# Catalytic Enantioselective Halofunctionalizations of Olefins

9 F fluorine

17 Cl chlorine

35 Br bromine

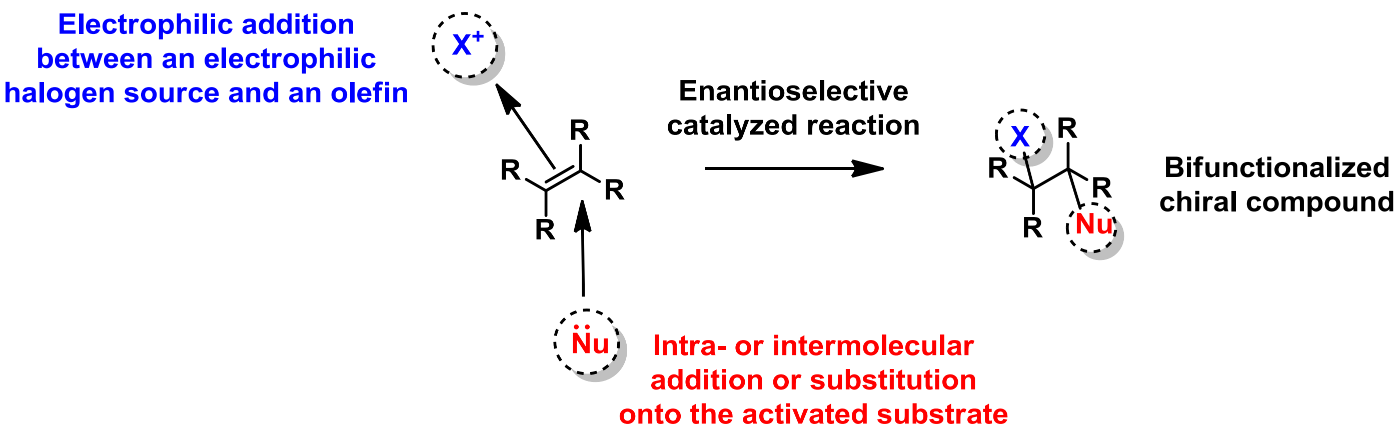
53 I iodine

*Jérémy Merad*

*January 15th 2015*

# Halofunctionalizations of olefins

Introduction



# The last chapter of a long story

Introduction

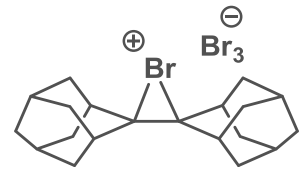
*1850s (Reynolds) : 1st electrophilic addition of halogen to alkene*

*1870s (Fittig) : 1st halolactonization*

*1900*

*1937 (Roberts and Kimball) : cyclic halonium ion proposed as intermediate*

*1950*




*1969 (Wynberg) : 1st stable cyclic bromonium*

*1992 (Tagushi) : 1st enantioselective halolactonization*

*2000*

*2003 (Kang) : 1st catalytic enantioselective halocyclization*

# The main challenges



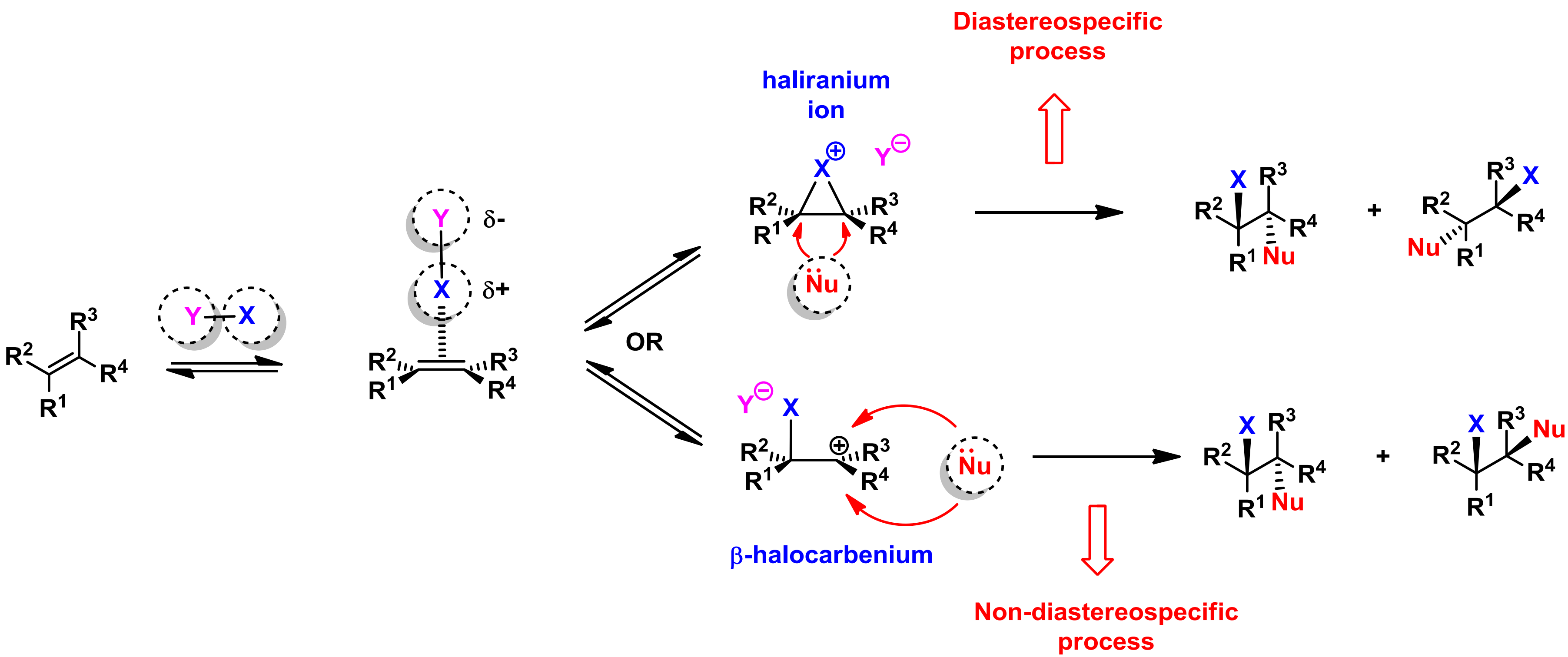
***Decrease the rate of the uncatalyzed reaction***

***Save the catalytic activity in the presence of highly electrophilic species***

→ ***Generate stereoselectivity with highly reactive intermediates***

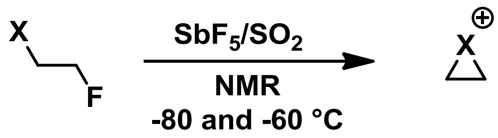
# Two possible mechanisms

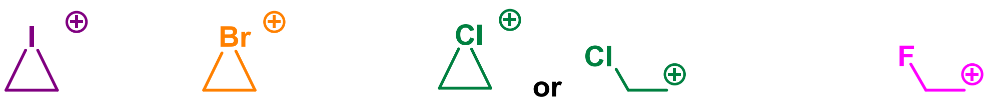
Introduction



# Haliranium vs β-halocarbenium

Introduction




stable haliraniums at low temperature

Substrate-dependant stability

acyclic β-fluoro-carbenium ion only

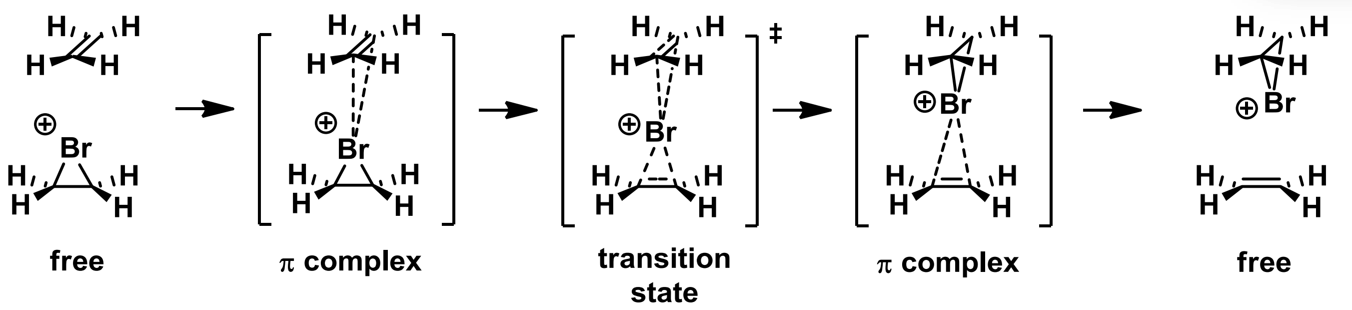
Diastereospecific nucleophilic addition

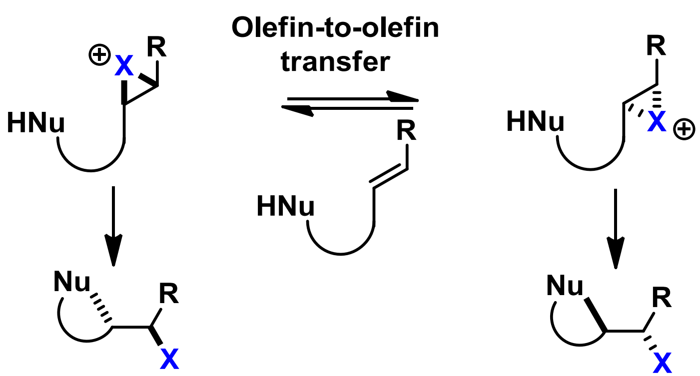
Non-stereospecific nucleophilic addition

Olah *et al.*, *J. Am. Chem. Soc.* **1967**, *89*, 4744.

# A major challenge : the olefin-to-olefin transfer





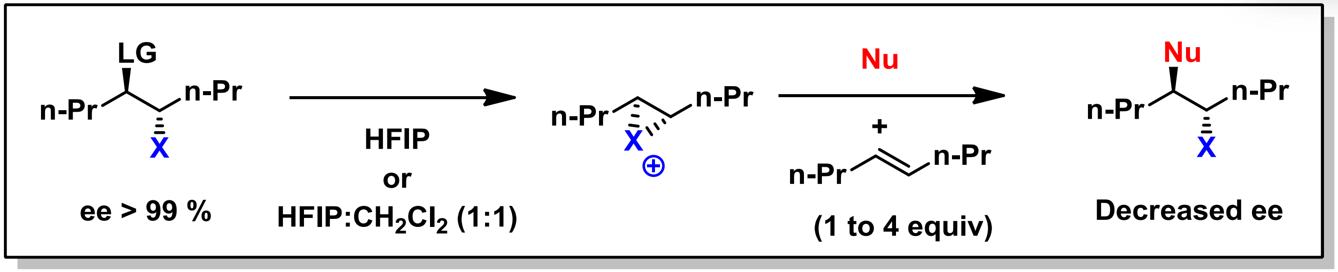



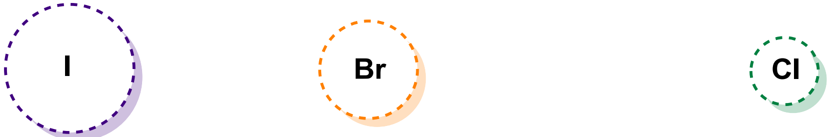

***Olefin-to-olefin transfer can racemize haliranium at rates that can compete with nucleophilic capture***

Brown *et al.*, *J. Am. Chem. Soc.* **1994**, *116*, 2448.

# Haliranium absolute configuration stability

Introduction




**Low electronegativity**

**Fast olefin-to-olefin transfer (low stereochemical stability)**

**High electronegativity**

**Slow olefin-to-olefin transfer (high stereochemical stability)**

Denmark *et al.*, *J. Am. Chem. Soc.* **2010**, *132*, 1232.

# Summary

Introduction

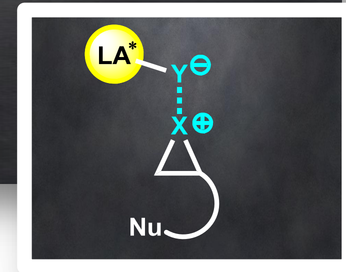
*I. Iodo- and bromocylizations*

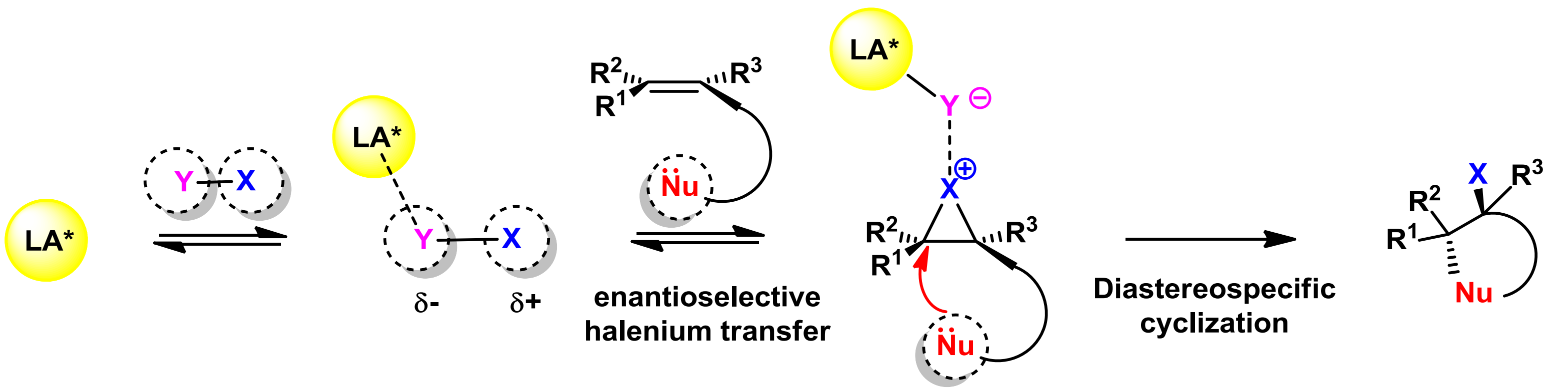
*II. Chloro- and fluorocyclizations*

*III. Intermolecular halofunctionalizations*

## *I. Iodo- and bromocyclizations*

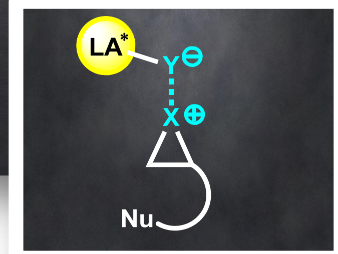
# Lewis acid catalysis - Concept



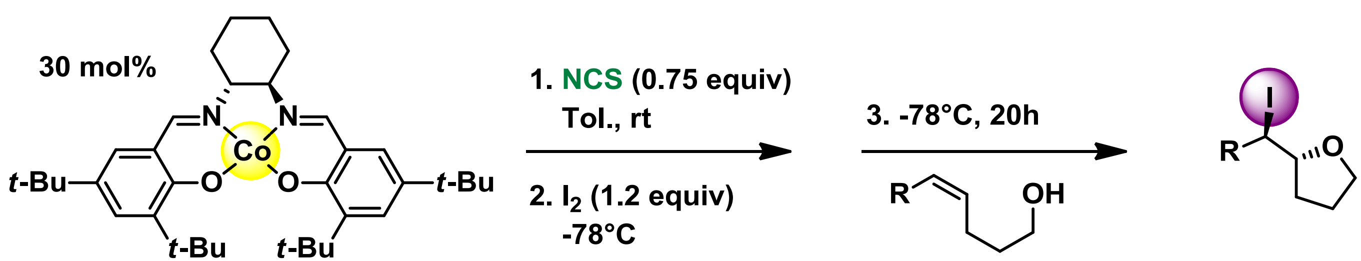




***Lewis acids polarize the Y-X bond, stabilize the counteranion generated and create the requisite chiral environment***

# Kang's iodoetherification




Reacts with $I_2$ to slowly release ICl further activated by the LA* and minimizes the uncatalyzed racemic pathway

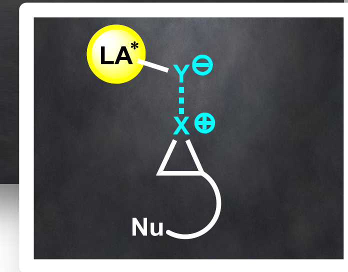


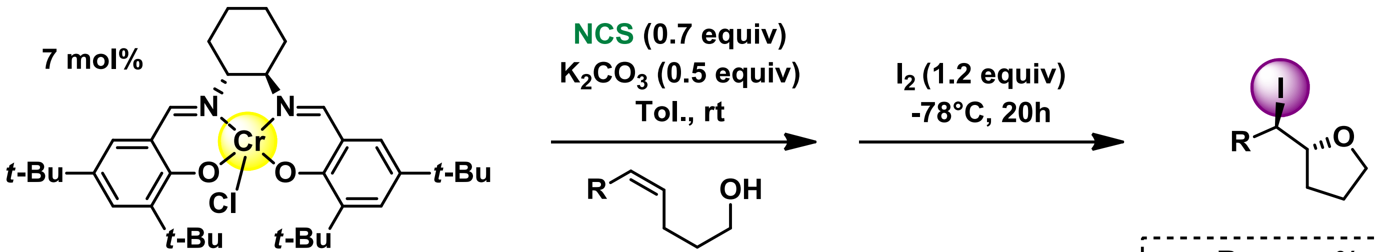

| R | % | ee |
|---|---|---|
| Me | 96 | 67 |
| *i*-Pr | 83 | 73 |
| $(CH_2)_3OTr$ | 89 | 90 |

High catalyst loading

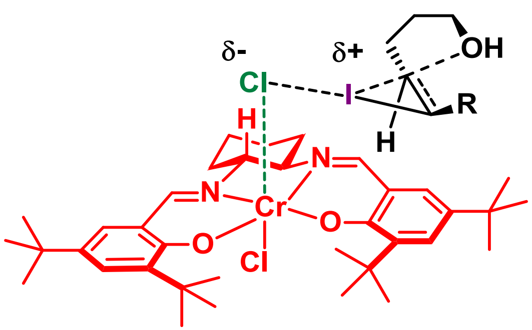
Kang *et al.*, *J. Am. Chem. Soc.* **2003**, *125*, 15748.

# Kang's iodoetherification

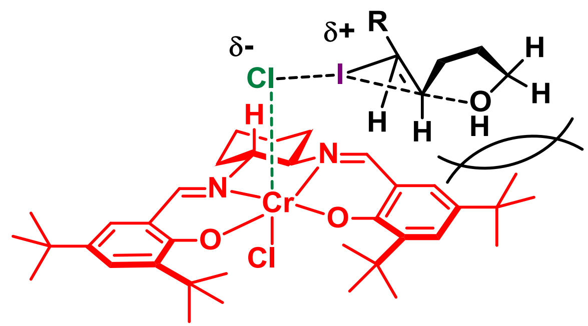



| R | % | ee |
|---|---|---|
| Me | 94 | 74 |
| *i*-Pr | 92 | 89 |
| $(CH_2)_3OTr$ | 90 | 93 |



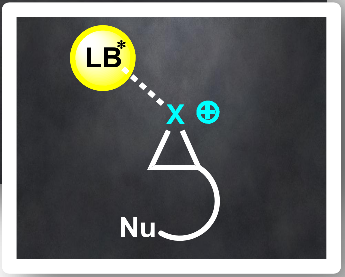

**Favored**

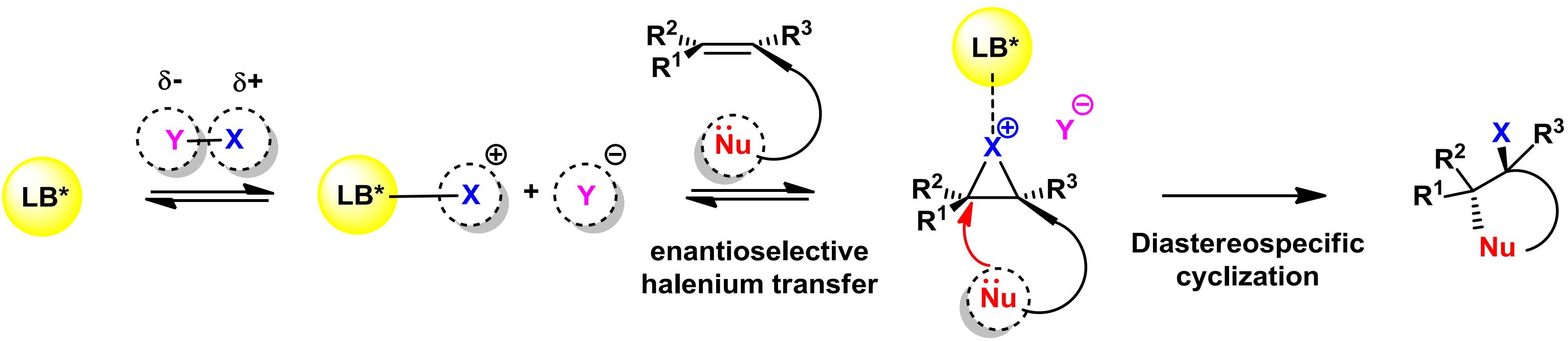



**Disfavored**

Kang *et al.*, *Chem. Eur. J.* **2008**, *14*, 1023.

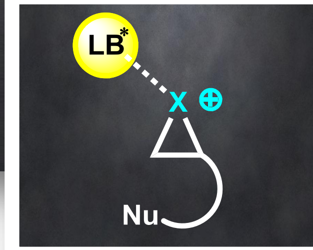
# Lewis base catalysis - Concept

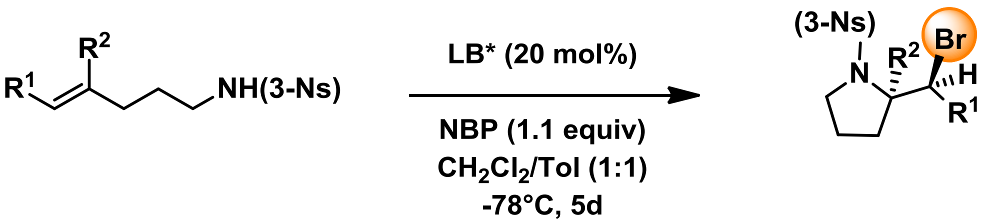



***Lewis bases polarize the Y-X bond, stabilize the the haliranium and create the requisite chiral environment***

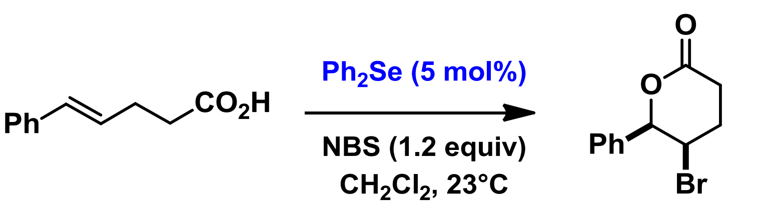
# LB catalyzed bromoaminocyclization




| $R^1$ | $R^2$ | % | ee |
|---|---|---|---|
| Ph | Ph | 15 | 79 |
| Et | Ph | 93 | 91 |
| *i*-Bu | Ph | 91 | 83 |
| Me | 4-Cl$C_6H_4$ | 62 | 59 |
| Me | 4-MeO$C_6H_4$ | 11 | 2 |

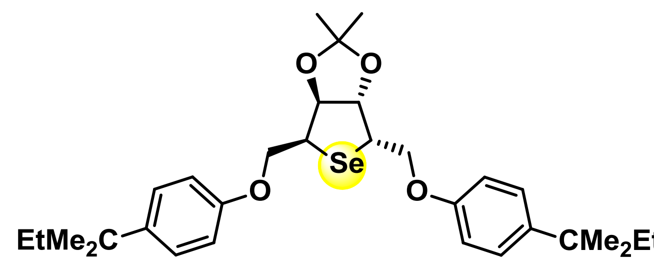
Yeung *et al.*, *J. Am. Chem. Soc.* **2013**, *135*,1232.




**t = 180 min, 13%**
**without catalyst**

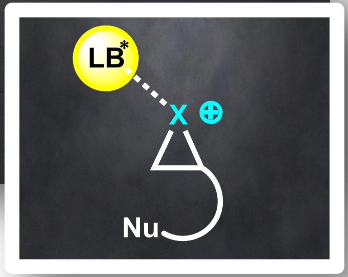
**t = 8 min, 84%**

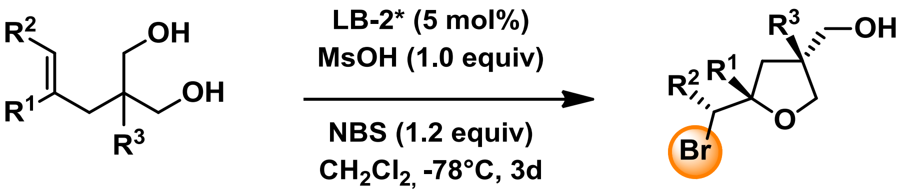
Denmark *et al.*, *PNAS*, **2010**, *107*, 20655.




**$C_2$ symmetric monofunctional Lewis base**

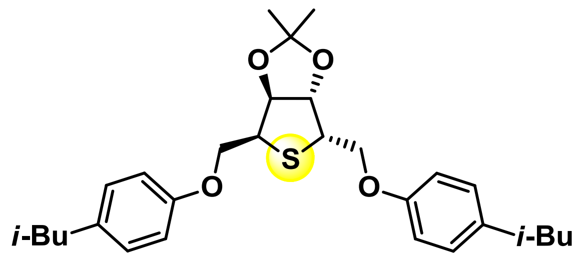
# LB catalyzed diol desymmetrization



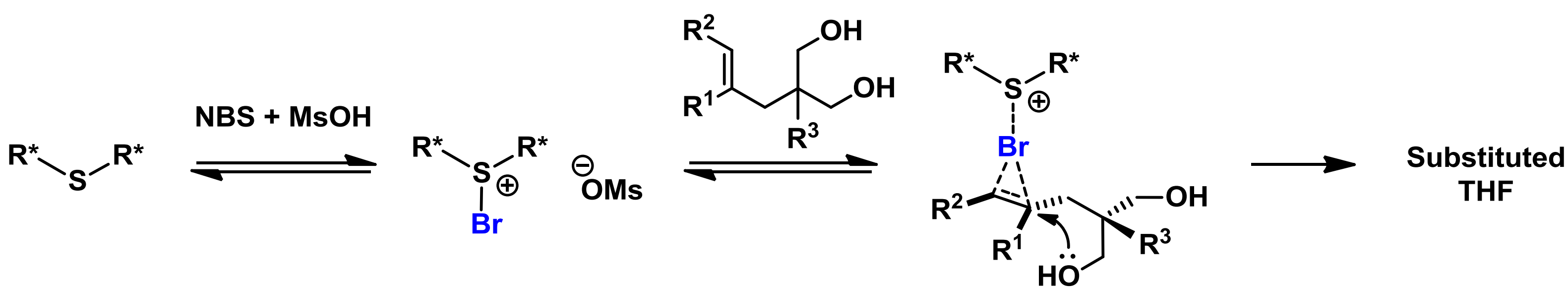




up to 92%, 95% ee

Three stereogenic centers in one step

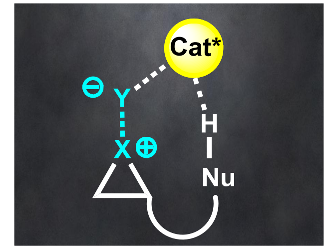


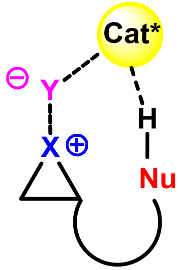

New $C_2$ symmetric cyclic sulfide as a monofunctional catalyst (LB*-2)




Yeung *et al.*, *J. Am. Chem. Soc.* **2014**, *136*, 5627.

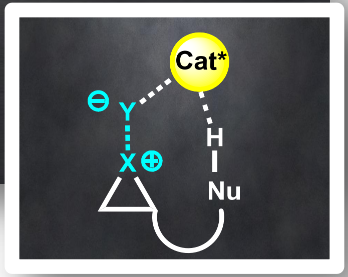
# Bifunctional catalysis - Concept

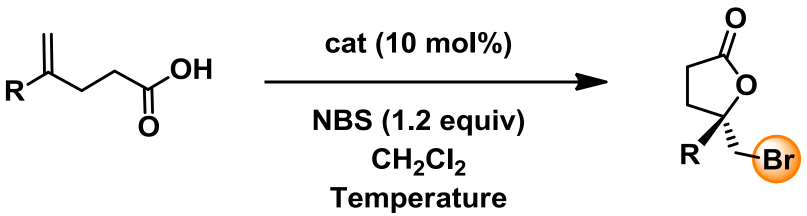


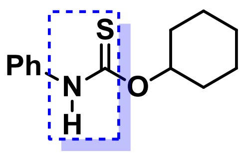




***Activation of the halenium source by H-bonding and nucleophile activation - Use of bifunctional catalyst***

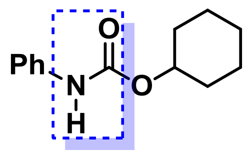
# Bifunctional catalysis



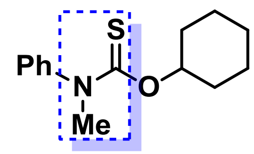



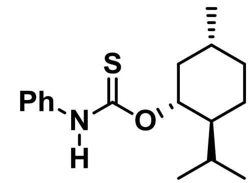

R = H, 84%
(25°C)



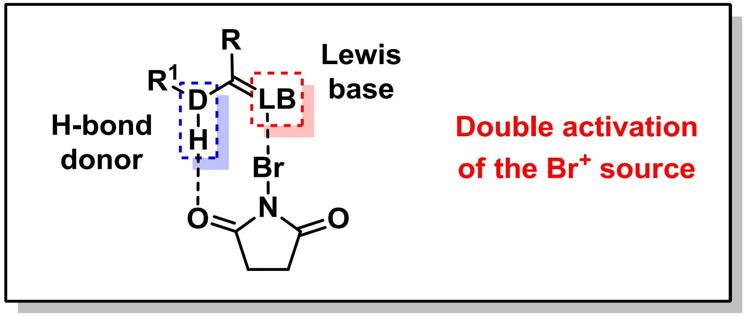

R = H, 18%
(25°C)




R = H, 73%
(25°C)



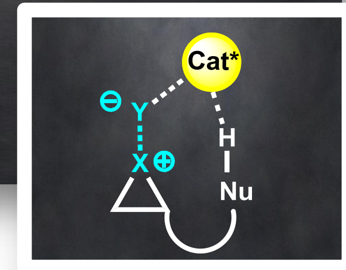

R = Ph, 0% ee
(-78°C)

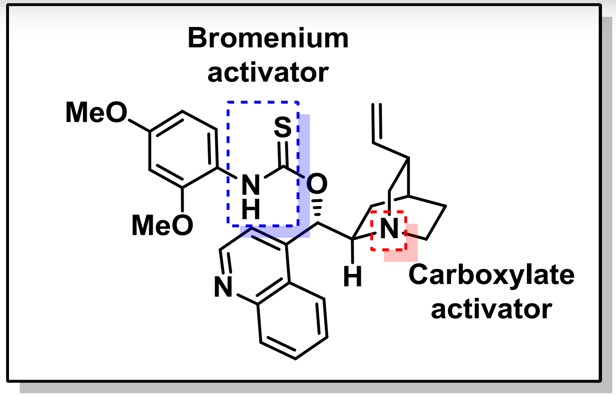


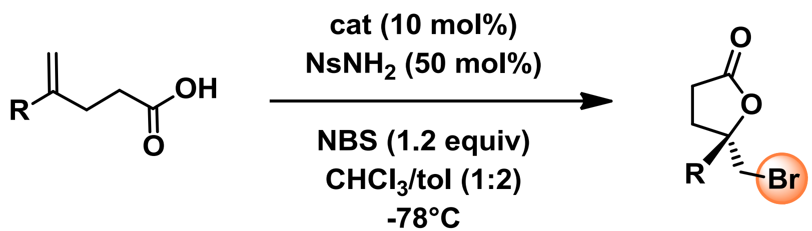

**Lewis basic sulfur atom and H-bond are not sufficient to provide stereoinduction**

Yeung *et al.*, *J. Am. Chem. Soc.* **2010**, *132*, 15474.

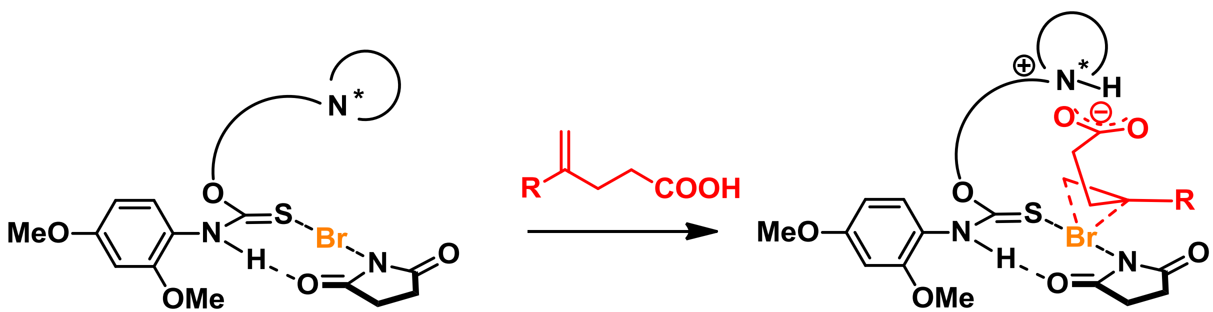
# Bifunctional catalysis



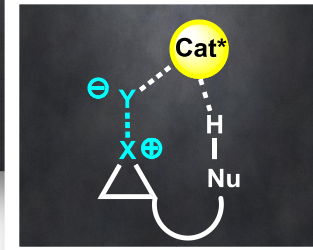



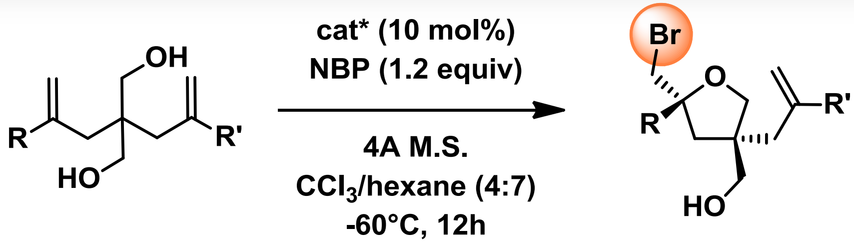

| R | % | ee |
|---|---|---|
| Ph | 99 | 90 |
| 4-$NO_2C_6H_4$ | 85 | 83 |
| 4-$MeOC_6H_4$ | 67 | 28 |
| Me | 81 | 41 |
| *t*-Bu | 97 | 93 |

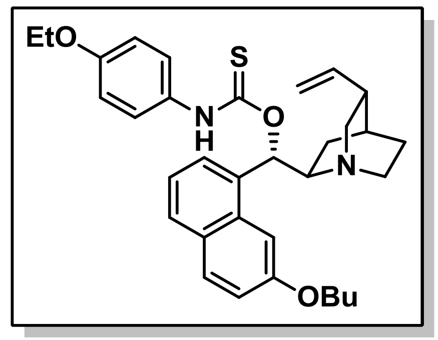



Yeung *et al.*, *J. Am. Chem. Soc.* **2010**, *132*, 15474.

# Bifunctional catalysis

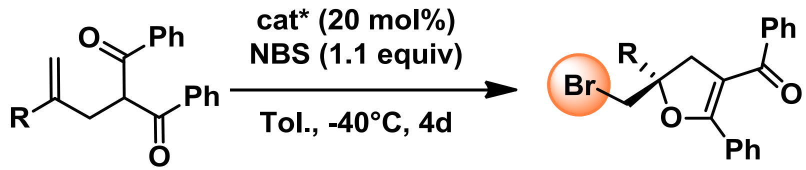


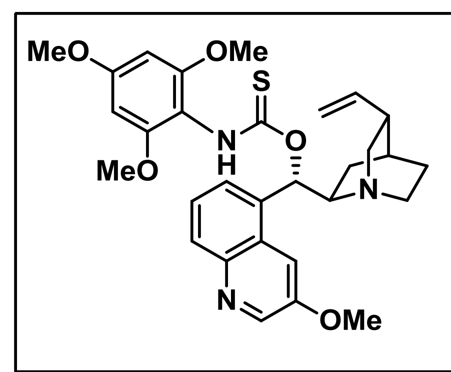




| R | R' | % | dr | ee |
|---|---|---|---|---|
| Ph | Ph | 93 | 84:16 | 92 |
| 4-ClC$_6$H$_4$ | 4-ClC$_6$H$_4$ | 92 | 76:24 | 64 |
| Ph | *t*-Bu | 91 | 94:6 | 80 |
| Me | Ph | 90 | 86:14 | 40 |

Yeung *et al.*, *Angew. Chem. Int. Ed.* **2014**, *53*, 5161.

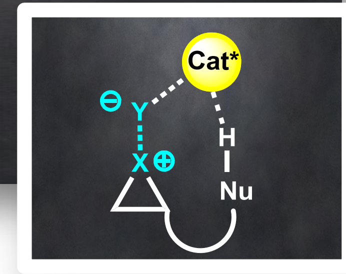


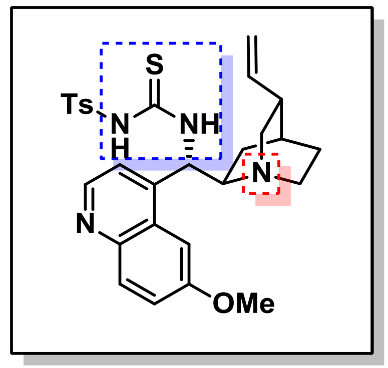



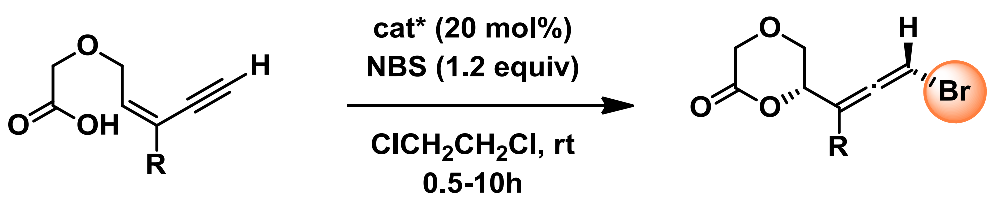

| R | % | ee |
|---|---|---|
| Ph | 89 | 96 |
| 4-ClC$_6$H$_4$ | 87 | 90 |
| 4-MeOC$_6$H$_4$ | 89 | 78 |
| *t*-Bu | 86 | 92 |
| Me | 80 | 55 |

Yeung *et al.*, *Angew. Chem. Int. Ed.* **2013**, *52*, 8597.

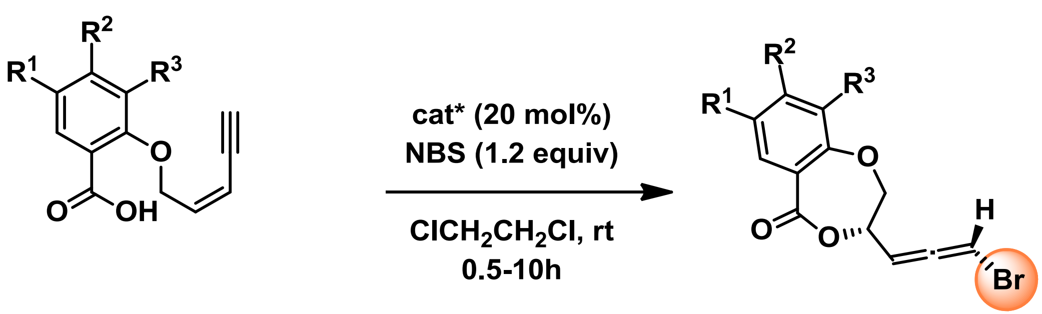
# Bifunctional catalysis



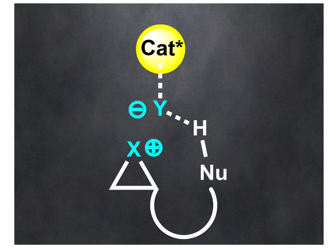

| R | % | ee |
|---|---|---|
| H | 71 | 90 |
| *n*-Pr | 77 | 90 |
| *t*-Bu | 72 | 90 |
| $CH_2OPMB$ | 70 | 92 |
| TES | 87 | 88 |

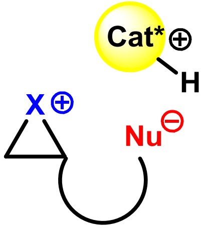



| R | % | ee |
|---|---|---|
| $R^1$=$R^2$=$R^3$=H | 79 | 97 |
| $R^1$=$R^2$=H, $R^3$=Cl | / | / |
| $R^1$=$R^2$=H, $R^3$=OMe | 72 | 98 |

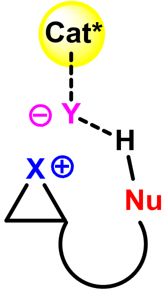
Tang *et al.*, *J. Am. Chem. Soc.* **2010**, *132*, 3664.

# Ion pairing - Concept



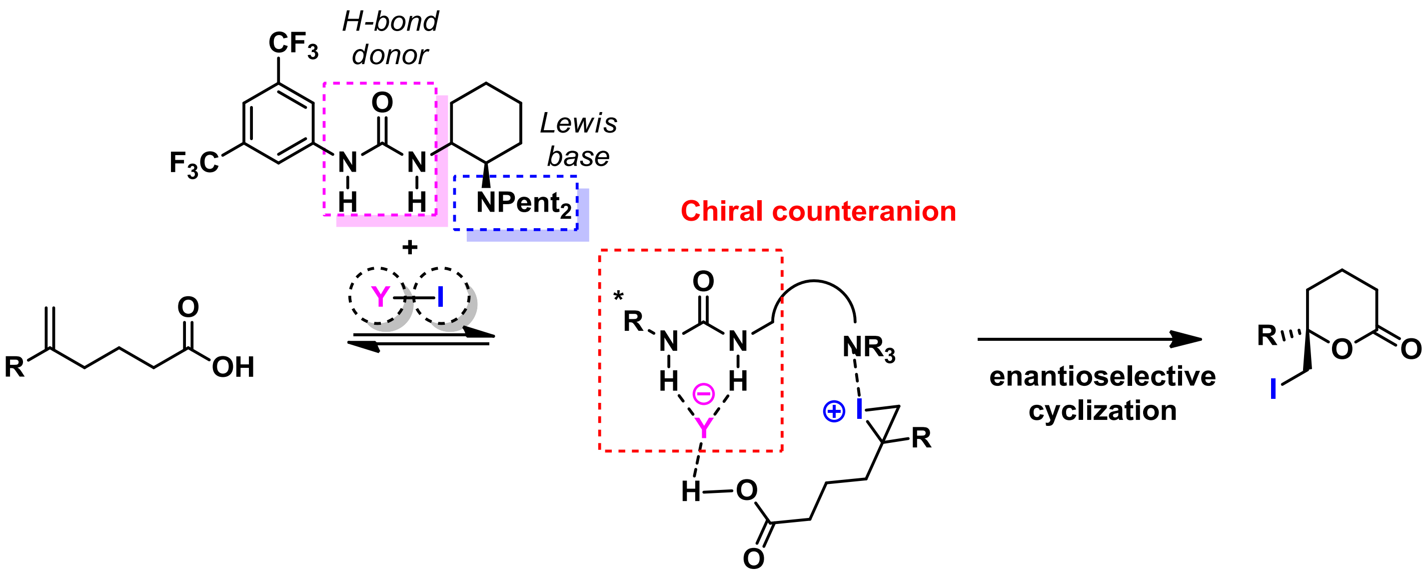




***Anion binding = the deprotonation of the nucleophile generate a chiral ion pair***



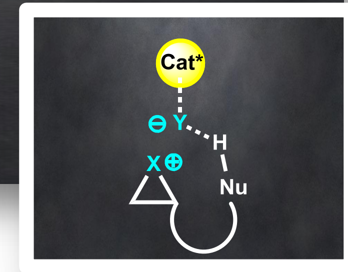

***Chiral counterion = the counteranion was made chiral by H-bonding with the catalyst***

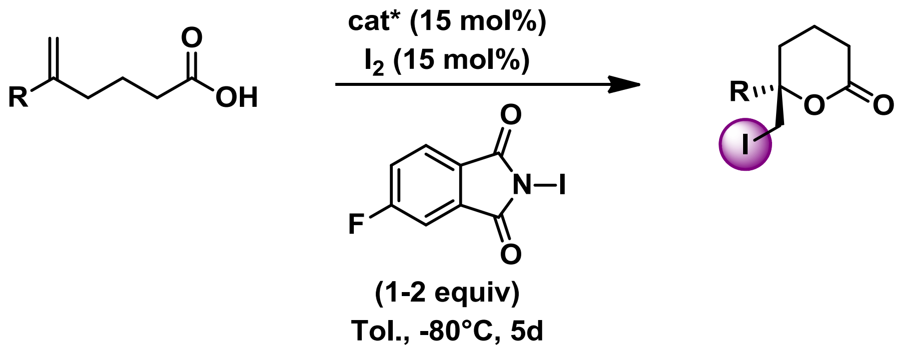
# H-bonding and chiral counteranion formation

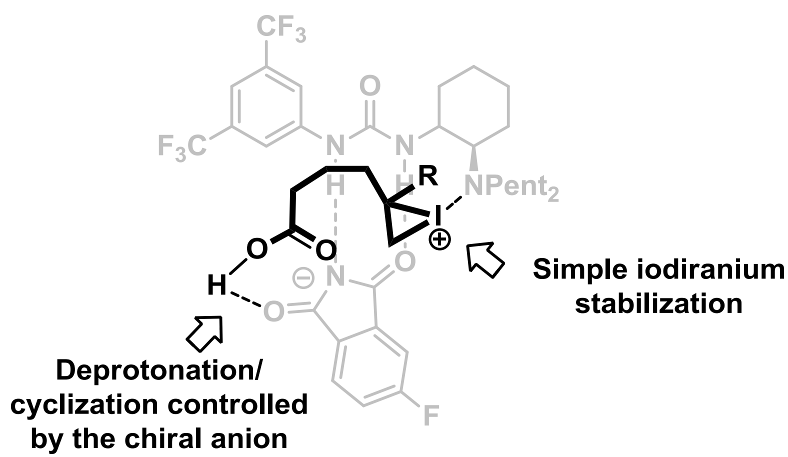

Jacobsen *et al.*, *Angew. Chem. Int. Ed.* **2010**, *49*, 7332.

# H-bonding and chiral counteranion formation



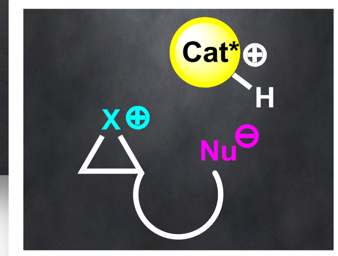



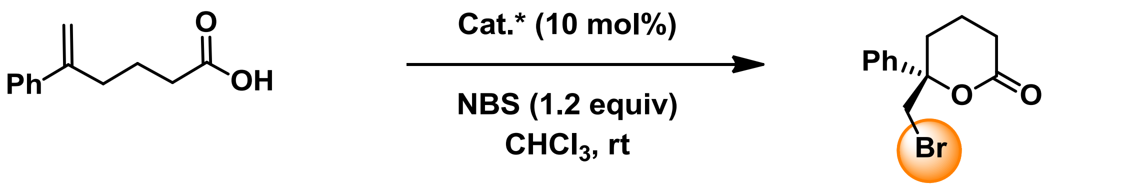

| R | % | ee |
|---|---|---|
| Ph | 87 | 94 |
| 4-MeO$C_6H_4$ | 91 | 48 |
| 4-Cl-$C_6H_4$ | 95 | 96 |
| *i*-Pr | 85 | 76 |



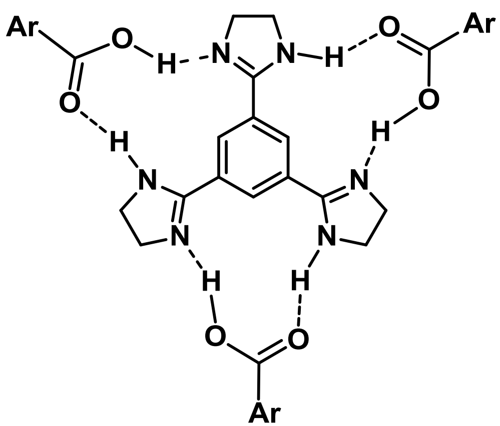

Jacobsen *et al.*, *Angew. Chem. Int. Ed.* **2010**, *49*, 7332.

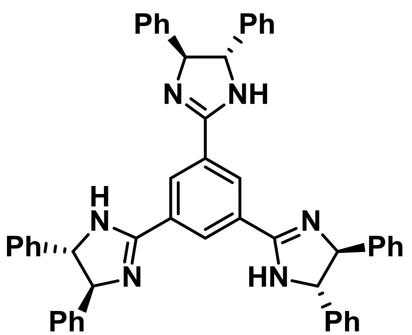
# $C_3$-symmetric trisimidazolines




**Reported 1:3 complex of**
**a trisimidazoline and a carboxylic acid**

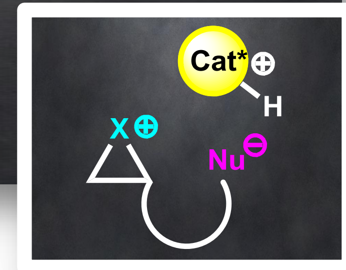


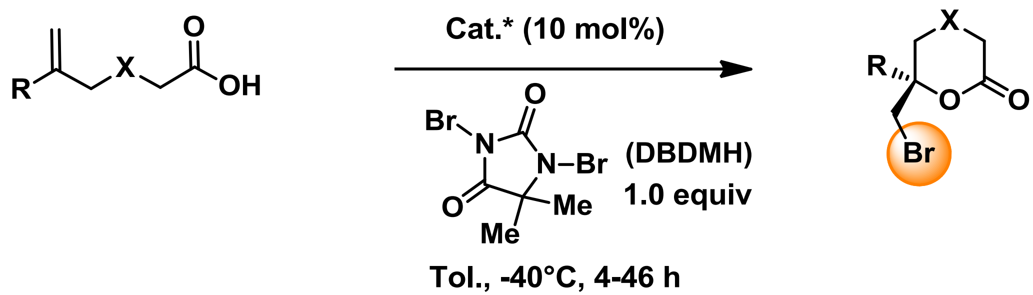




***$C_3$*-symmetric**
**chiral trisimidazoline**
**95%, 69% ee**

Fujioka *et al.*, *Angew. Chem. Int. Ed.* **2010**, *49*, 9174.

# $C_3$-symmetric trisimidazolines



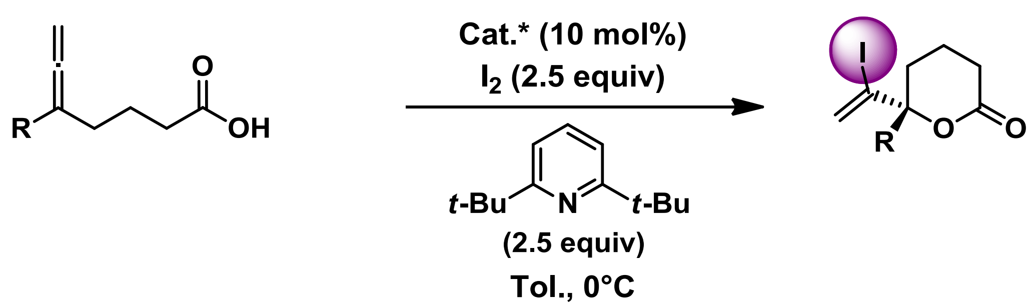





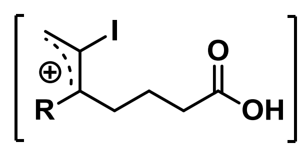
| R | % | ee |
|---|---|---|
| Ph | 99 | 91 |
| 4-$BrC_6H_4$ | 93 | 87 |
| 4-$MeOC_6H_4$ | 74 | 80 |
| cyclohexyl | 95 | 72 |

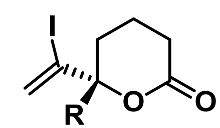
| X | % | ee |
|---|---|---|
| $CMe_2$ | 96 | 81 |
| O | 74 | 71 |
| NTs | 89 | 75 |

Fujioka *et al.*, *Angew. Chem. Int. Ed.* **2010**, *49*, 9174.




π-allyl cation intermediate

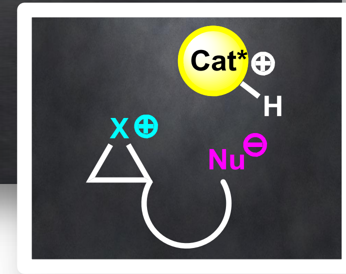


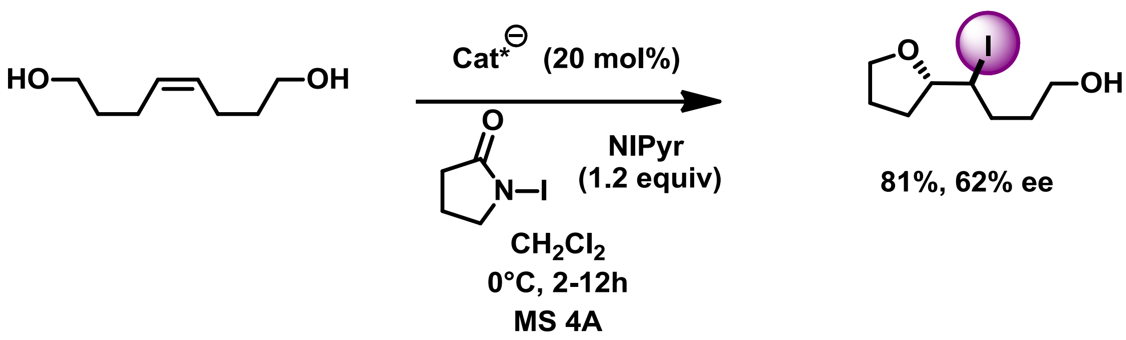



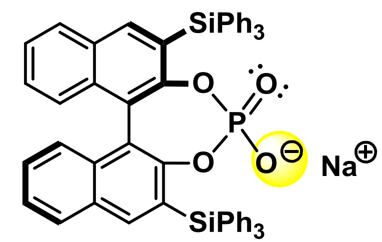

| R | % | ee |
|---|---|---|
| Ph | 83 | 66 |
| 4-*t*Bu-$C_6H_4$ | 88 | 82 |
| 4-*t*BuO-$C_6H_4$ | 85 | 2 |
| $BnCH_2$ | 74 | 34 |

Fujioka *et al.*, *Angew. Chem. Int. Ed.* **2010**, *49*, 9174.

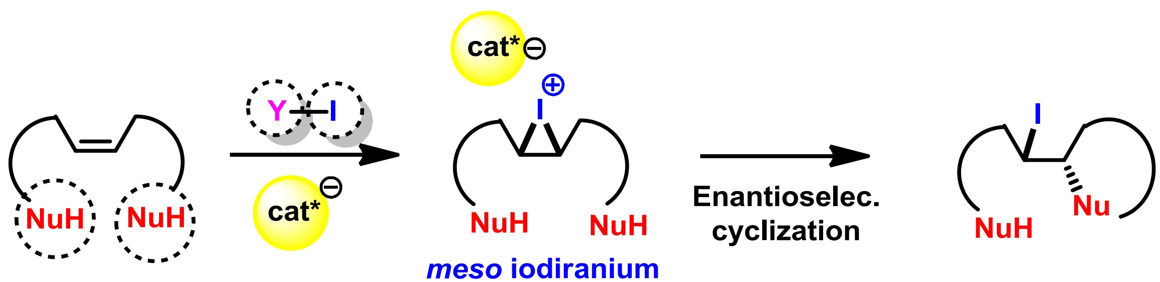
# *Enantioselective cyclization – Proof of concept*




Chiral phosphate as an anionic Lewis base

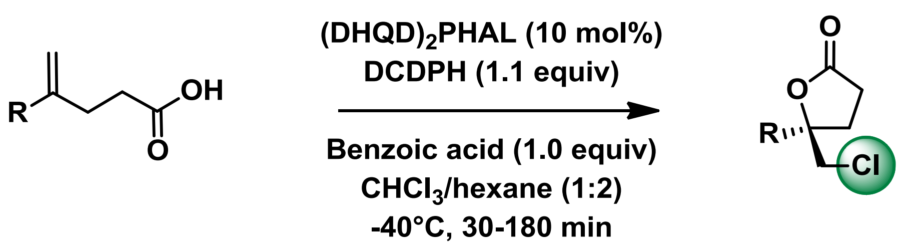



Hennecke *et al.*, *Org. Lett.* **2011**, *13*, 860.

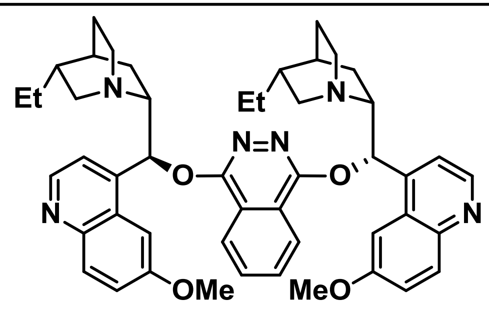
## *II. Chloro- and fluorocyclizations*

# *Enantioselective chlorolactonization*

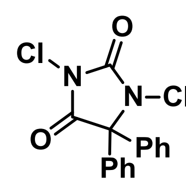
17
Cl
chlorine




| R | % | ee |
|---|---|---|
| Ph | 86 | 89 |
| Ph | 75(*ent*) | 77 |
| 4-MeOC$_6$H$_4$ | 99 | <5 |
| 4-CF$_3$C$_6$H$_4$ | 61 | 90 |
| cyclohexyl | 55 | 43 |




(DHQD)$_2$PHAL

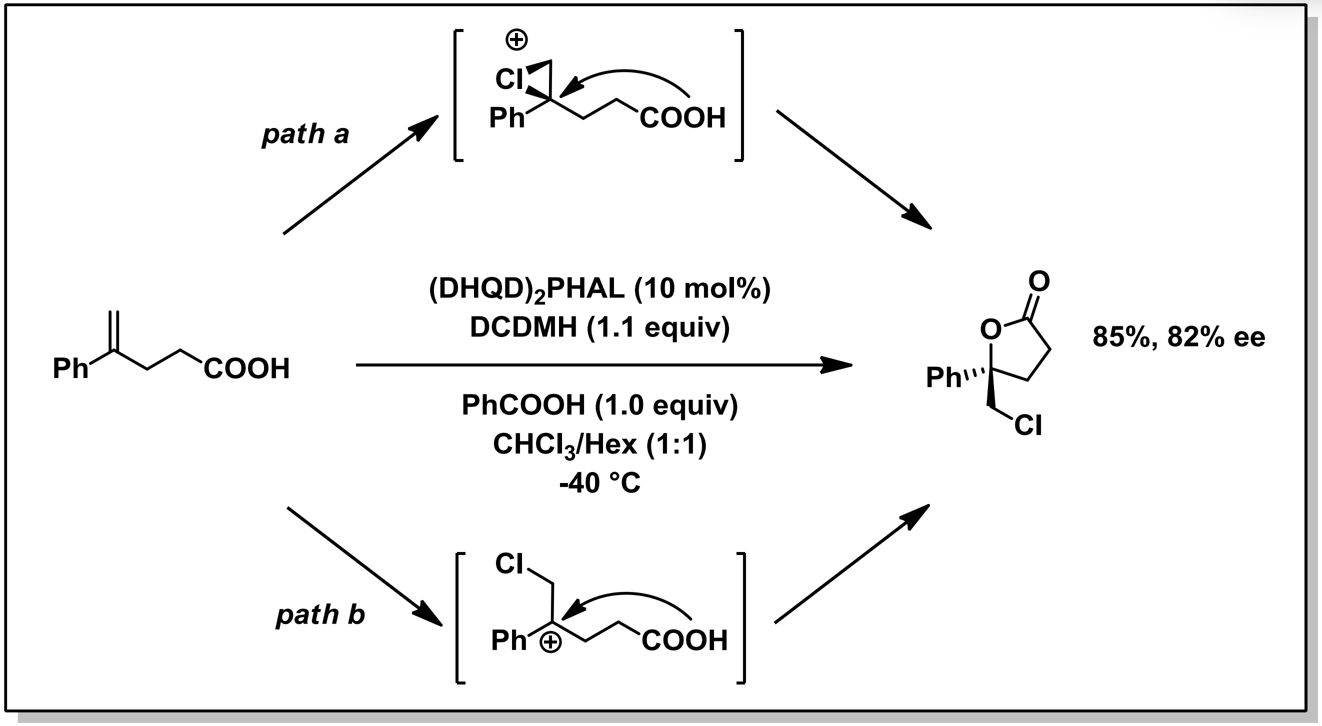



DCDPH

Borhan *et al.*, *J. Am. Chem. Soc.* **2010**, *132*, 3298.

# *Enantioselective chlorolactonization*

17
Cl
chlorine




**Bridged chloronium or carbocation intermediate ?**

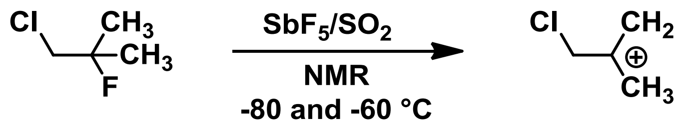
**Face-selective chlorenium delivery ?**

**Stereochemical relationship between the chlorenium delivery and the nucleophilic attack ?**

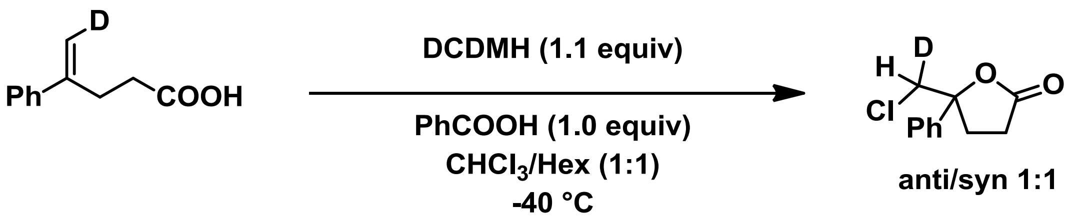
Borhan *et al.*, *J. Am. Chem. Soc.* **2013**, *135,* 14524.

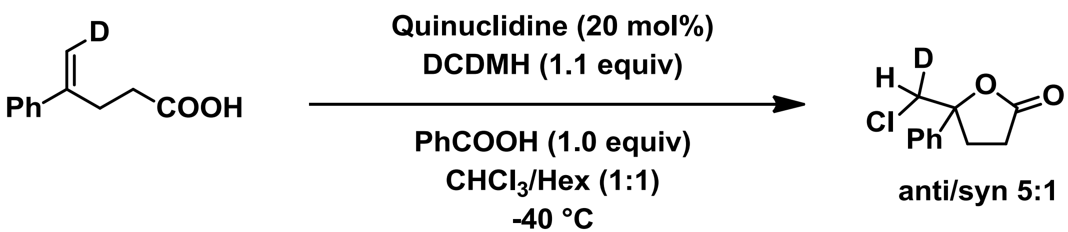
# *Enantioselective chlorolactonization*

17
Cl
chlorine




Chlorofunctionalization of 1,1-substituted alkenes does not imply the formation of a cyclic chloronium



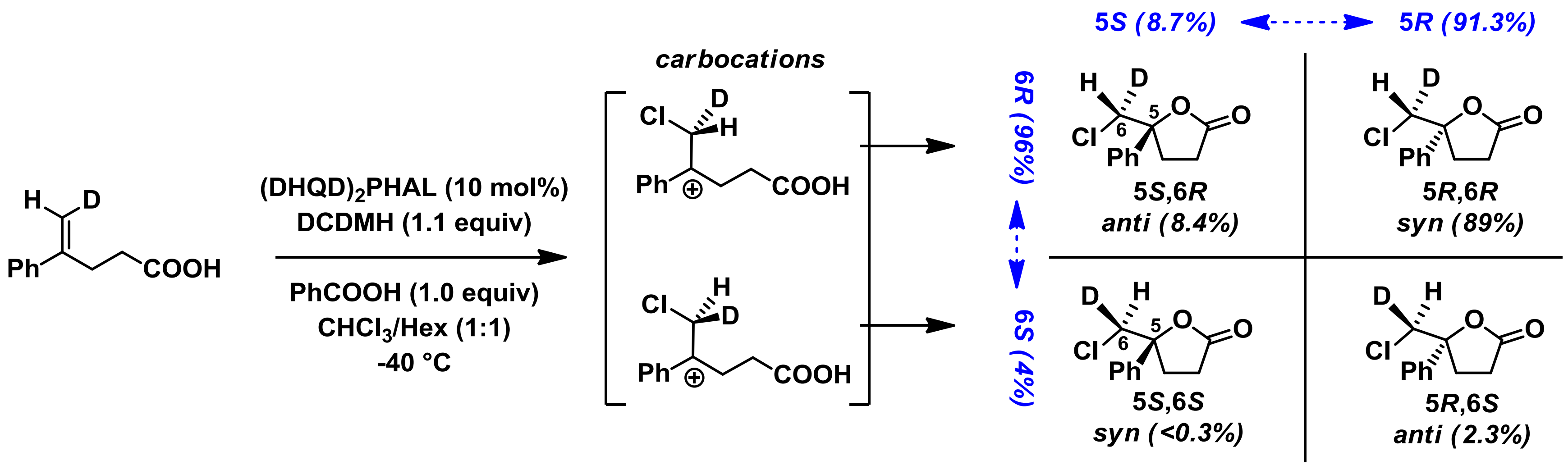




**Formation of both diastereomers ⇨ Excludes the formation of a bridged chloronium**

Borhan *et al.*, *J. Am. Chem. Soc.* **2013**, *135,* 14524.

# Enantioselective chlorolactonization

17
Cl
chlorine

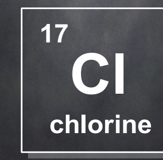


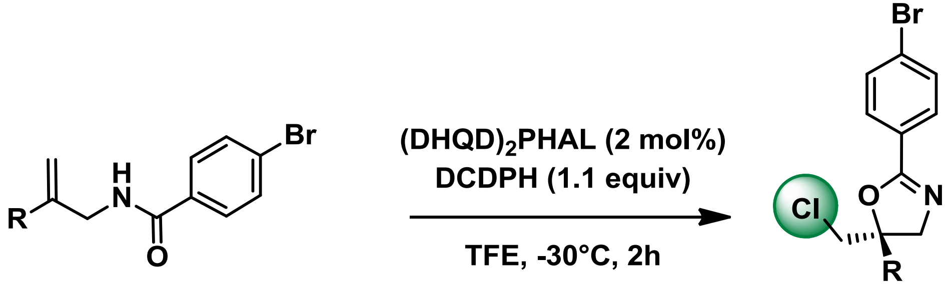

- Highly pro-*R* selective chlorenium transfer
- pro-*R* selective nucleophilic addition
- *Syn* relative configuration excludes the formation of a bridged chloronium

***Two stereoselective steps controlled by a single catalyst***

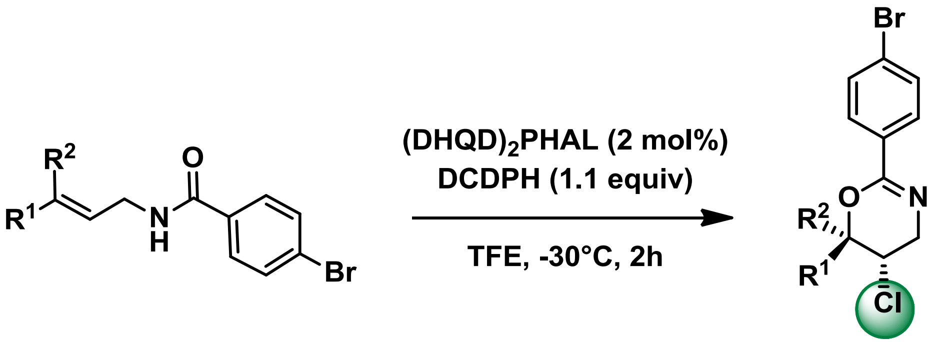
Borhan *et al.*, *J. Am. Chem. Soc.* **2013**, *135,* 14524.

# *Chlorocyclization of unsaturated amides*




| R | % | ee |
|---|---|---|
| Ph | 93 | 98 |
| 3-MeOC$_6$H$_4$ | 72 | 93 |
| 4-ClC$_6$H$_4$ | 94 | 87 |

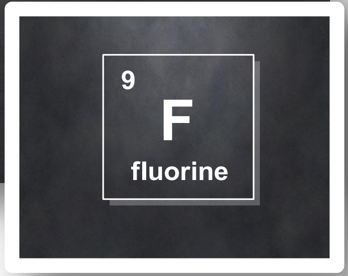


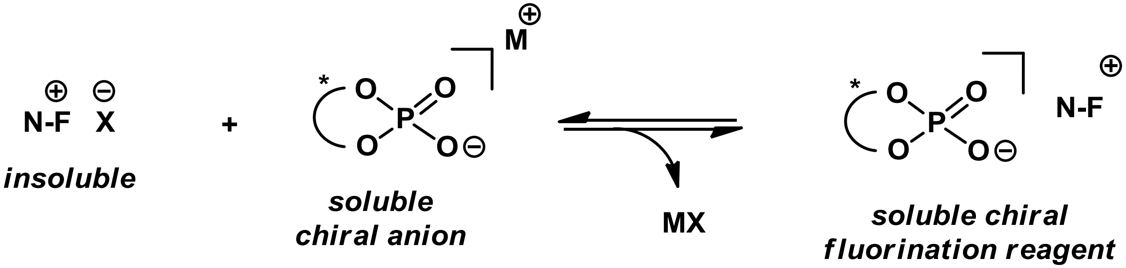

| R$^1$ | R$^2$ | % | ee |
|---|---|---|---|
| Ph | H | 91 | 99 |
| 4-BrC$_6$H$_4$ | H | 85 | 93 |
| 4-MeOC$_6$H$_4$ | H | 84 | 20 |
| Ph | Ph | 92 | 86 |
| Cy[a] | H | 77 | >99 |

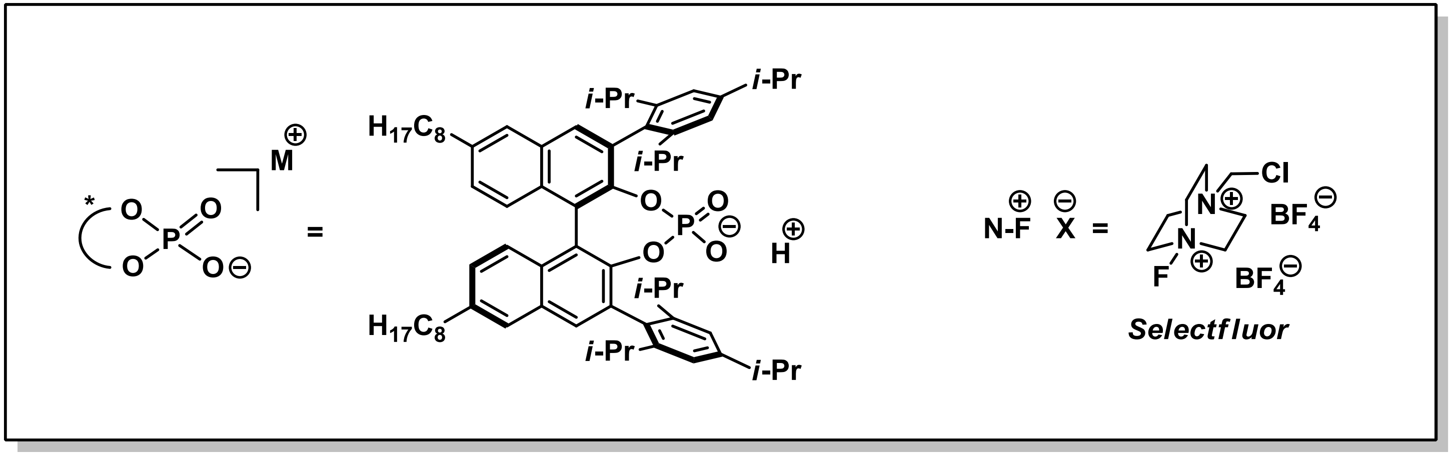
[a] reaction was run in 1-nitropropane

Borhan *et al.*, *Angew. Chem. Int. Ed.* **2011**, *50,* 2593.

# Fluorocyclization using anionic chiral phase-transfer catalysis

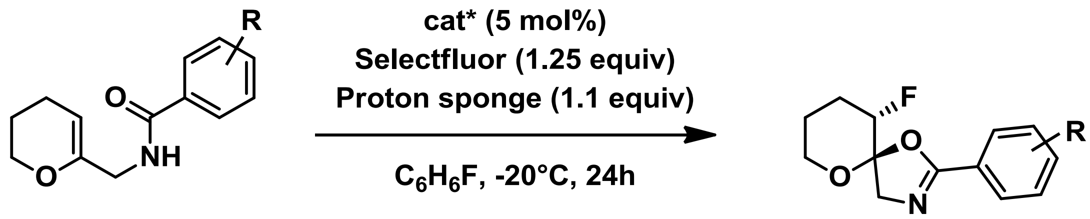


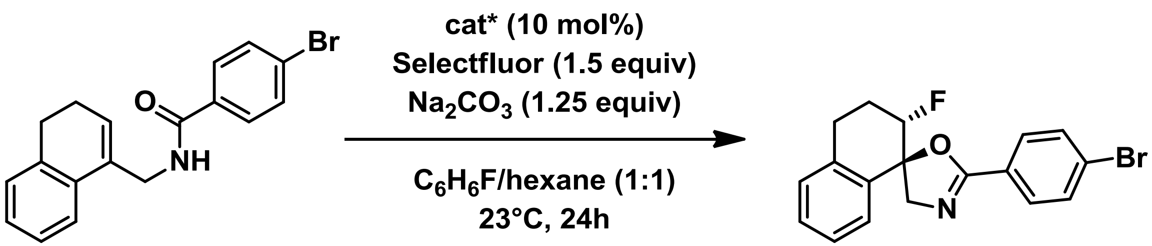




Toste *et al.*,*Science*, **2011**, *334,* 1681.

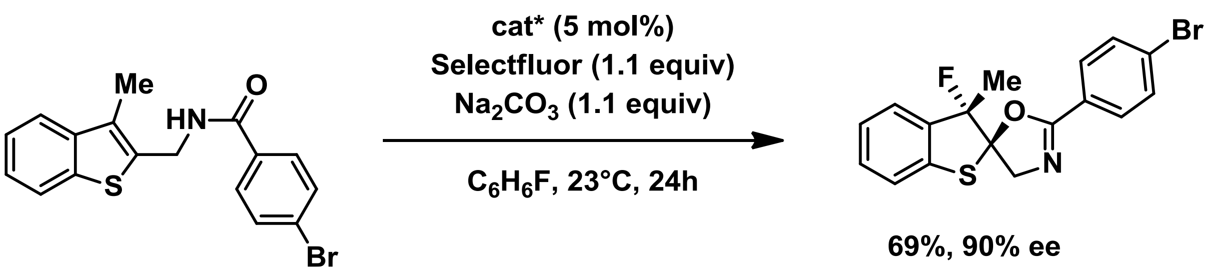
# *Fluorocyclization using anionic chiral phase-transfer catalysis*




| R | % | ee |
|---|---|---|
| H | 86 | 92 |
| Cl | 95 | 97 |
| *t*-Bu | 96 | 95 |




87%, 93% ee



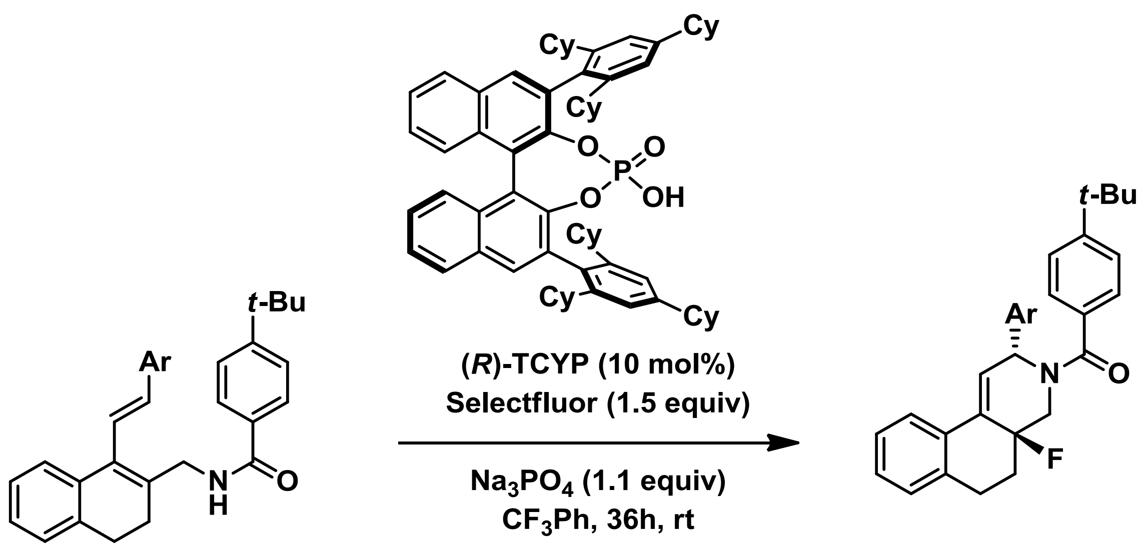

69%, 90% ee

Complexe mixture under homogeneous conditions

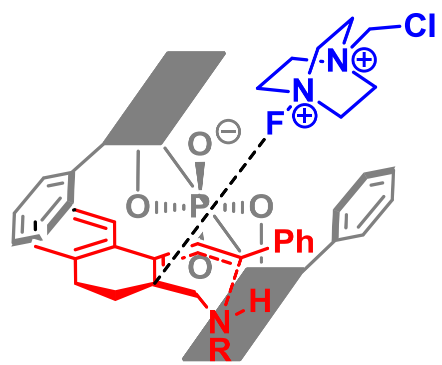
Toste *et al.*,Science, **2011**, *334,* 1681.

# *Fluorocyclization using anionic chiral phase-transfer catalysis*

9
F
fluorine



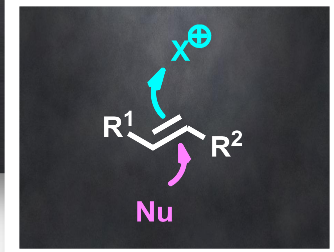

| Ar | % | dr | ee |
| --- | --- | --- | --- |
| Ph | 90 | 6.9:1 | 92 |
| 4-$CF_3C_6H_4$ | 94 | 10:1 | 95 |
| 4-$MeOC_6H_4$ | 89 | 7.5:1 | 93 |

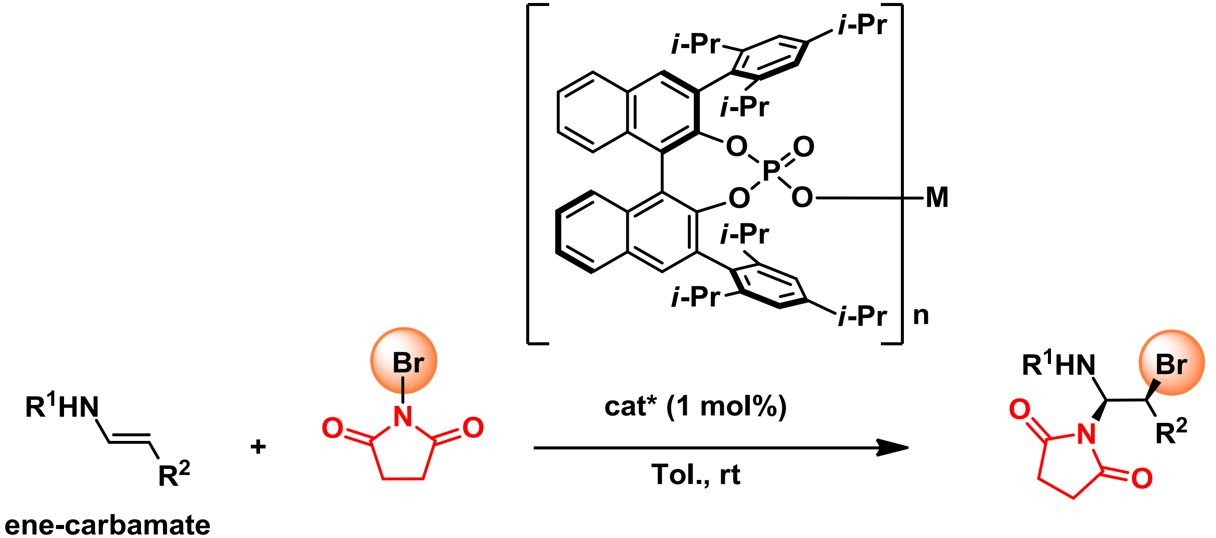



Toste *et al.*, *Angew. Chem. Int. Ed.* **2013**, *52*, 7724.

## *III. Intermolecular halofunctionalizations*

# *Enantioselective bromoamination*

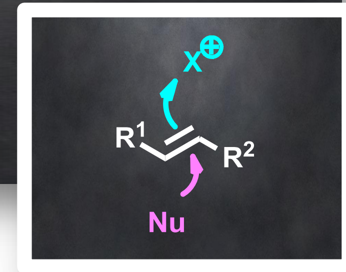


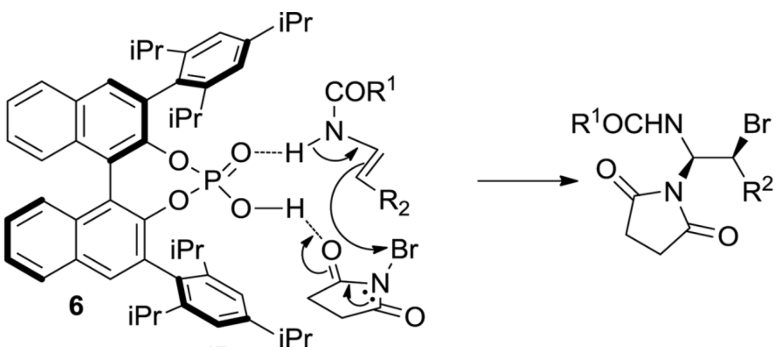



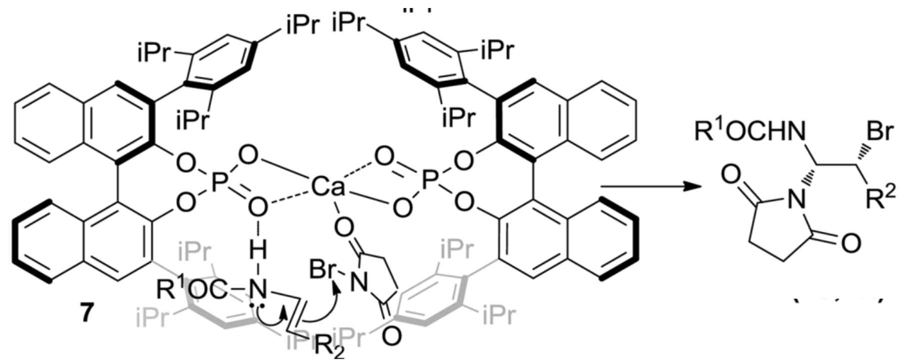

| R1 | R2 | M | % | ee |
|---|---|---|---|---|
| Cbz | Me | H | 64 | 98 |
| Cbz | Me | Ca | 78 | -98 |
| Boc | Pr | H | 92 | 90 |
| Boc | Pr | Ca | 67 | -81 |
| Cbz |  | H | 90 | 97 |

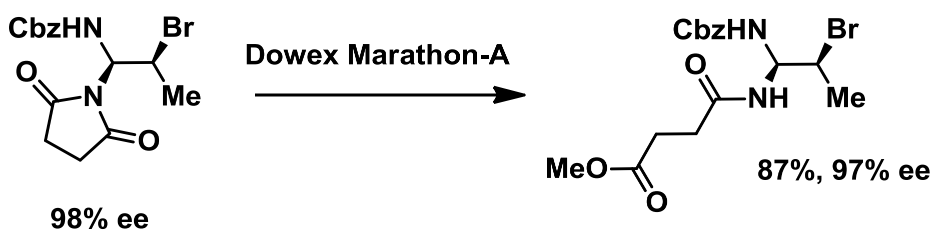
Masson *et al.*, *J. Am. Chem. Soc.* **2012**, *134,* 10389.

# *Enantioselective bromoamination*



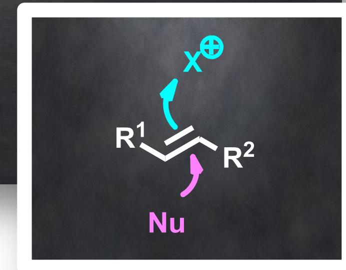



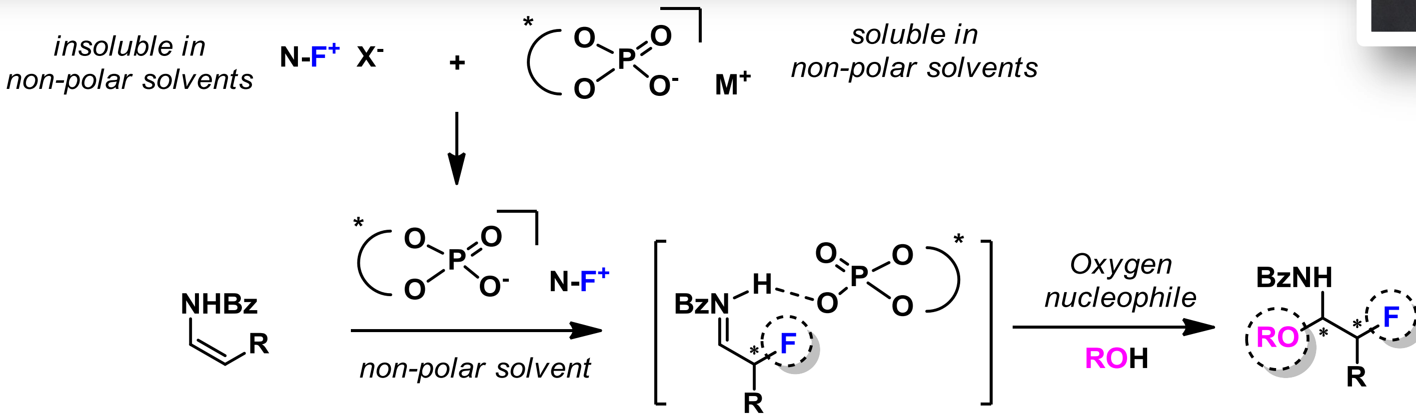



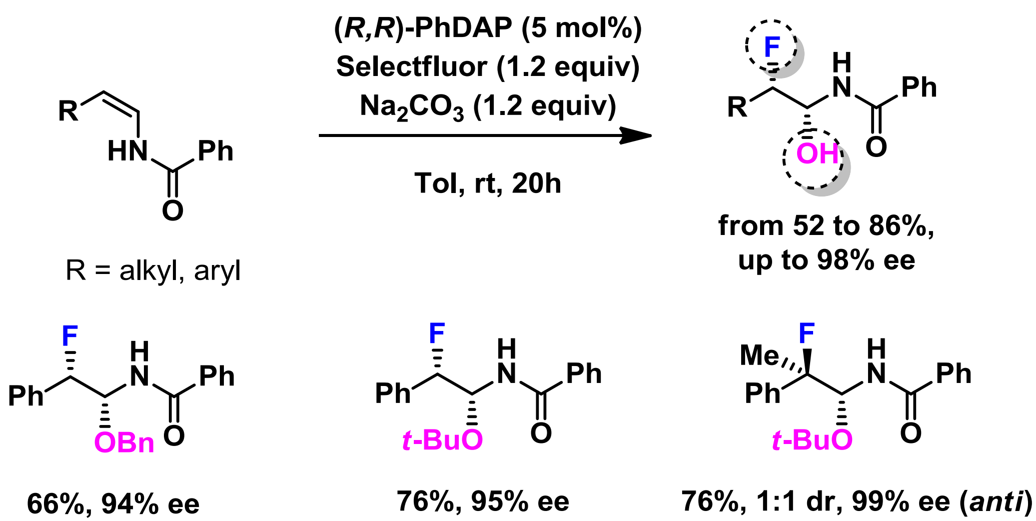



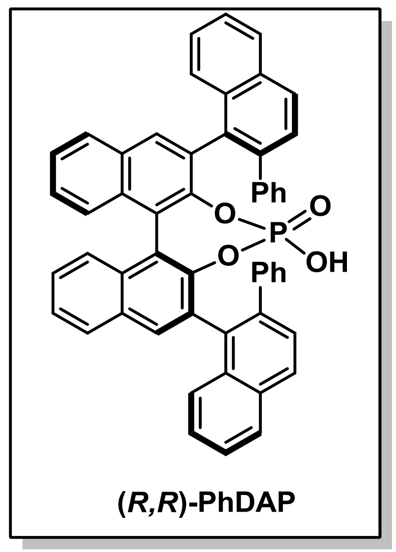

Masson *et al.*, *J. Am. Chem. Soc.* **2012**, *134,* 10389.

# Anionic phase-transfer catalysis



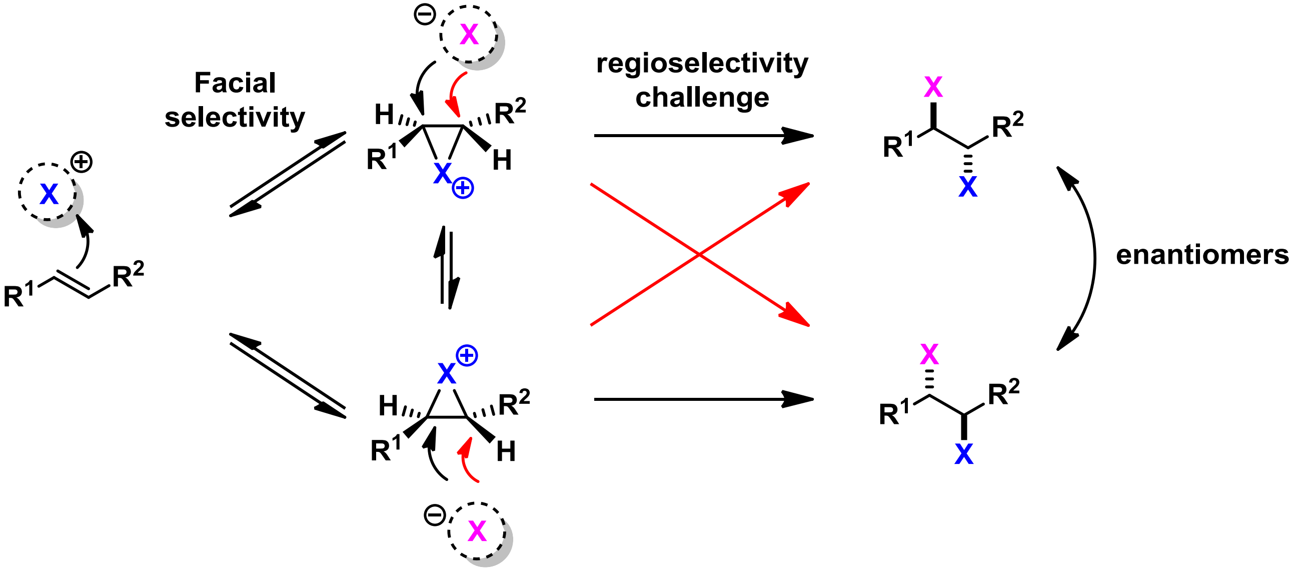



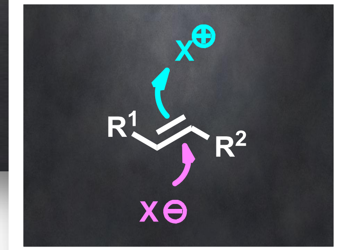




Toste *et al.*, *Angew. Chem. Int. Ed.* **2012**, *51*, 9684.

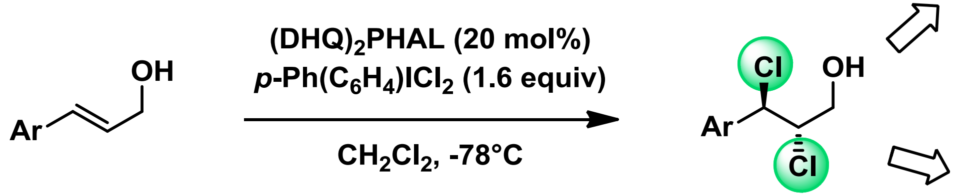
# *Enantioselective dihalogenation*

# *Enantioselective dichlorination*

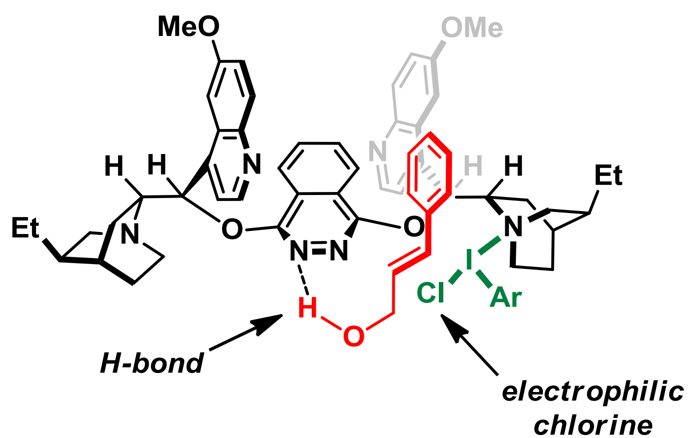



Free alcohol is essential to ensure stereocontrol



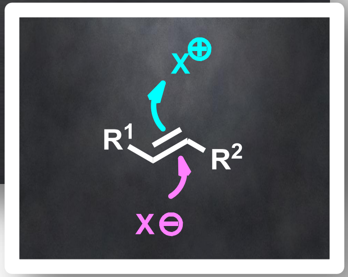

from 63 to 90%, up to 81% ee

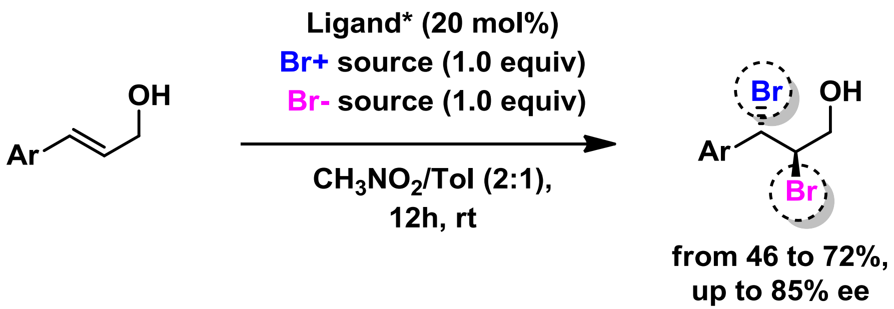
*syn* dichloro-compound obtained starting with *Z*-olefins = diastereospecific reaction



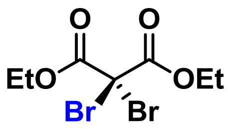

Nicolaou *et al.*, *J. Am. Chem. Soc.* **2011**, *133,* 8134.

# *Enantioselective dibromination*



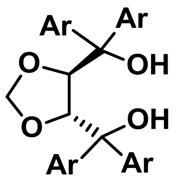




Br+ source =




Br- source = BrTi(O*i*-Pr)$_3$

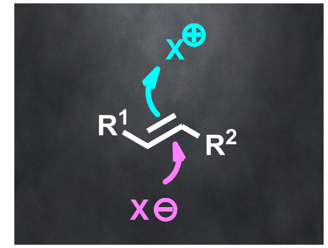
Ligand* =

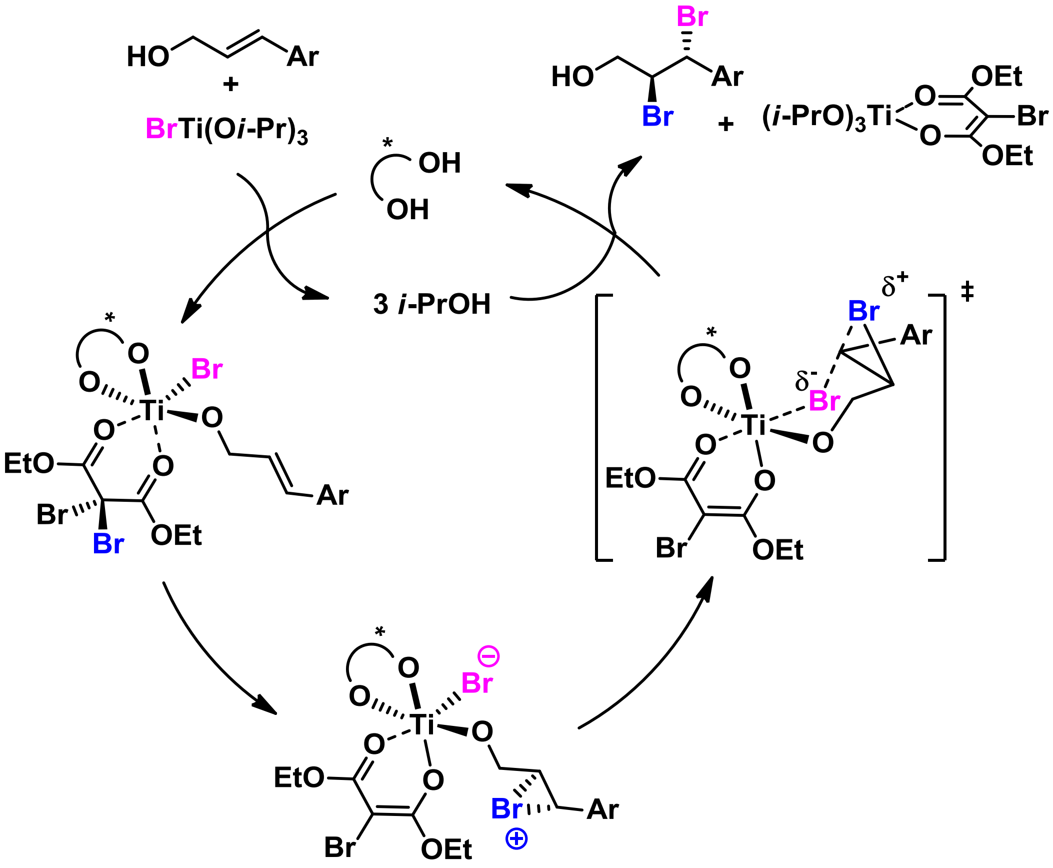



Ar = 2-naphtyl

Burns *et al.*, *J. Am. Chem. Soc.* **2013**, *135,* 12690.

# Enantioselective dihalogenation




Burns *et al.*, *J. Am. Chem. Soc.* **2013**, *135,* 12690.

# To conclude

***Many examples for iodo- and bromocyclization but no general procedure described***

***Chlorofunctionalizations remain underdeveloped***

***Fluorofunctionalizations need activated double bonds to be efficient***

***Intermolecular halofunctionalizations still constitute a major challenge***