focused on carbonylative reactions
- Only now are people beginning to use oxetanes as substrates for new, exciting transition metal catalyzed reactions

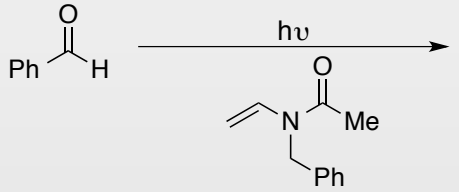
Questions

1. Predict the product for the following reactions.

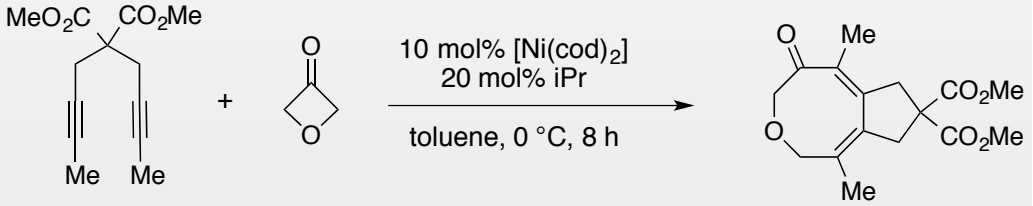




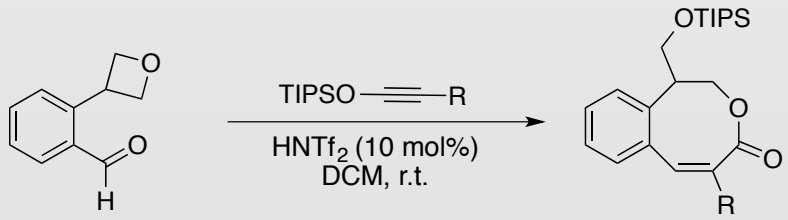




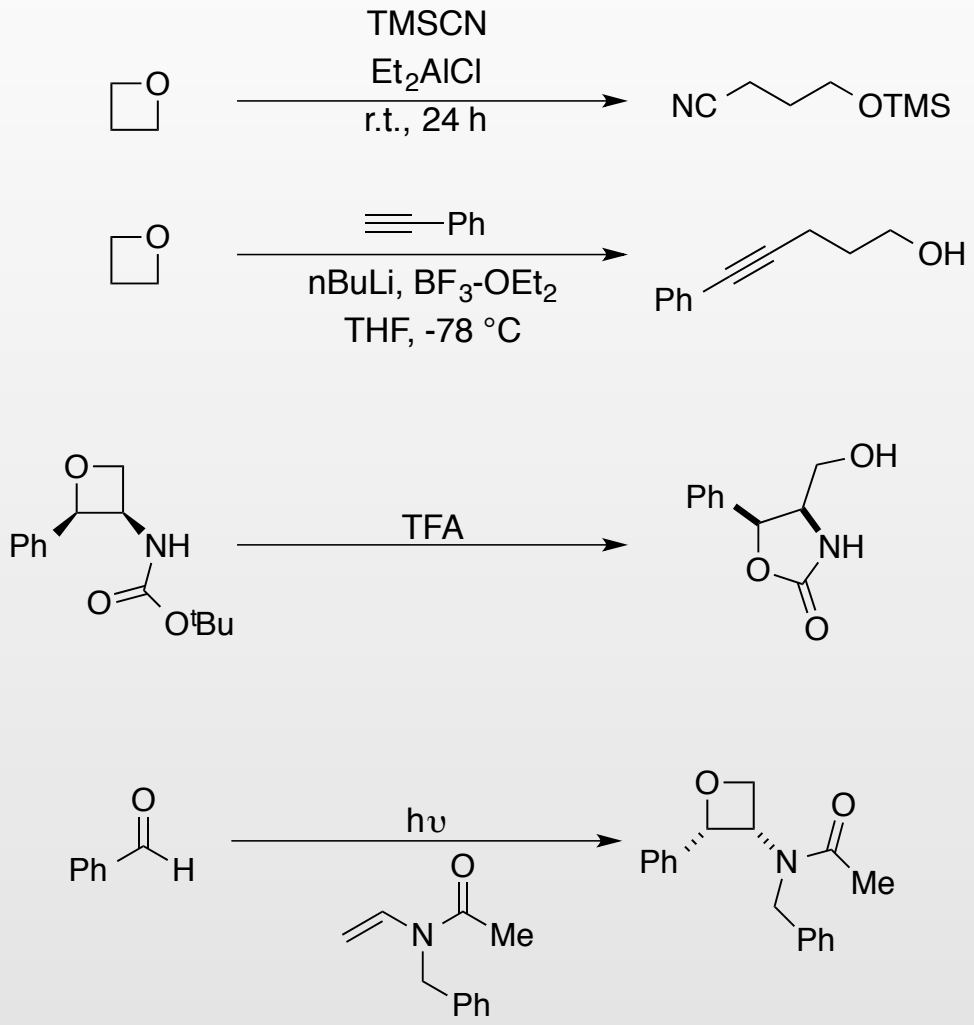
3. Please propose a mechanism for the reaction below.



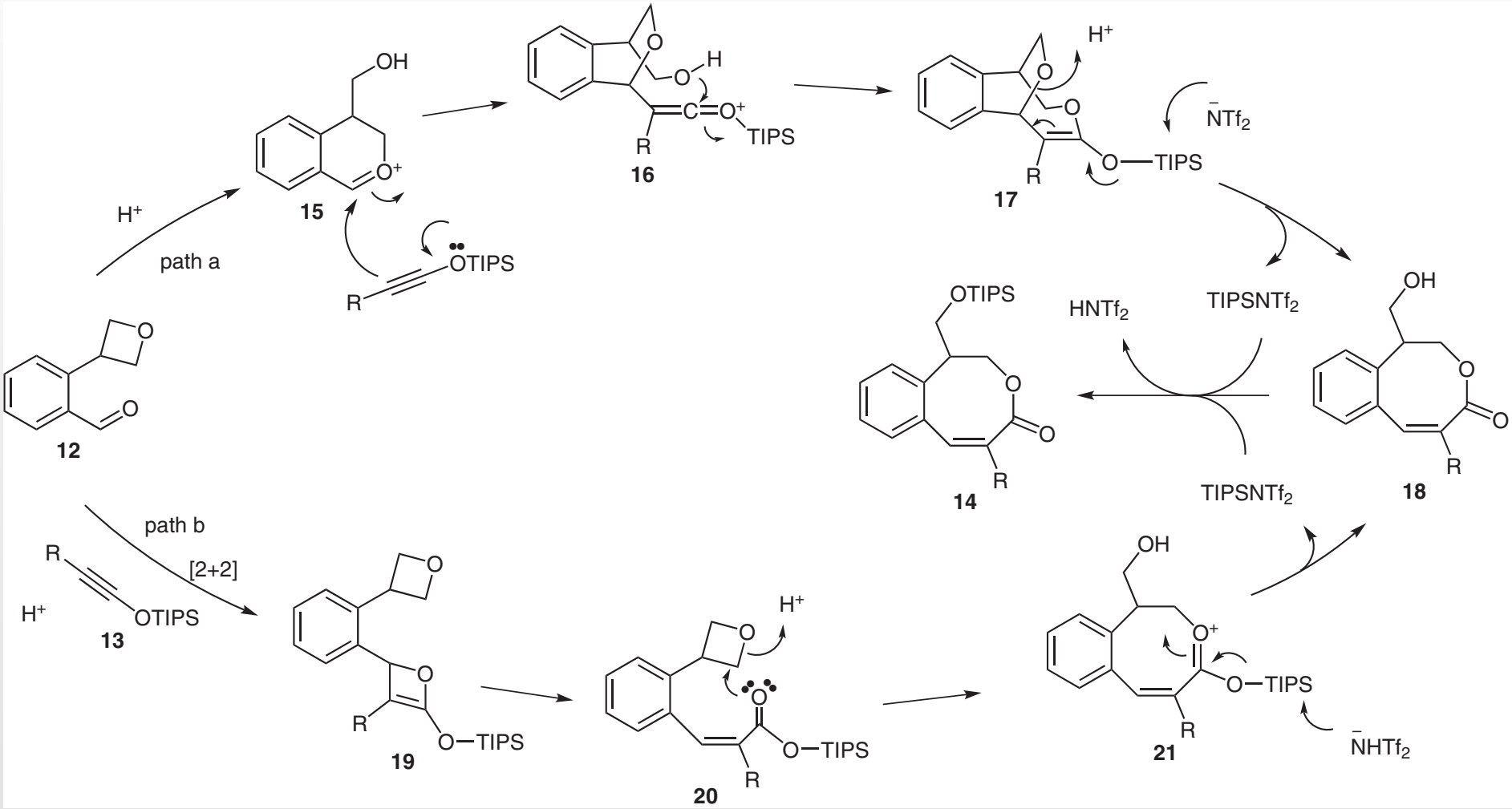
2. Please propose a mechanism for the reaction below.



Question 1


TMSCN
Et2AlCl
r.t., 24 h
O
NC
OTMS
Ph
nBuLi, BF3-OEt2
THF, -78 °C
OH
TFA
NH
OtBu
hυ
Me

Question 2


12
H+
path a
15
OH
OTIPS
R
16
H
O
C
O+
TIPS
17
H+
NTf2
O—TIPS
TIPSNTf2
18
OH
HNTf2
14
OTIPS
TIPSNTf2
path b
[2+2]
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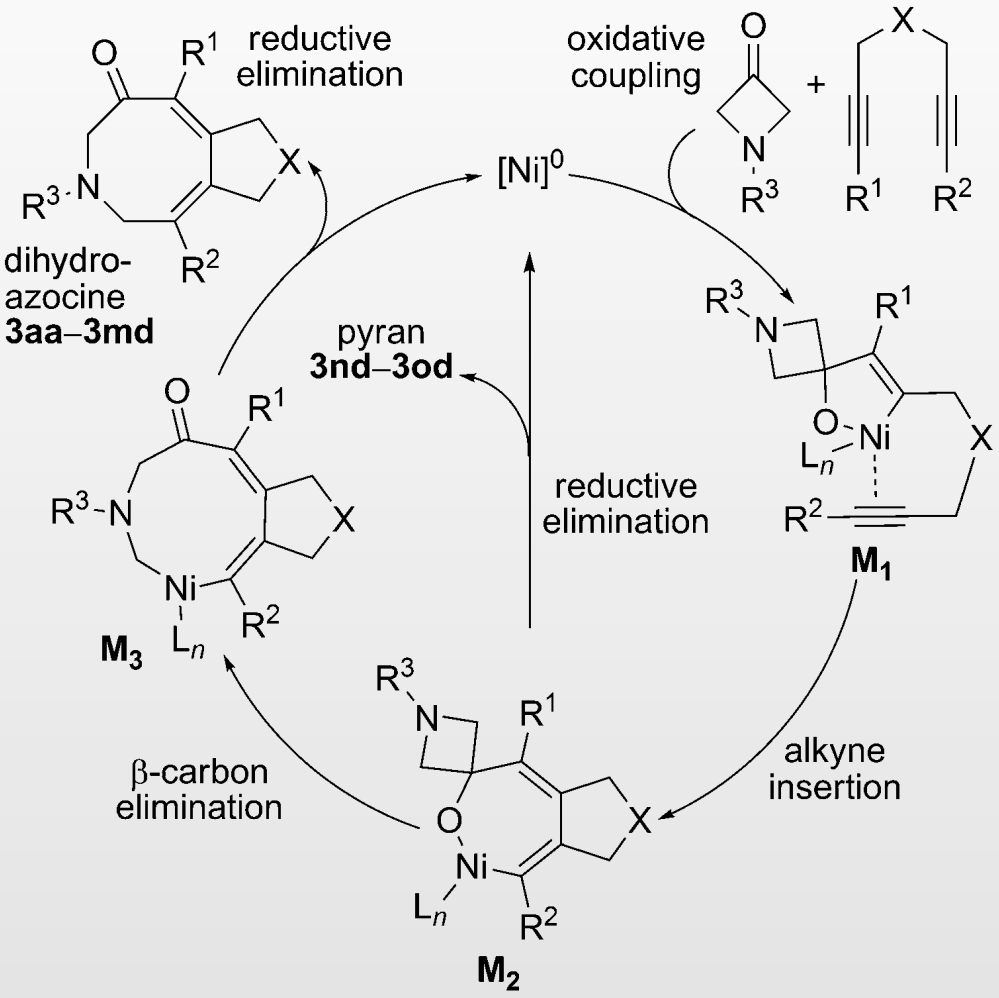
H+
R
OTIPS
19
O—TIPS
20
H+
21
O+
NHTf2

Question 3



for symmetrical diynes: $R^1 = R^2 = Me$

for unsymmetrical diynes: $R^1 = Me$ and $R^2 = H/OEt$