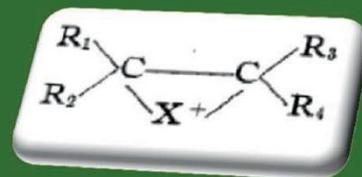


# **Catalytic, Stereoselective Dihalogenation of Alkenes: Challenges and Opportunities**

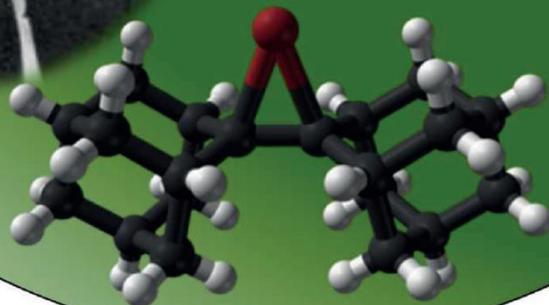
*Alexander J. Cresswell, Stanley T.-C. Eey, and Scott E. Denmark\**

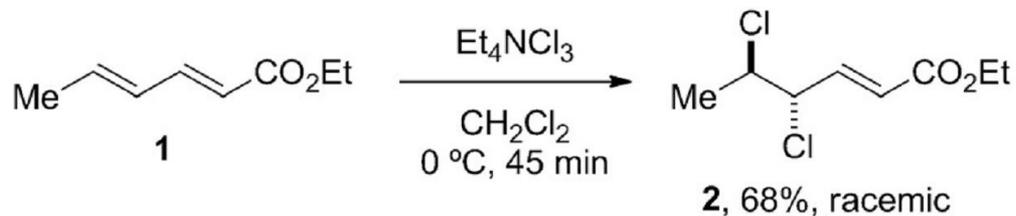
**Reporter: Sixuan Meng  
Supervisor: Prof. Huang  
2016-01-09**



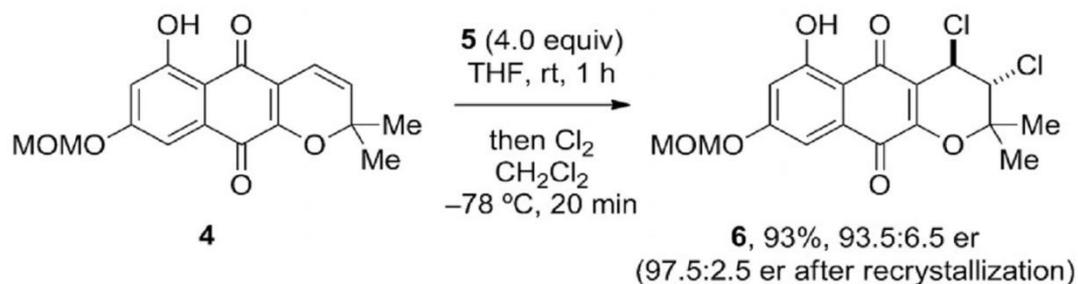
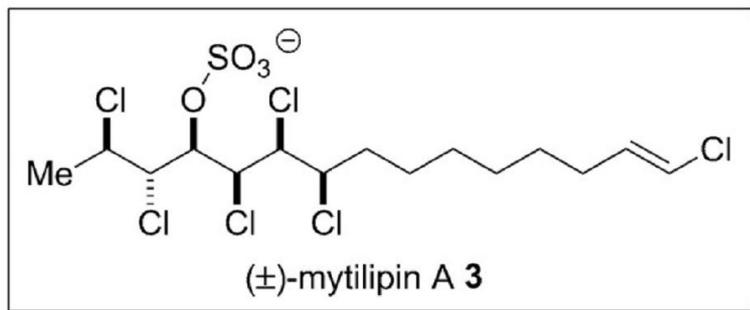
Recent work by Bartlett and Tarbel has shown that the first step in the reaction of halogen molecules with the ethylene linkage leads to the formation of a negative halide ion and a positively charged organic ion..... Another possible structure of the ion is one in which the positive charge is on the halogen. The  $X^+$ , being isoelectronic with a member of the oxygen family, should show a valence of two, i. e., it should form a structure of the ethylene oxide type....

Roberts and Kimball, *J. Am. Chem. Soc.* 1937, 59, 946

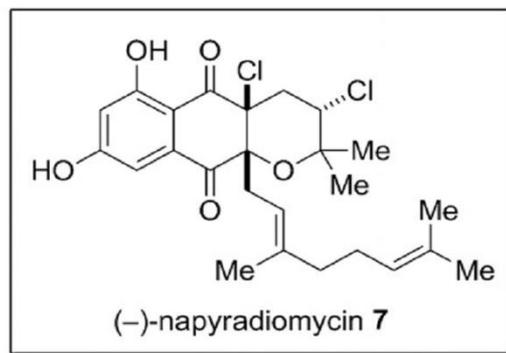
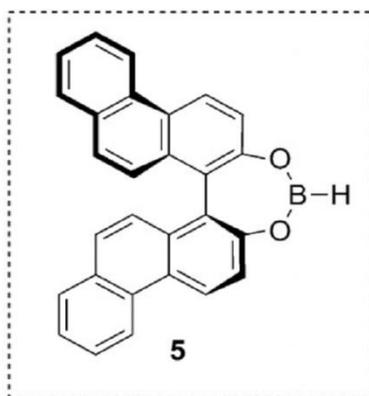




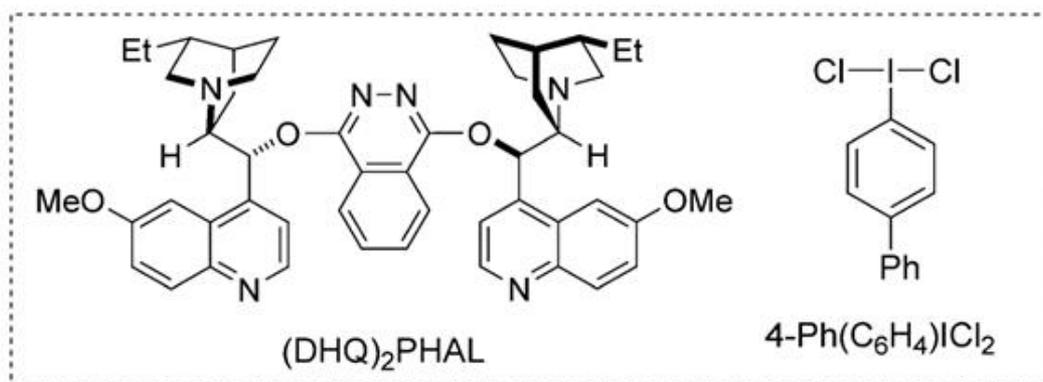
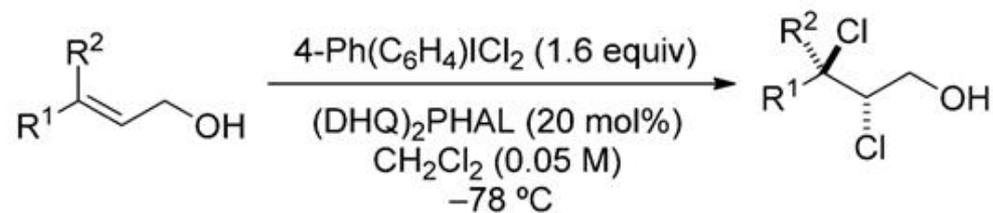
A racemic alkene dichlorination as the first step of Carreira's chlorosulfolipid total synthesis.



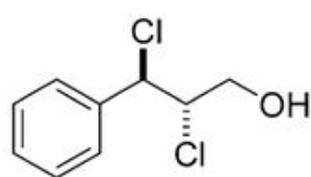
Snyder's stoichiometric, enantioselective alkene dichlorination en route to (-)-napyradiomycin



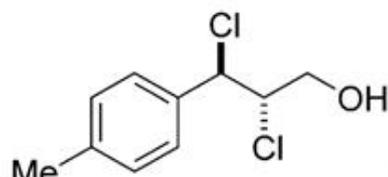
# \* Example for diclorination



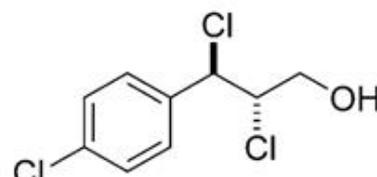
## selected examples



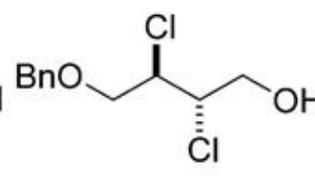
63%, 90.5:9.5 er



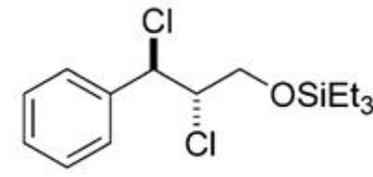
65%, 72:28 er



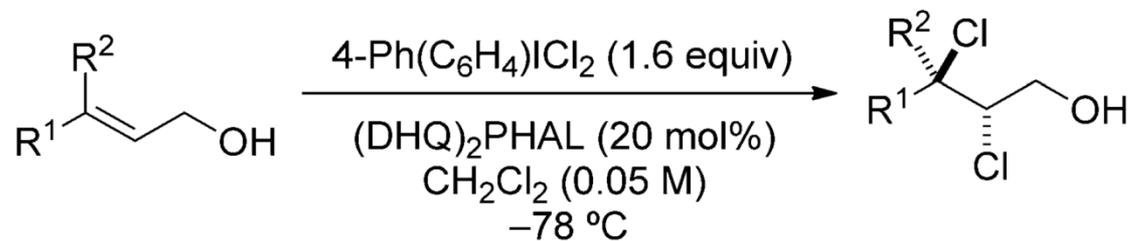
81%, 85.5:14.5 er



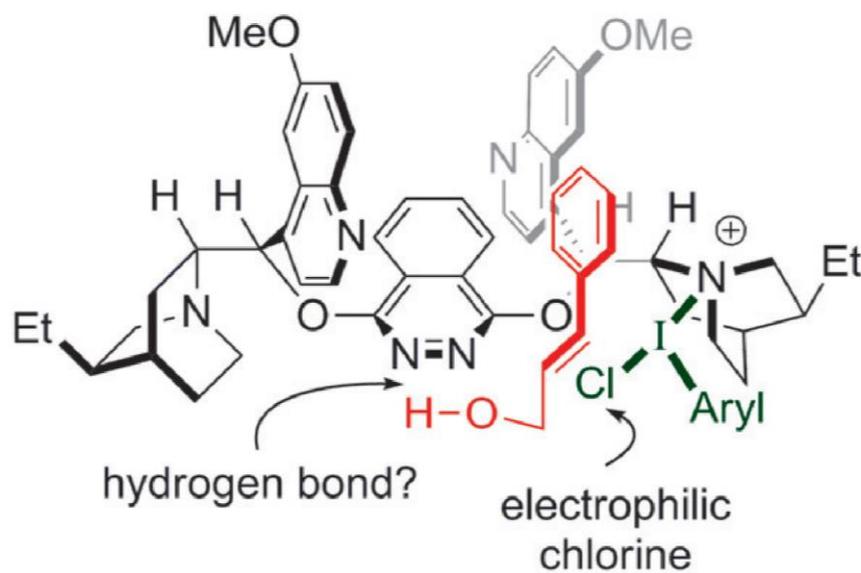
48%, 71.5:28.5 er



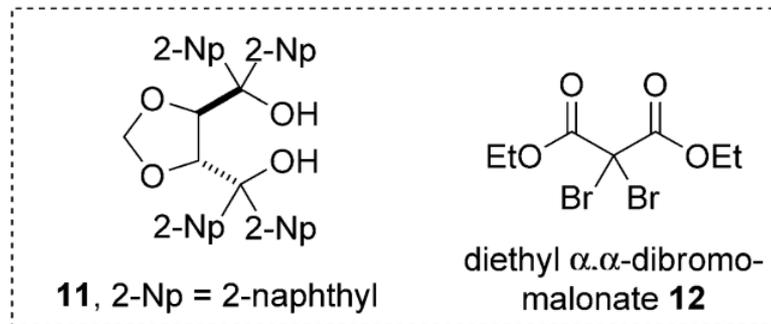
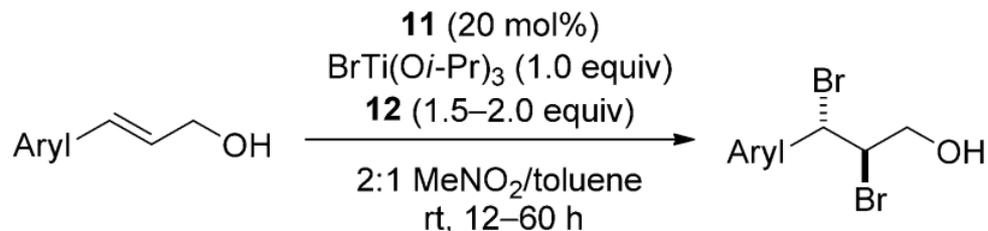
32%, <52.5:47.5 er



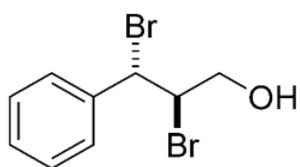
## Proposed stereoreinduction model



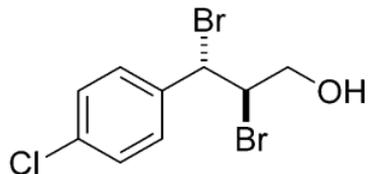
# \* Example for dibromination



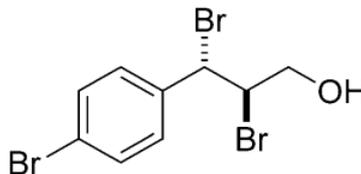
## selected examples



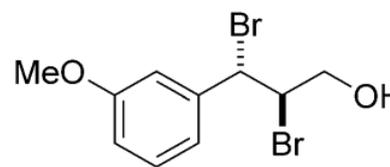
60%, 88:12 er  
[63%, 93:7 er with  
100 mol% **11**]



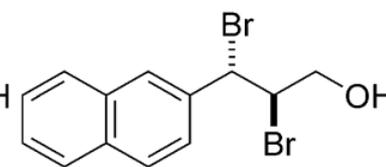
60%, 92.5:7.5 er  
[64%, 95:5 er with  
100 mol% **11**]



51%, 92:8 er  
[64%, 95:5 er with  
100 mol% **11**]



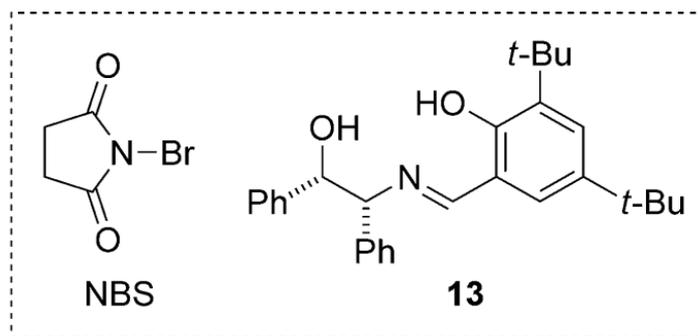
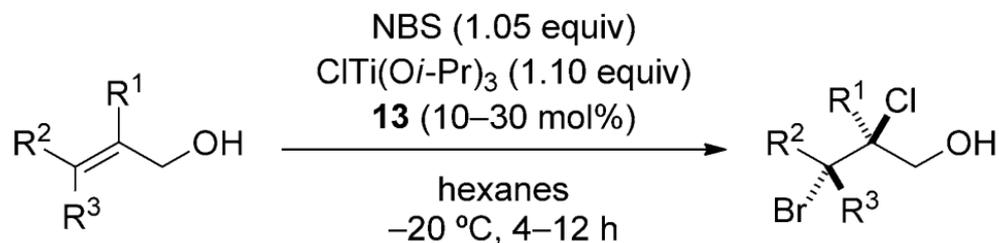
72%, 88:12 er  
[71%, 91.9 er with  
100 mol% **11**]



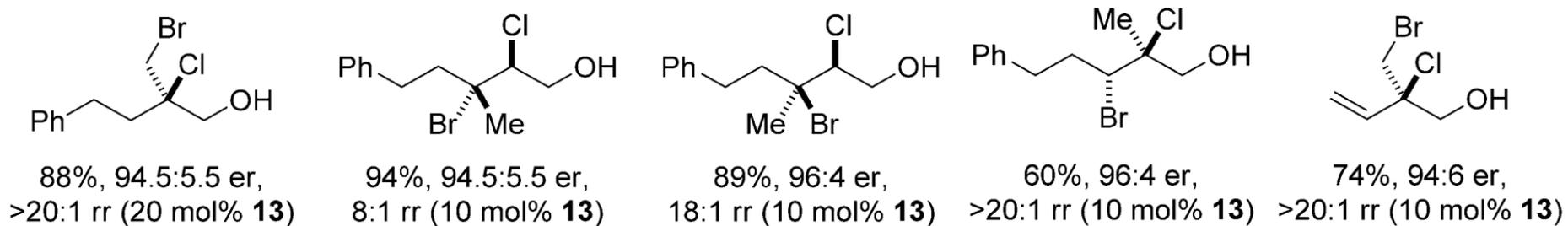
60%, 86.5:13.5 er  
[70%, 91.5:8.5 er with  
100 mol% **11**]



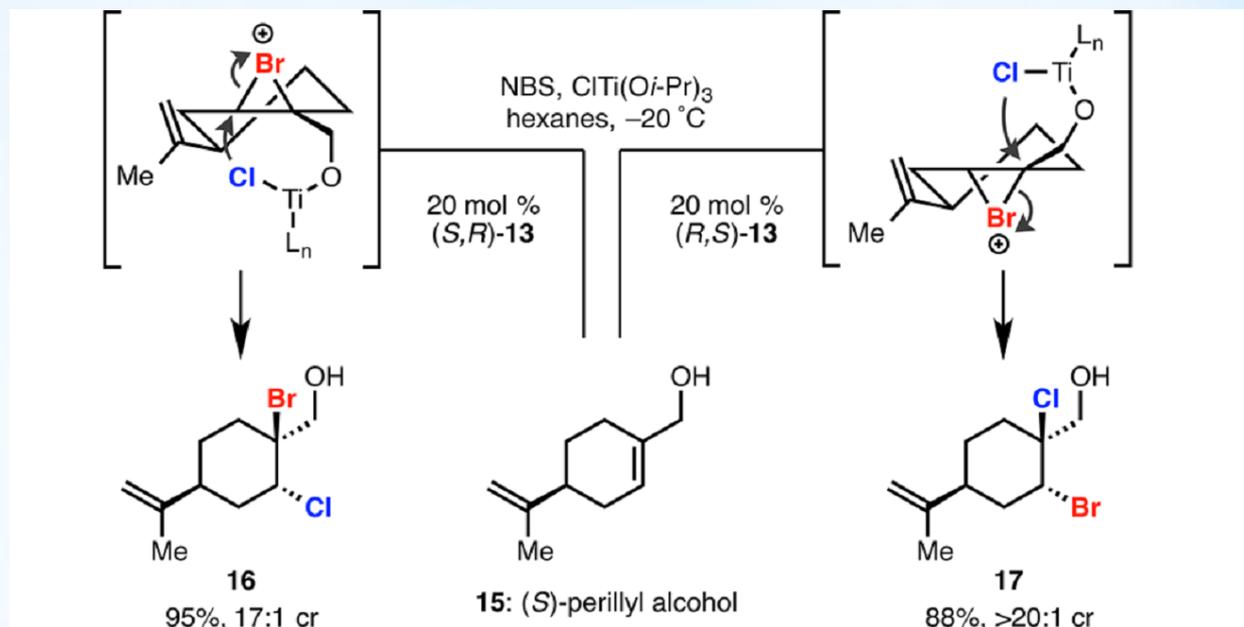
# \* Example for chlorobromination



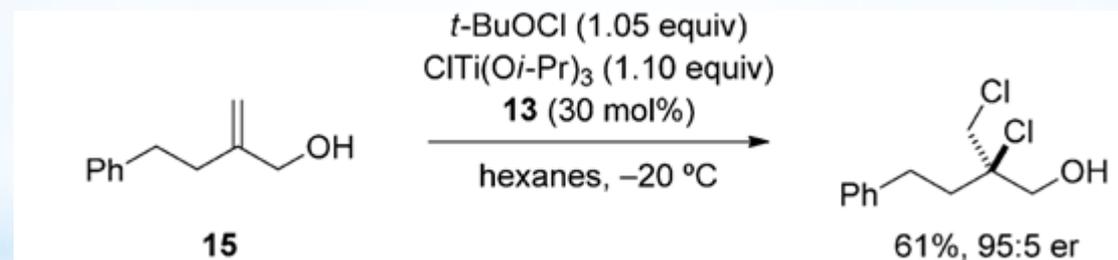
## selected examples



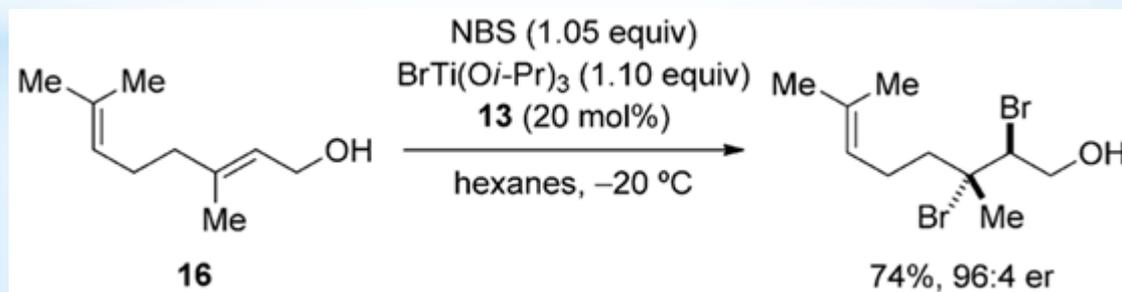
# Selective Bromochlorination



## Dichlorination:



## Dibromination:



- \* **Challenges for Stereoselective Catalysis**
  - \* **The dihalogenating reagents problem**
  - \* **The catalysis problem**
  - \* **The enantioselectivity problem**
  - \* **The product racemization problem**
  - \* **The diastereocontrol problem**

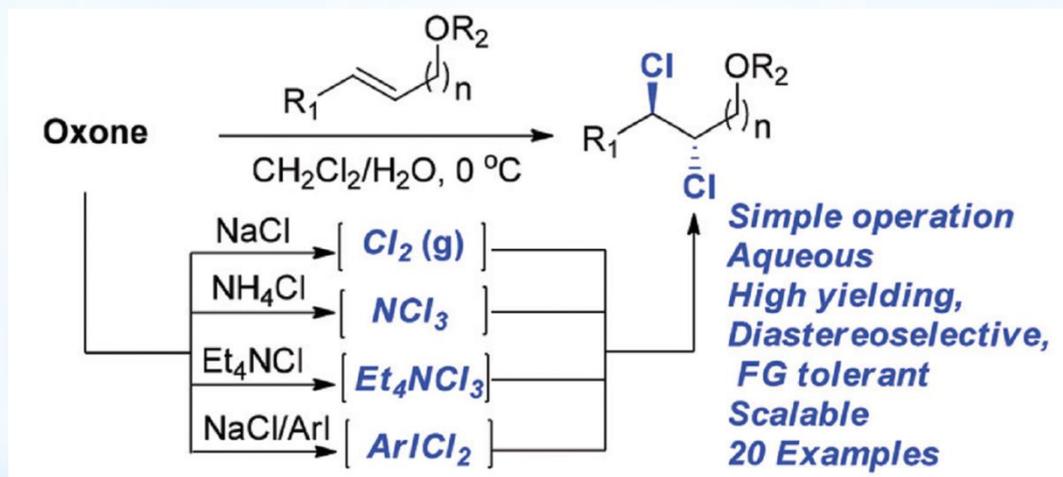
\* “Dihalogen carrier”

eg: ammonium polyhalide salts  $[R_4N]^+[(X_2)_nX]^-$ ,

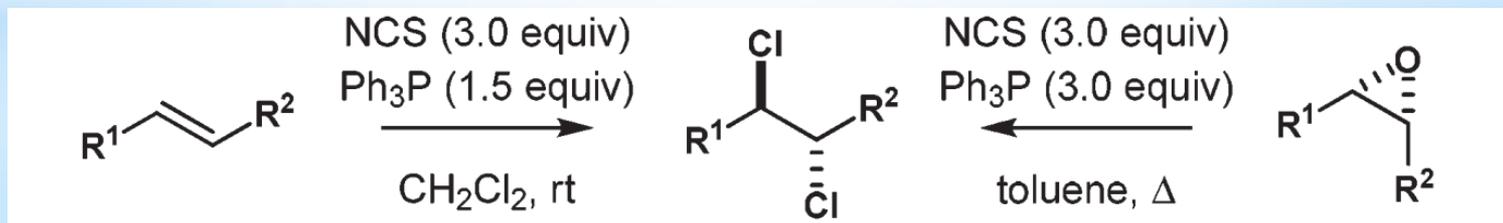


\* In situ generation

halide oxidation:  $H_2O_2-HCl$ ,  $KMnO_4-Me_3SiCl-BnEt_3NCl$ , Oxone- $NaCl$ .



halenium reduction: a 2:1 NCS: $Ph_3P$  reagent system



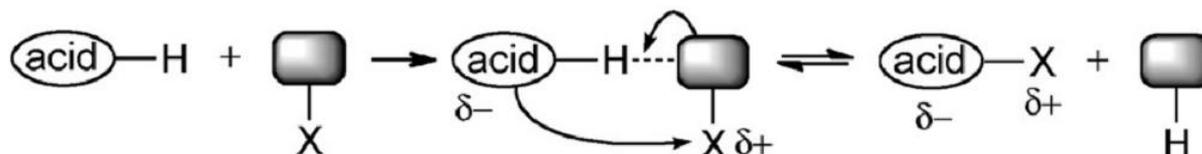
J. Ren *et al.* *Org. Biomol. Chem.* 2013, 11, 4312

T. Yoshimitsu *et al.* *Org. Biomol. Chem.* 2013, 11, 1598

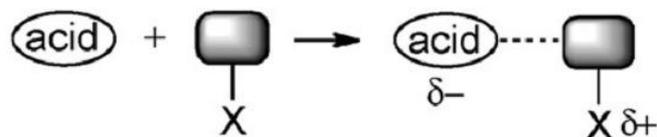
# \* The catalysis problem

## General strategies

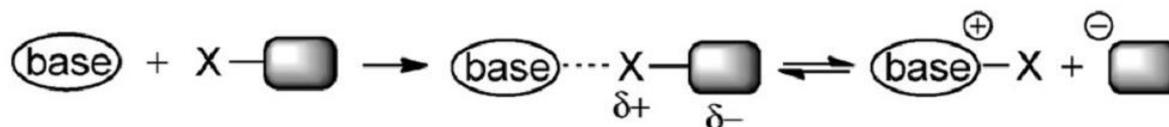
### Brønsted acid



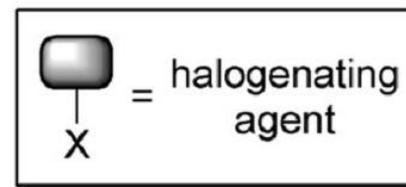
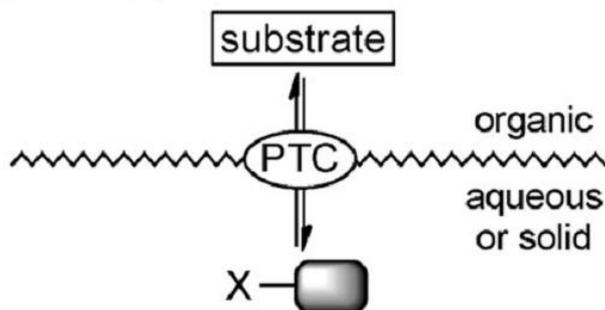
### Lewis acid



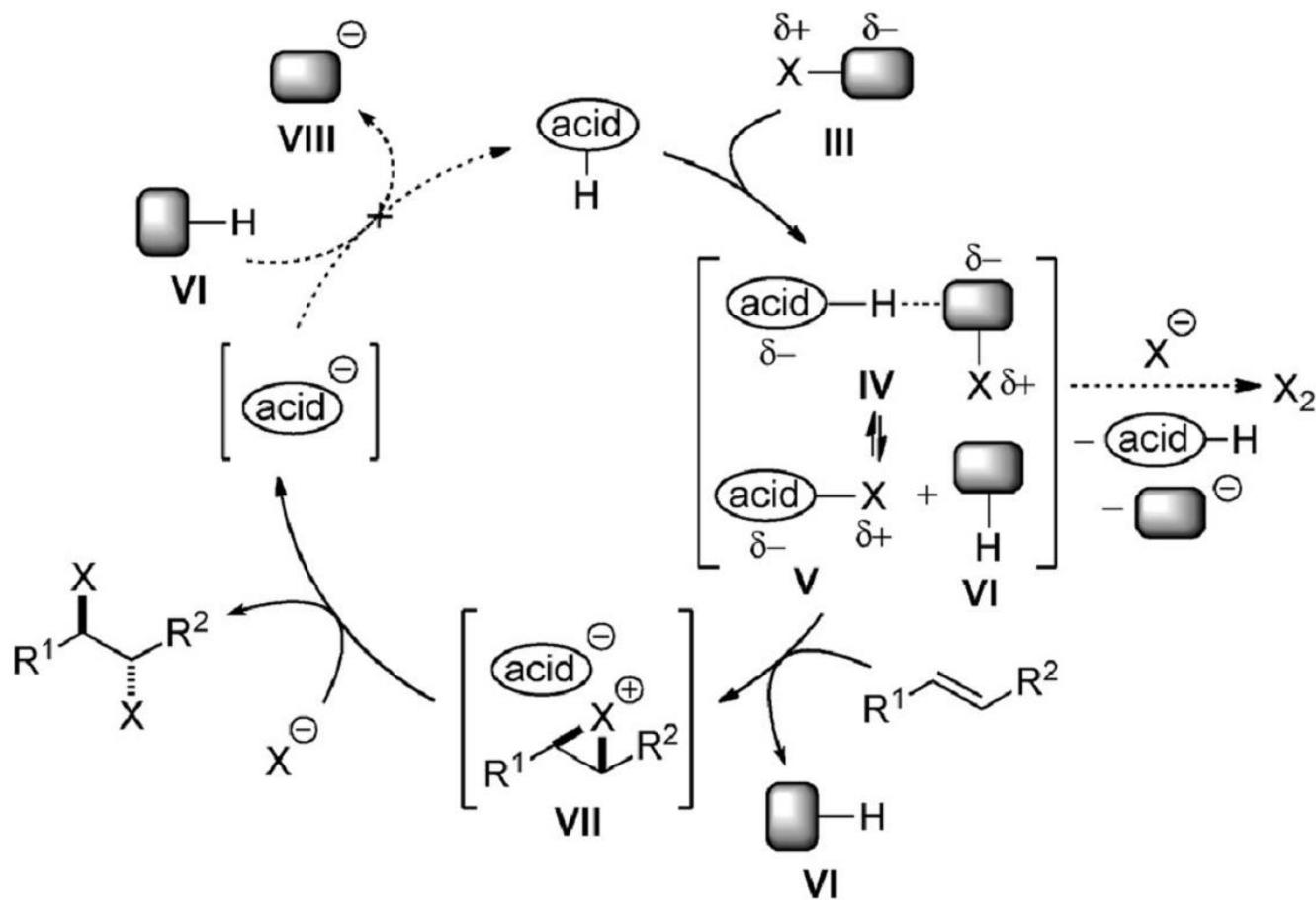
### Lewis base



### Phase transfer

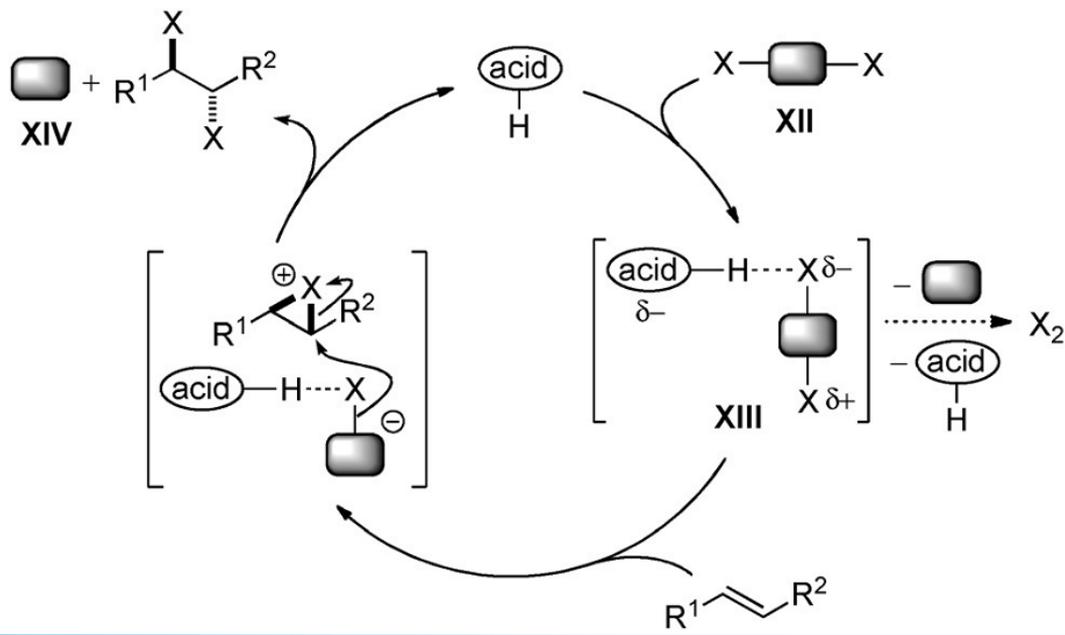
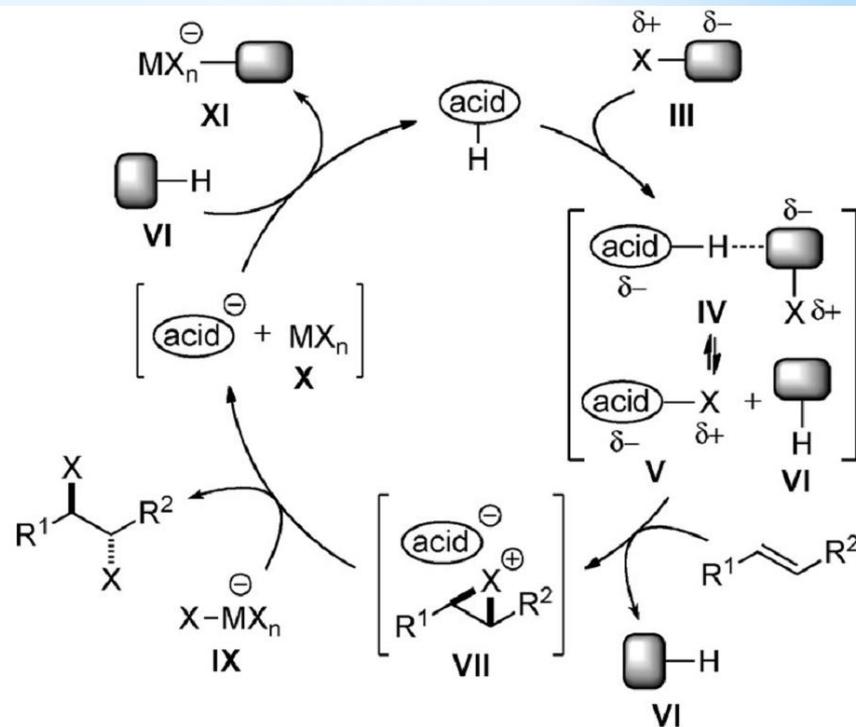


## \*Bronsted acid catalysis



**Scheme 11.** A Brønsted acid-catalyzed alkene dihalogenation using separate  $X^+$  and  $X^-$  sources.

Using a complex anion of the halide as an X<sup>-</sup> source.

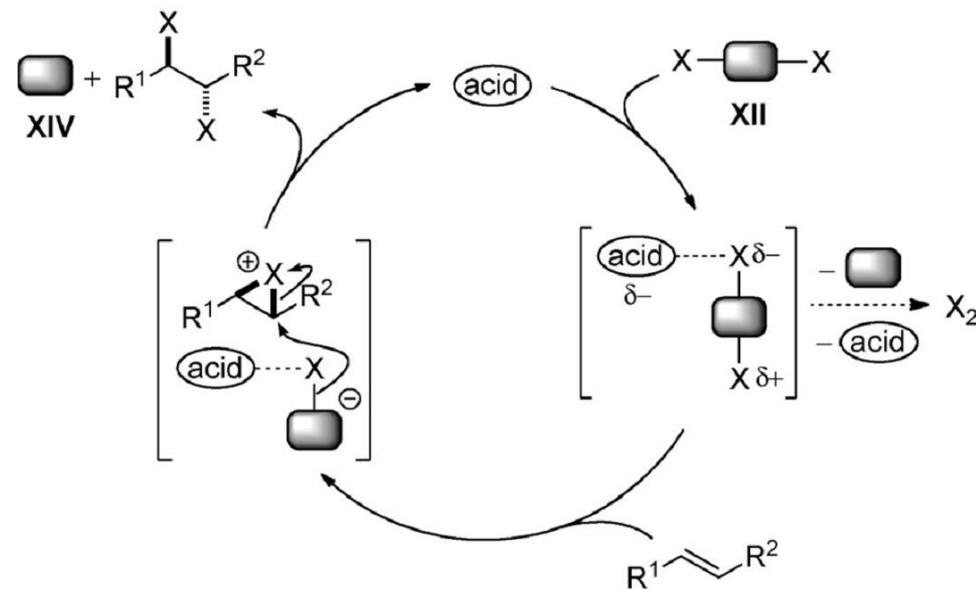
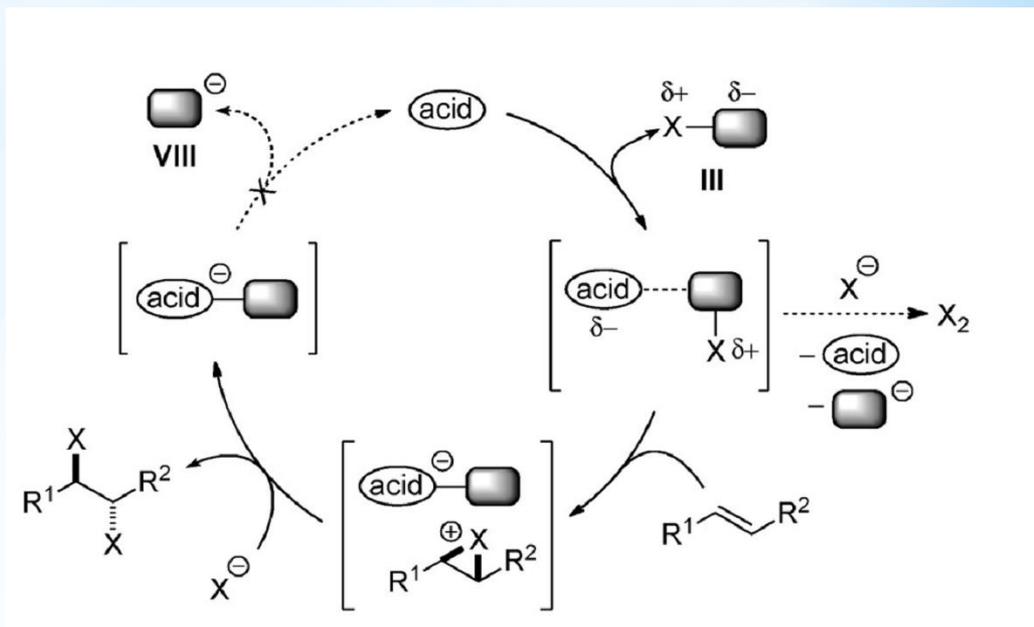


using a dihalogen equivalent XII as a single reagent.

only a neutral by-product XIV is generated

# \* Lewis acid catalysis

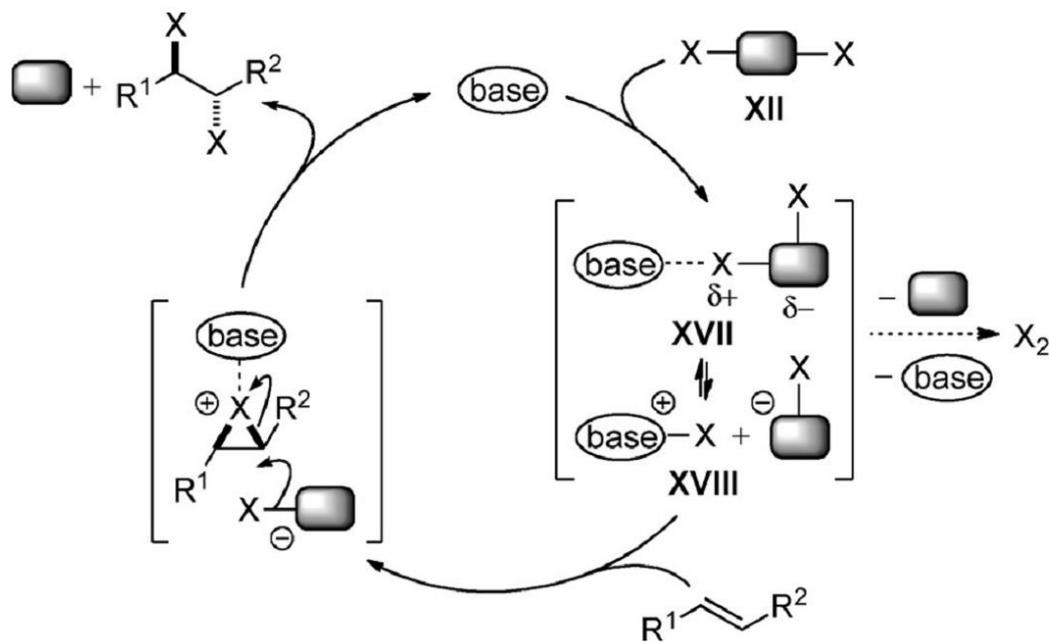
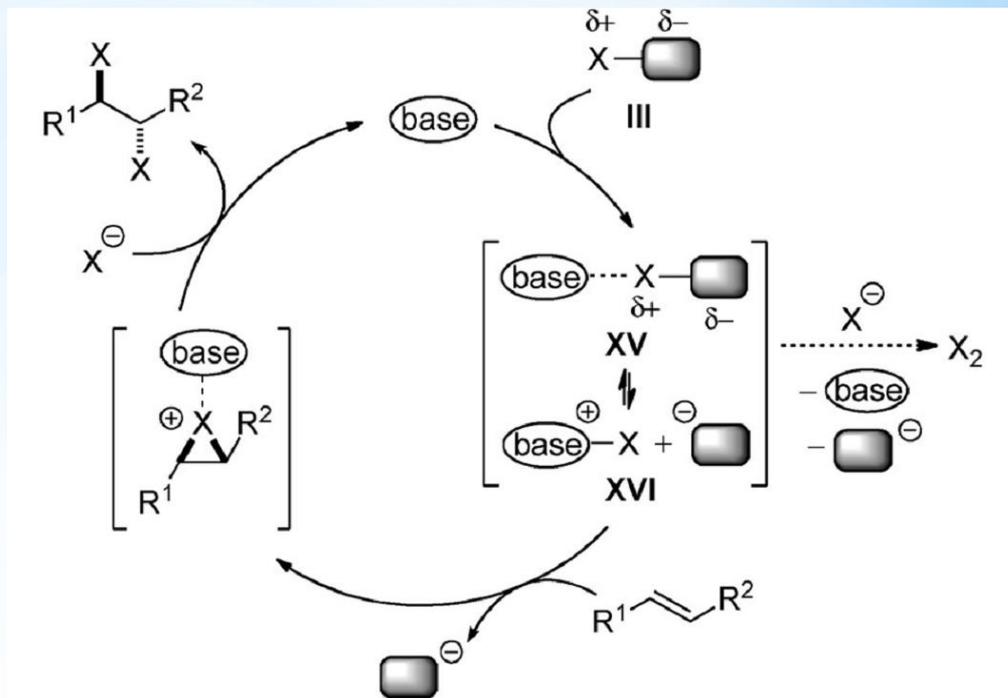
using separate  $X^+$  and  $X^-$  sources



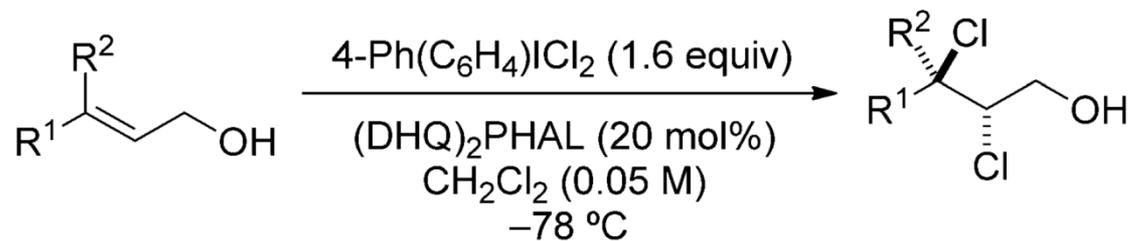
using a dihalogen equivalent XII as a single reagent.

# \* Lewis base catalysis

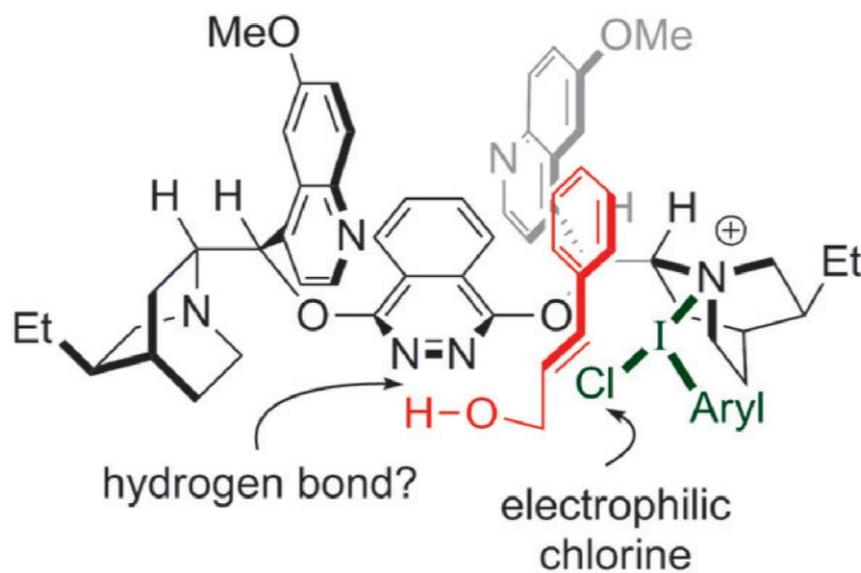
using separate  $X^+$  and  $X^-$  sources



using a dihalogen equivalent XII as a single reagent.

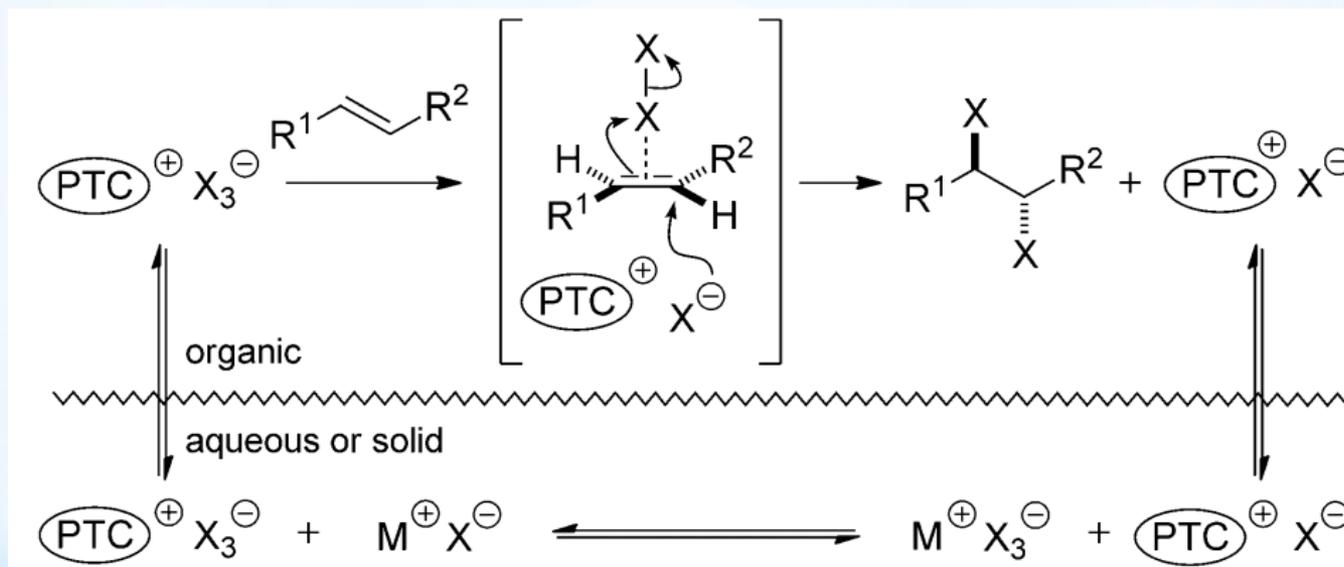


## Proposed stereinduction model



# \*Phase transfer catalysis

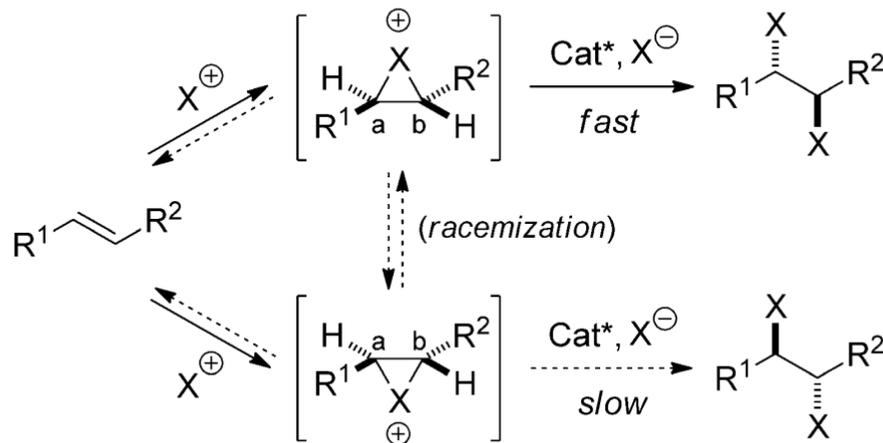
## Cationic phase transfer-catalyzed alkene dihalogenation





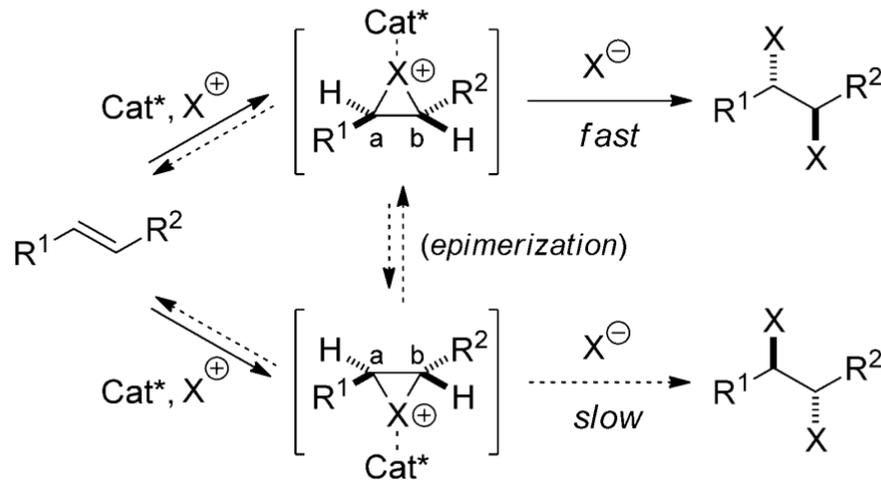
# \* Enantiodetermining nucleophilic trapping

**Dynamic kinetic resolution** (with substrate- or catalyst-controlled halide attack at carbon "a")



Depends on  $k_A/k_B$

**Dynamic kinetic asymmetric transformation (type 1)**  
(with substrate- or catalyst-controlled halide attack at carbon "a")

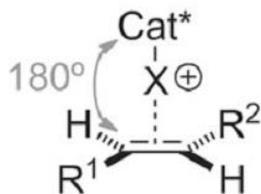


Depends on  $k_A/k_B$ ,  $[I_A]/[I_B]$   
e.g.

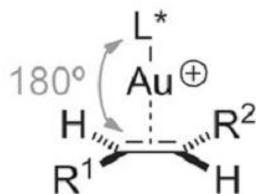
a  $k_A/k_B$  value of 5 in combination with  $[I_A]/[I_B]=4$  would still give 20:1 er in favor of A

# \* Enantiodetermining haliranium ion formation

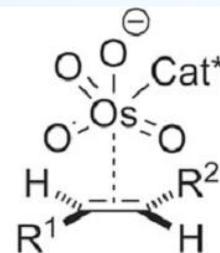
## Haliranium ion formation:



*difficult to relay  
stereochemical information  
via  $\sigma^*$  orbital*

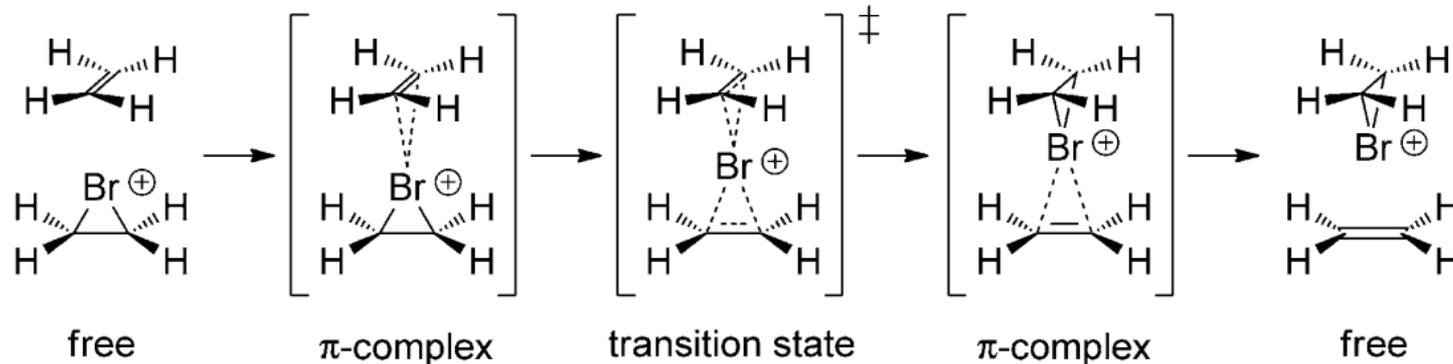


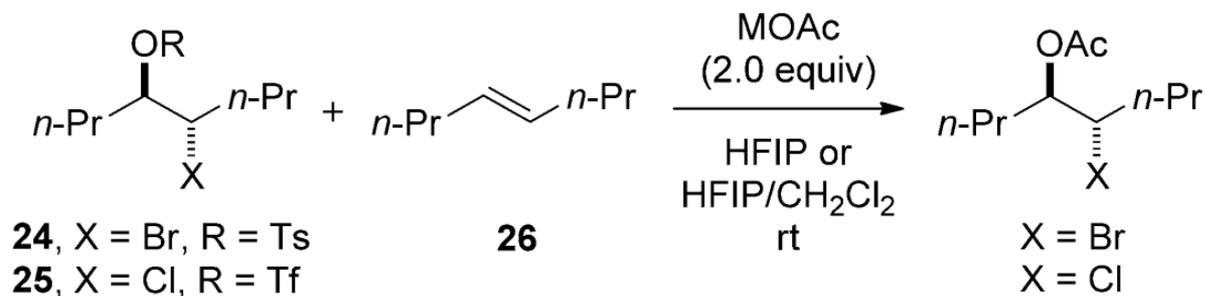
*similar issue in  
Au(I) catalysis due  
to linear  
coordination  
geometry*



*access to  $\pi^*$  enables  
more diverse geometries  
and better stereochemical  
communication*

## Alkene-to-alkene transfer:

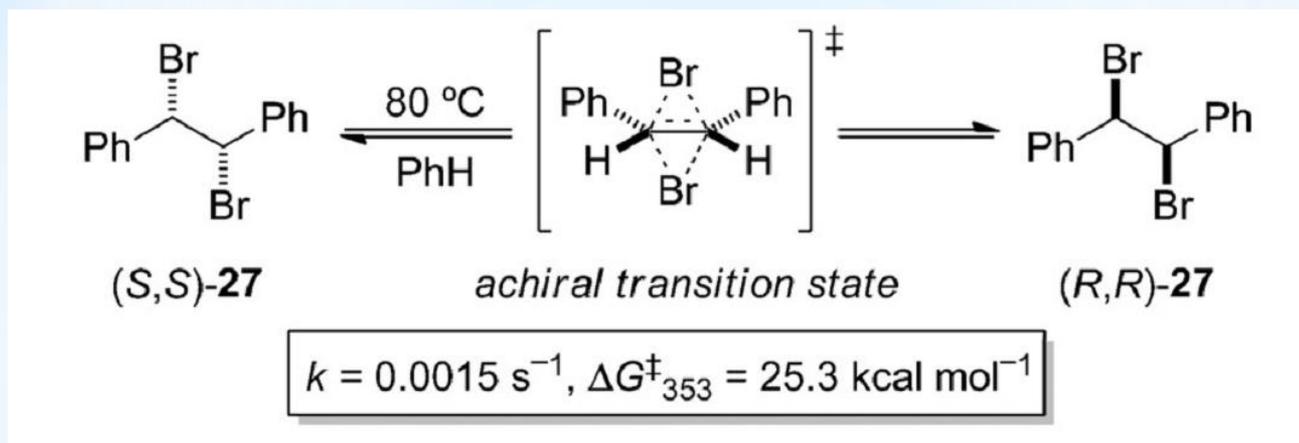




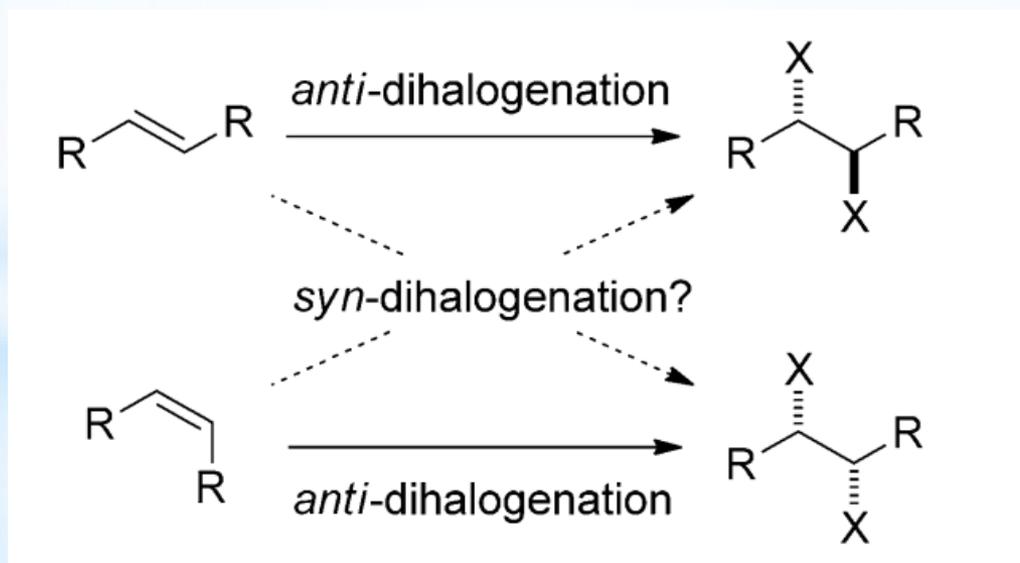
X	M	<b>26</b> , Equiv	es (%)
Br	Na	0.0	100
Br	Na	1.0	26
Br	<i>n</i> -Bu <sub>4</sub> N	1.0	81
Cl	<i>n</i> -Bu <sub>4</sub> N	1.0	100

**Scheme 28.** Erosion of enantiospecificity in acetolysis from alkene-to-alkene transfer. HFIP = hexafluoroisopropanol, Tf = trifluoromethanesulfonyl, Ts = 4-toluenesulfonyl,  $es = (ee_{\text{product}}/ee_{\text{starting material}}) \times 100\%$ .

## \* The product racemization problem



## \* The diastereocontrol problem



# \* Mechanistic Classification of Alkene Dihalogenations

\* Type I Dihalogenation

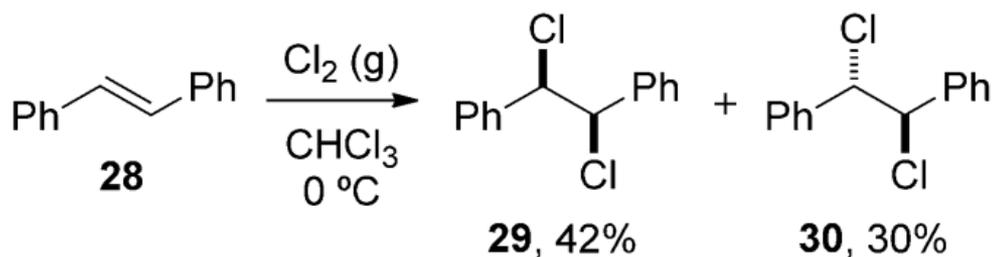
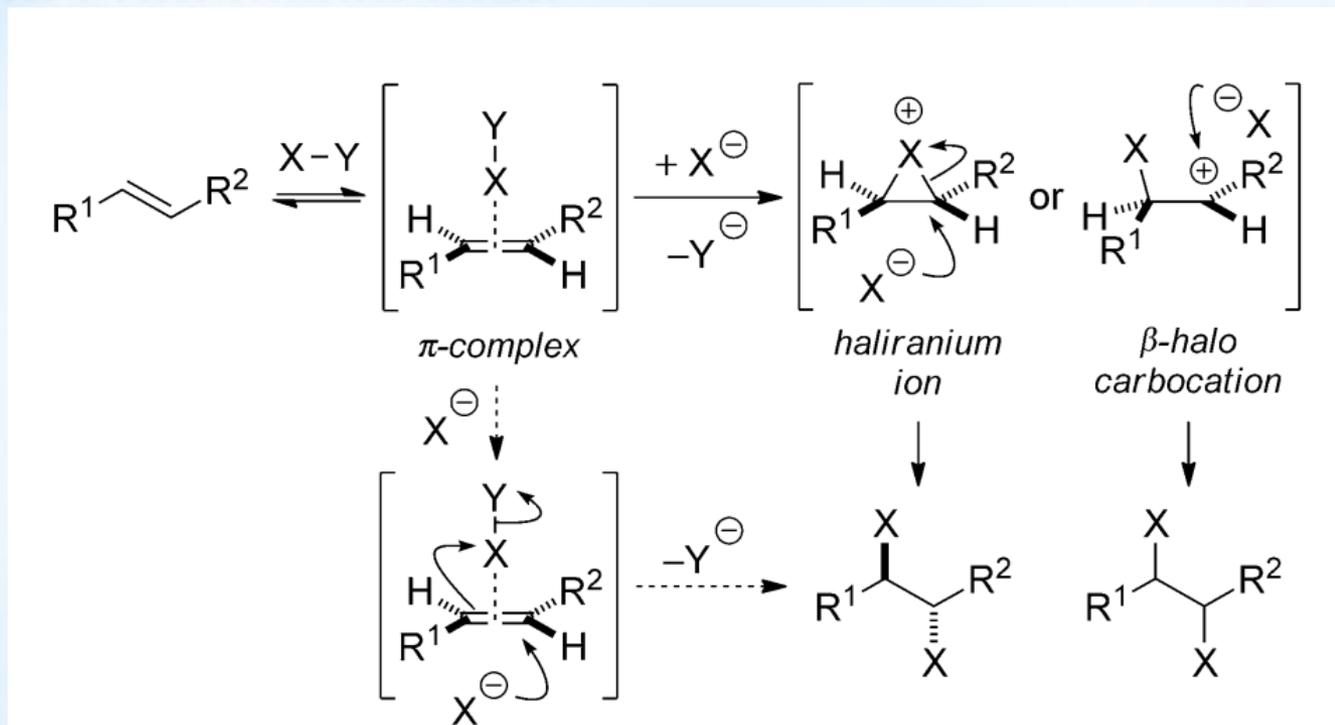
\* Type II Dihalogenation

\* Type III Dihalogenation

\* Type IV Dihalogenation

\* Type V Dihalogenation

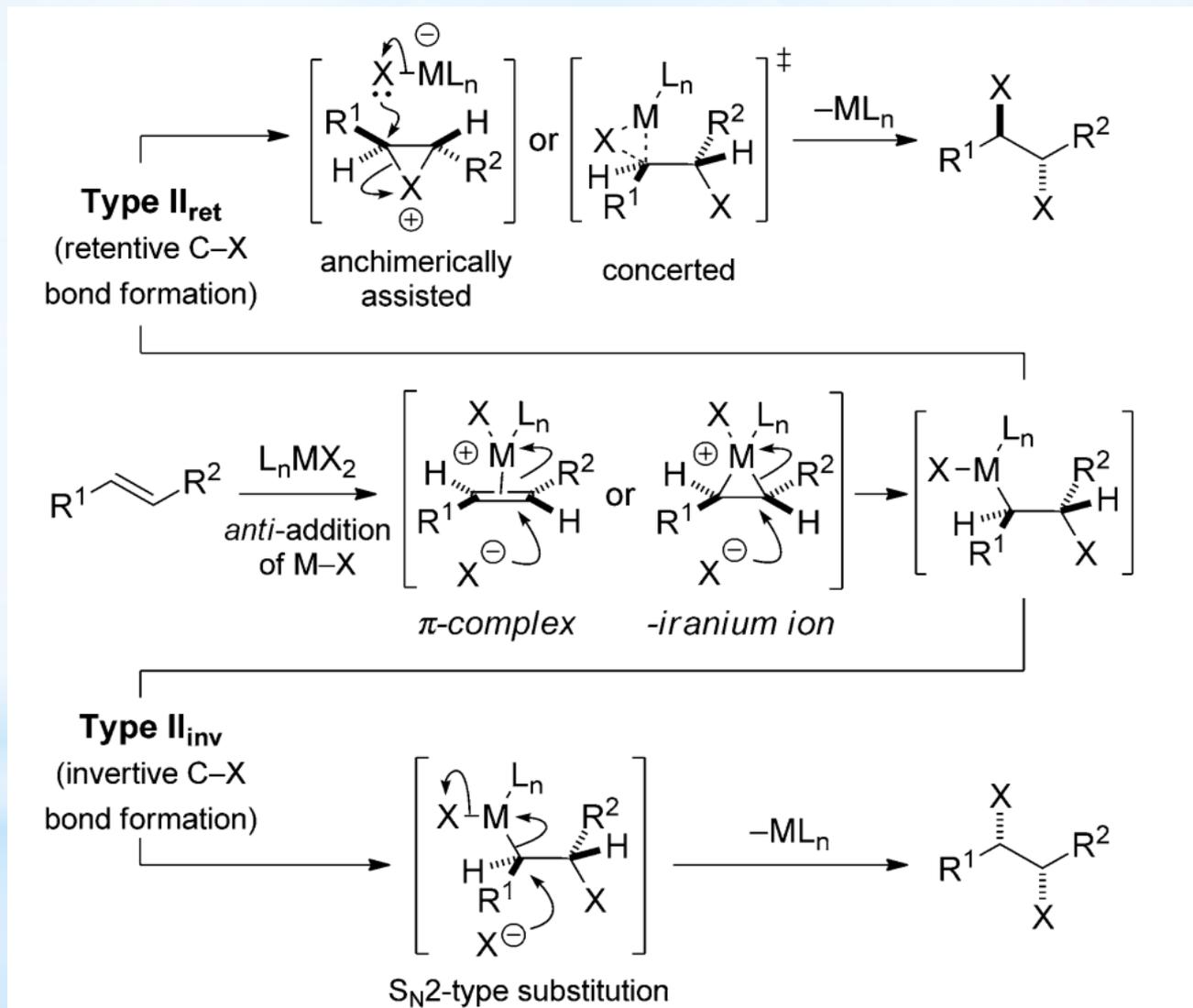
## \* Type I Dihalogenation



Factors to reduce the halogen bridging:

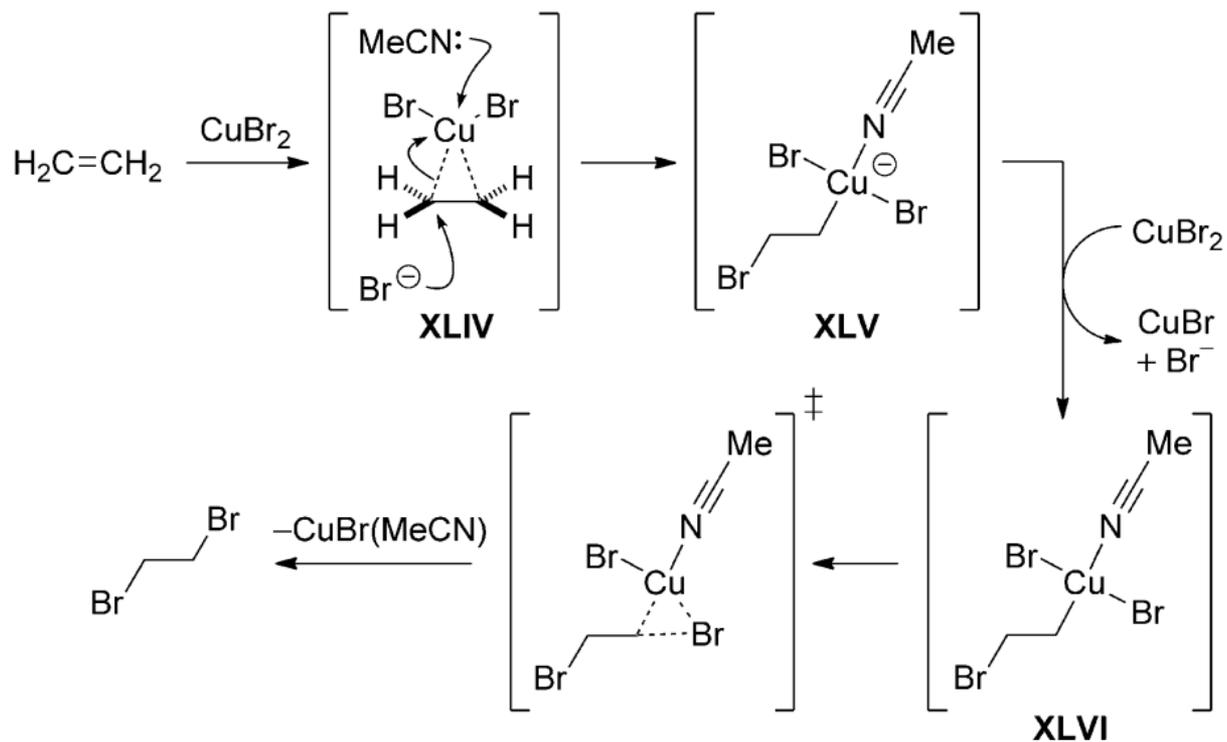
- Cation-stabilizing substituents at one end of the halonium ion
- High dielectric solvents
- Chlorine as the halogen

# \* Type II Dihalogenation



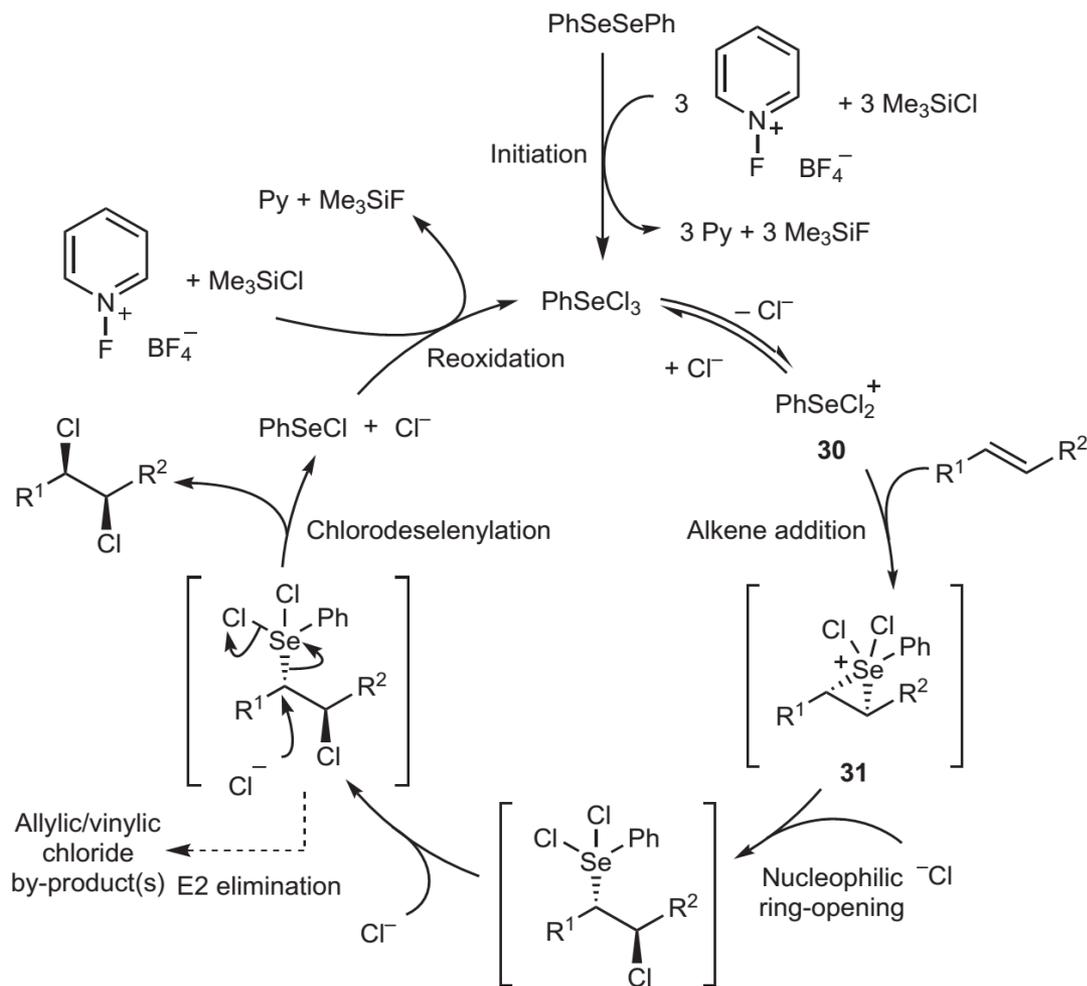
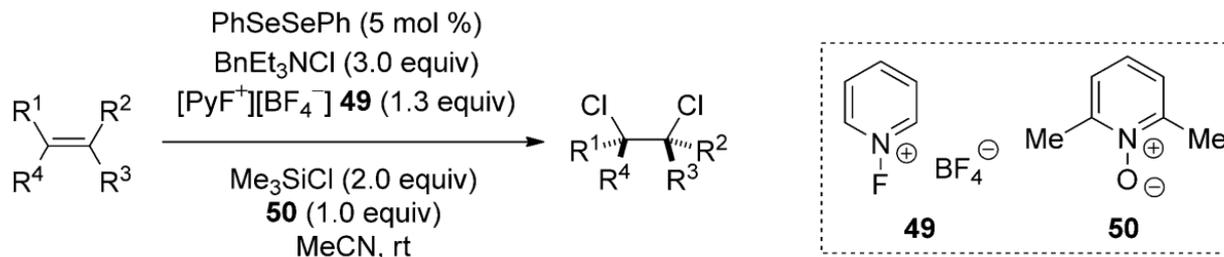
**M = a metal or main group electrophile**

\*Type II<sub>ret</sub>

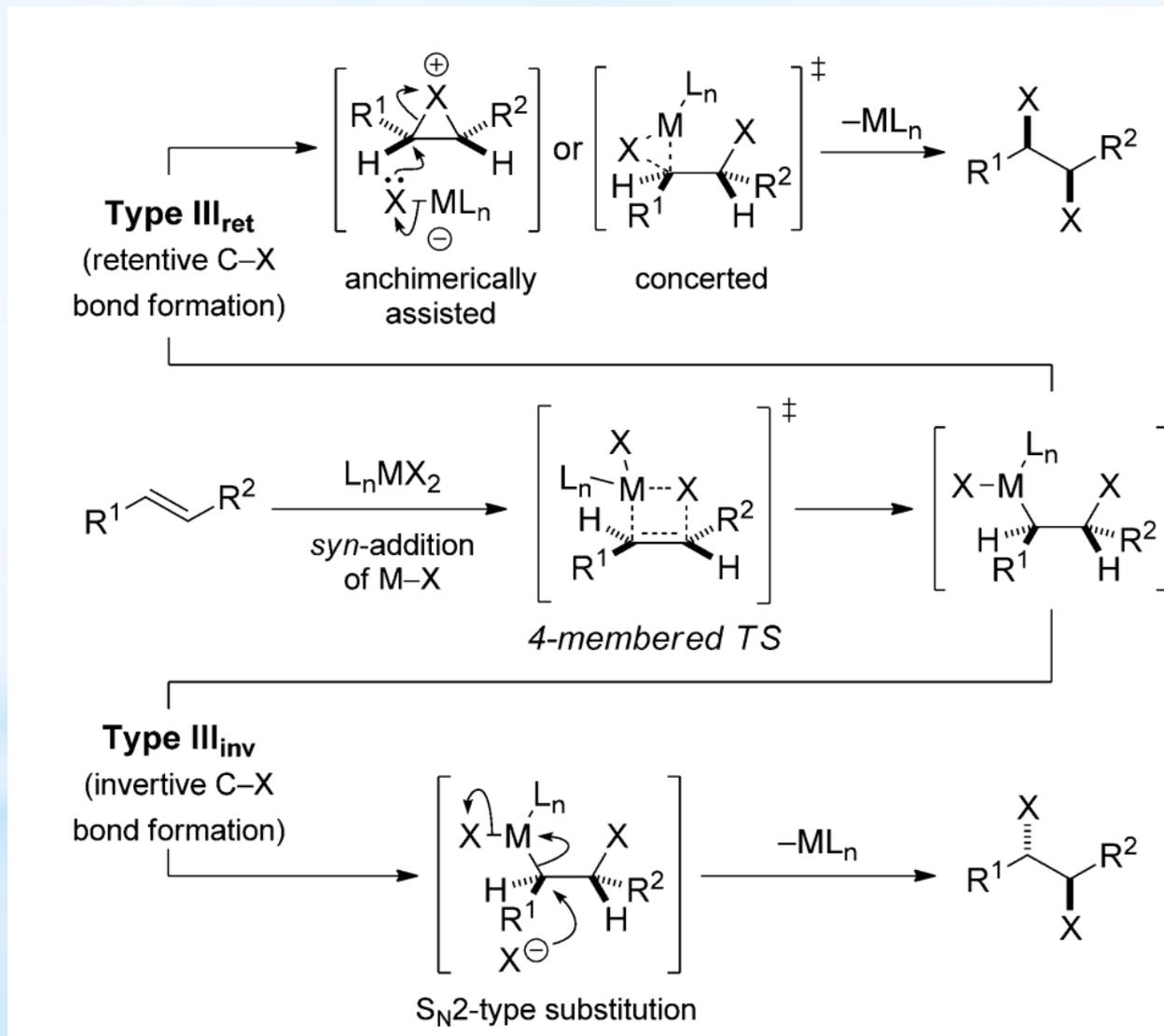


**Scheme 84.** Calculated Type II<sub>ret</sub> mechanism for alkene dibromination with  $\text{CuBr}_2$  and  $\text{LiCl}$  in  $\text{MeCN}/\text{THF}$ .

# \*Type II<sub>inv</sub>

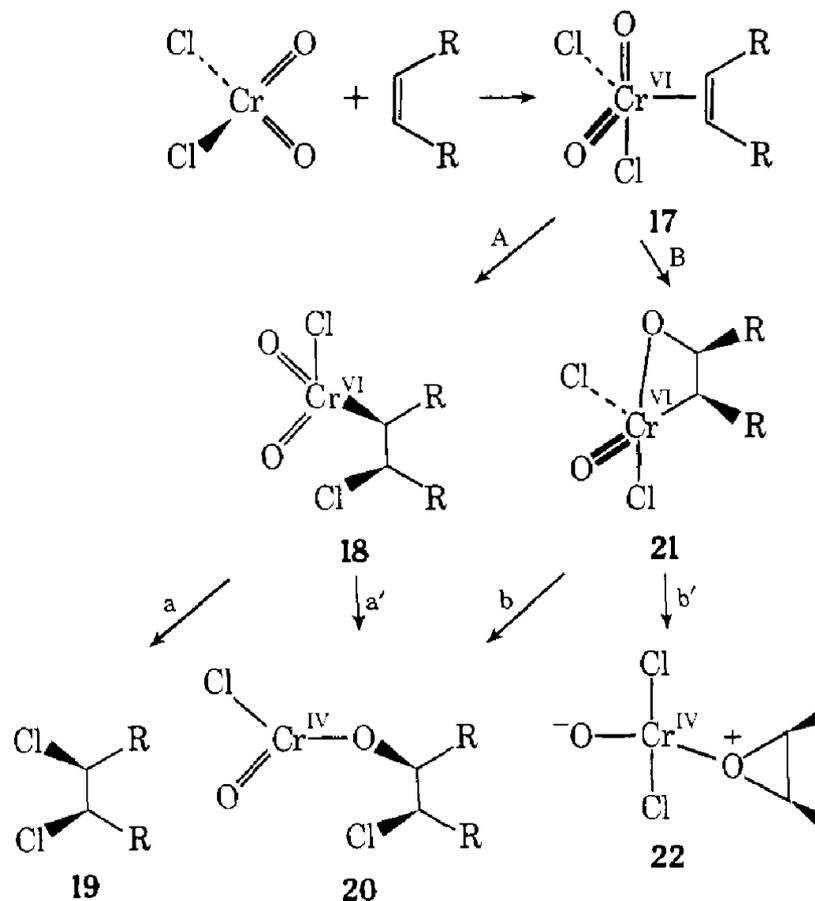


# \* Type III Dihalogenation

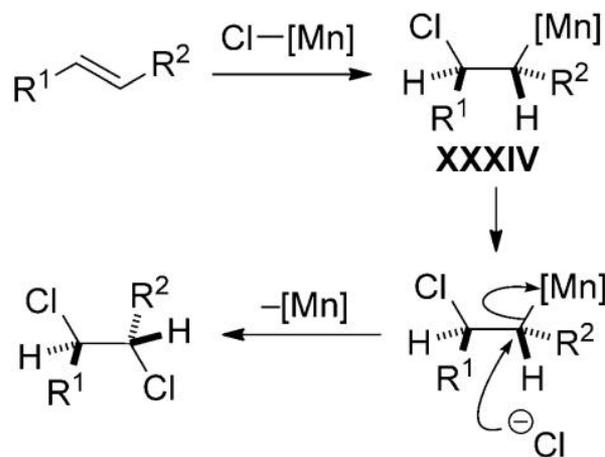
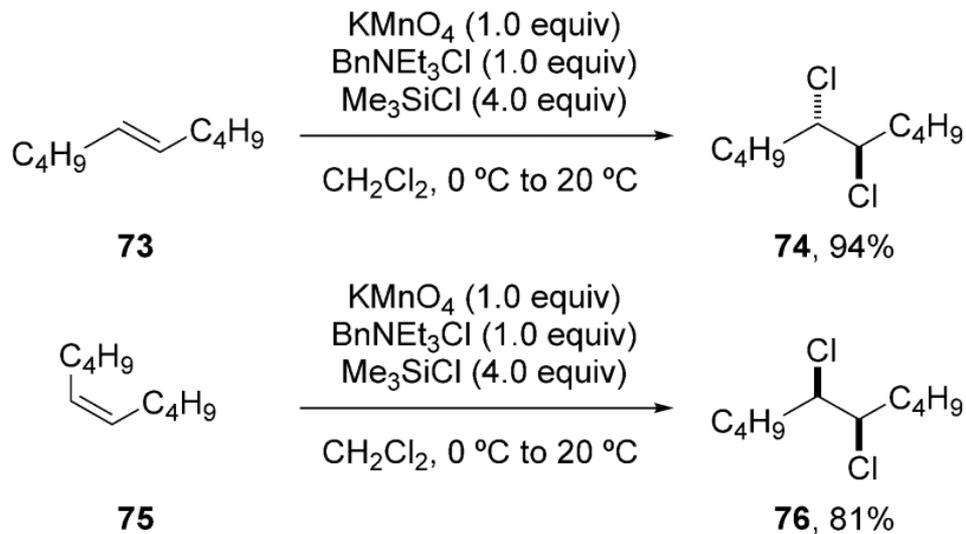


Chromyl Chloride Oxidations of Olefins. Possible Role of Organometallic Intermediates in the Oxidations of Olefins by Oxo Transition Metal Species

Scheme III. Mechanism Involving Organometallic Intermediates

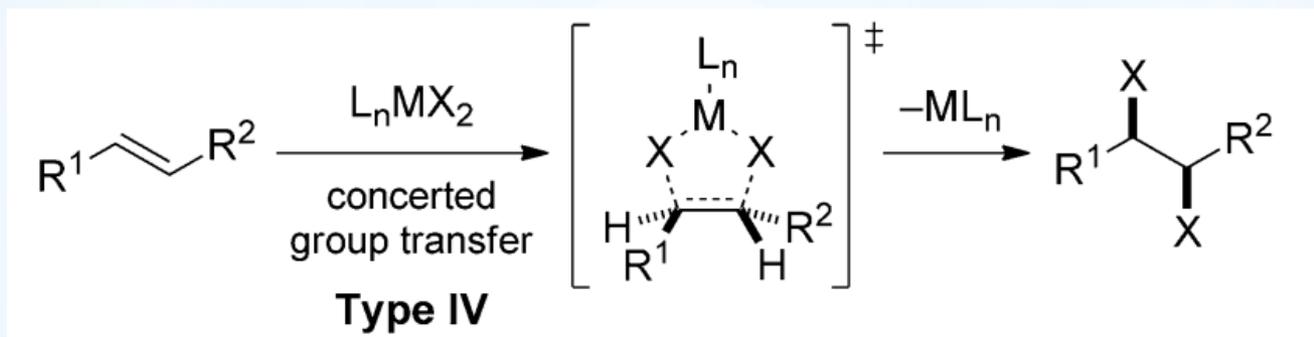


\*Type III<sub>inv</sub>

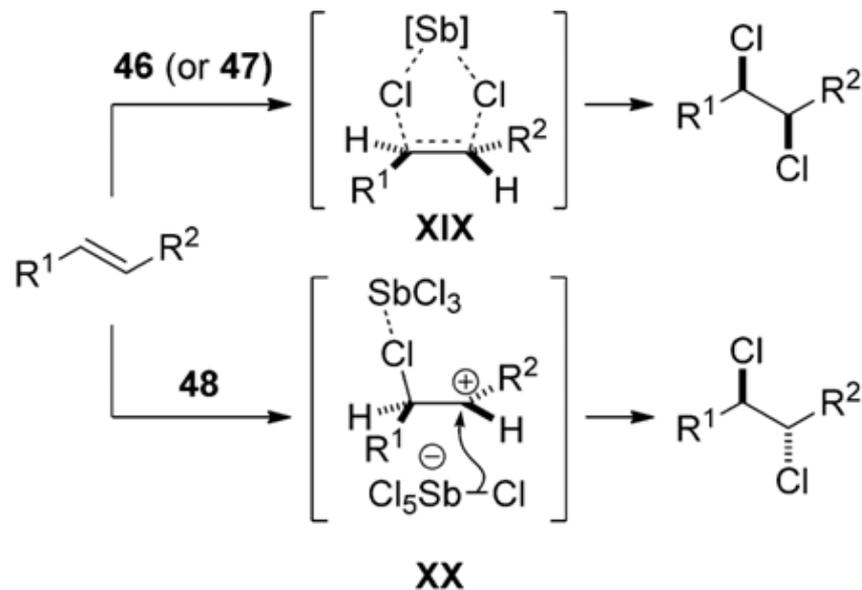
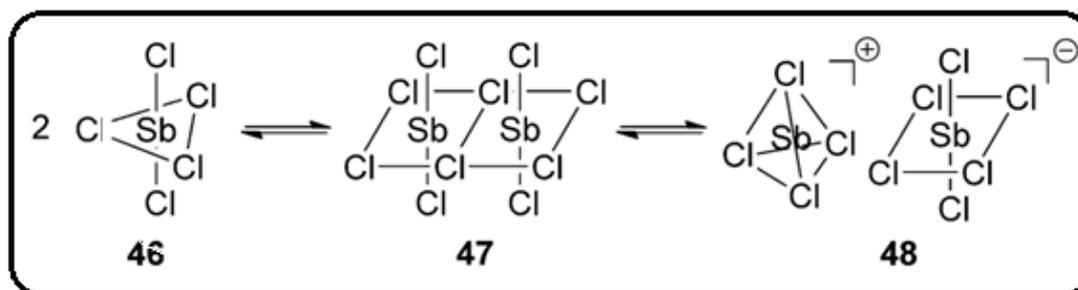
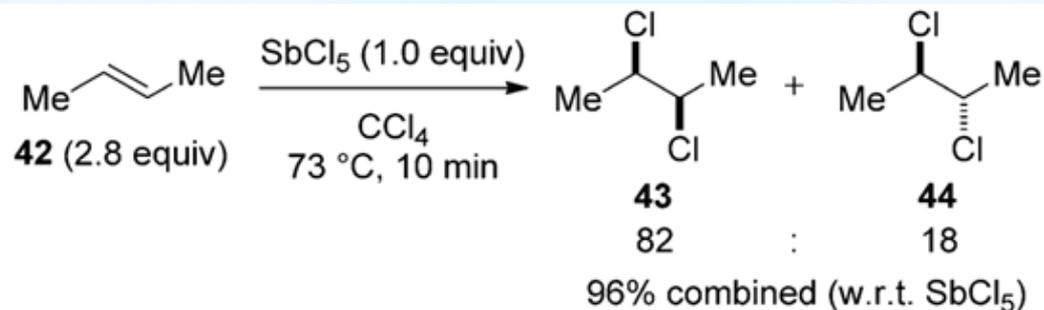


**Scheme 65.** Mechanistic proposal for the *anti*-dichlorination of alkenes by Markó's reagent.

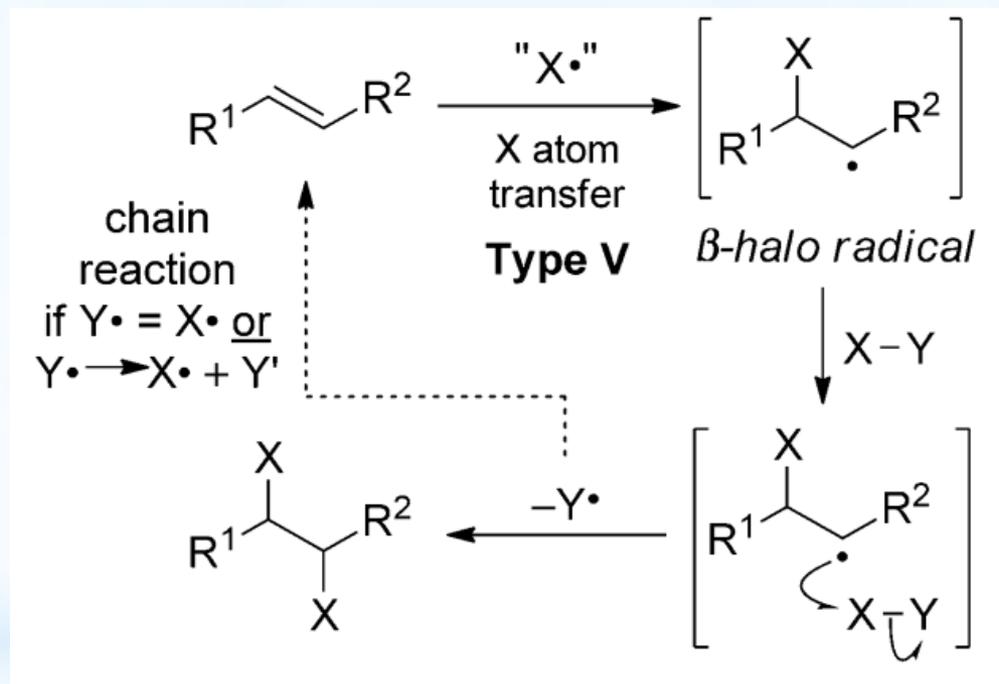
## \* Type IV Dihalogenation



# \* Type IV Dihalogenation



# \* Type V Dihalogenation



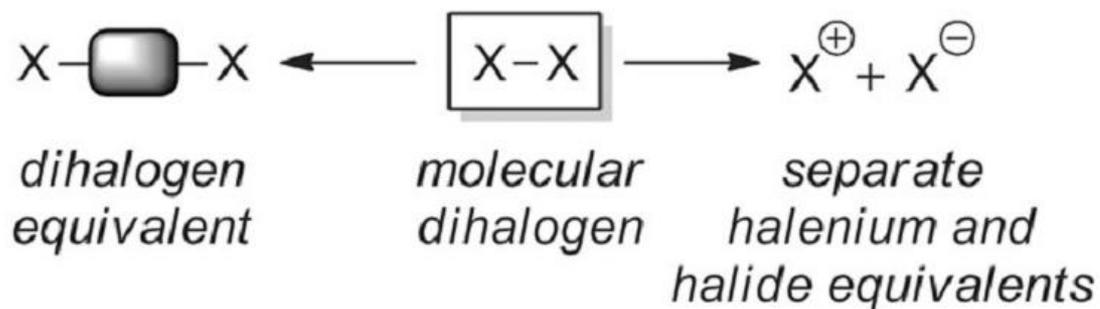
**\* Problem:**

- \* 1) control of regioselectivity in the nucleophilic trapping with halide ion**
- \* 2) difficulties in transmitting stereochemical influence from a catalyst covalently bound to the halogen atom**
- \* 3) potential for alkene-to-alkene halonium ion transfer processes causing racemization of enantioenriched haliranium ions.**
- \* 4) the control of relative configuration is limited, as the reactions are stereoelectronically mandated to deliver antidihalogenated products, with no general means of overturning this selectivity.**
- \* 5) a number of these mechanistic proposals are speculative, and some of them lack rigorous experimental or theoretical support.**

**\*Thank you for your attention!**

## \* The dihalogenating reagents problem

### \* Strategies for avoiding the use of molecular dihalogens



# \* The enantioselectivity problem

