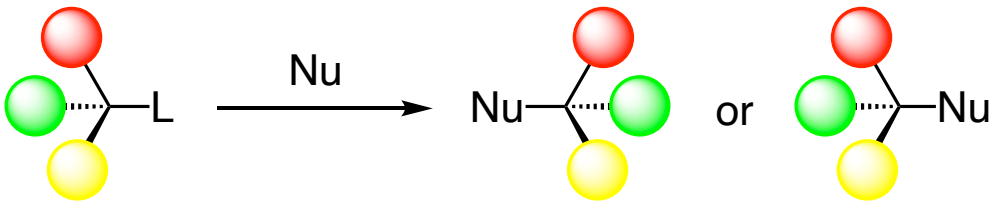
Stereoselective nucleophilic substitution reaction at tertiary carbon centers



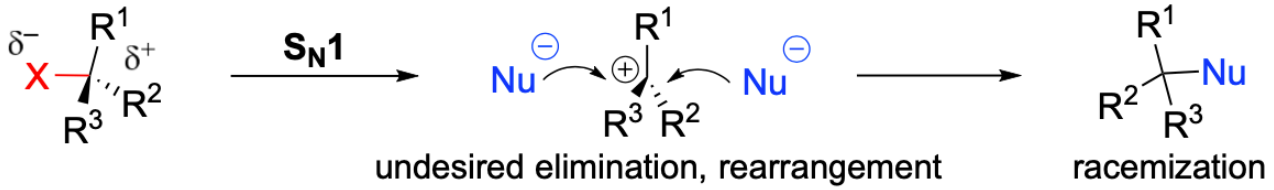
2021/12/11 (Sat)
YASUO Tsukimori

Contents

1. Introduction

Nucleophilic Substitution

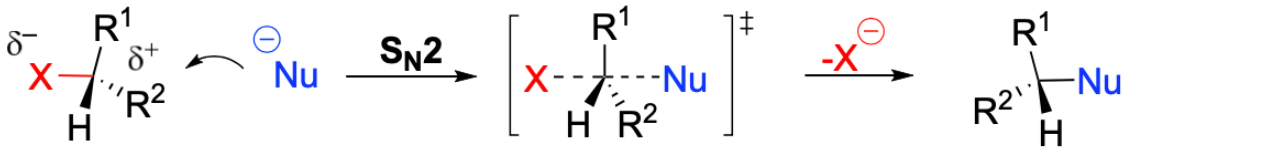
S_N1 reaction



undesired elimination, rearrangement

racemization

S_N2 reaction

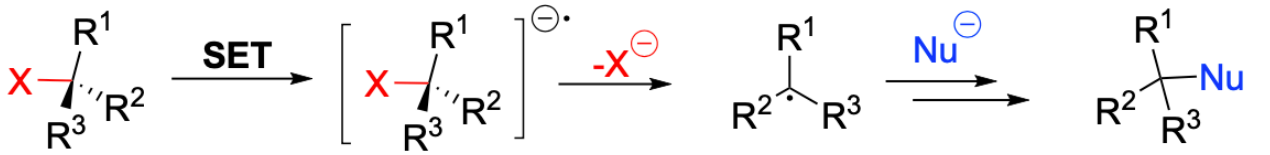


attack from the backside

penta-coordinate TS

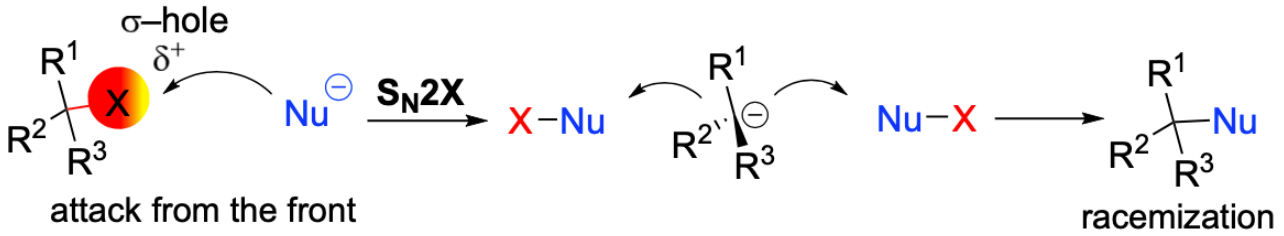
stereoinversion;
intolerance for tertiary carbon
(Walden inversion)

$S_{RN}1$ reaction



racemization

S_N2X reaction



attack from the front

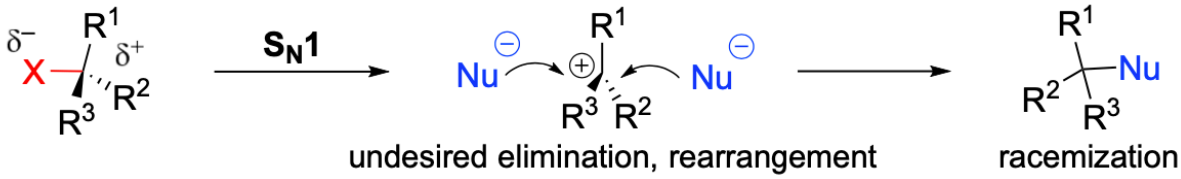
racemization

1) Zhang. X, Tan. C-H, *Chem.* **2021**. *7*. 1451-1486.
2) Marek, L. Chem. Sci., **2020**, *11*, 9378-9385

2. S_N1 reaction

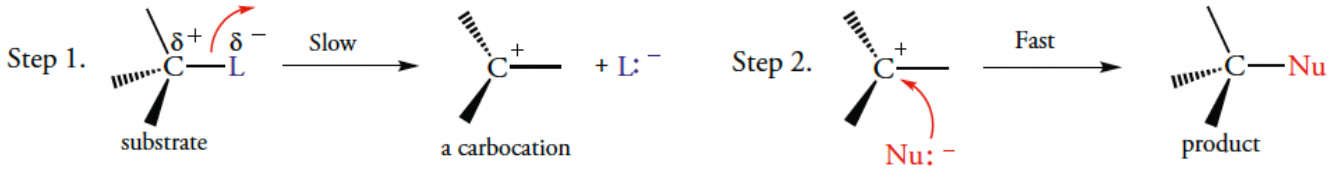
2-1. About S_N1 reaction

"S_N" stands for "nucleophilic substitution"
and the "1" says that the rate-determining step is unimolecular.



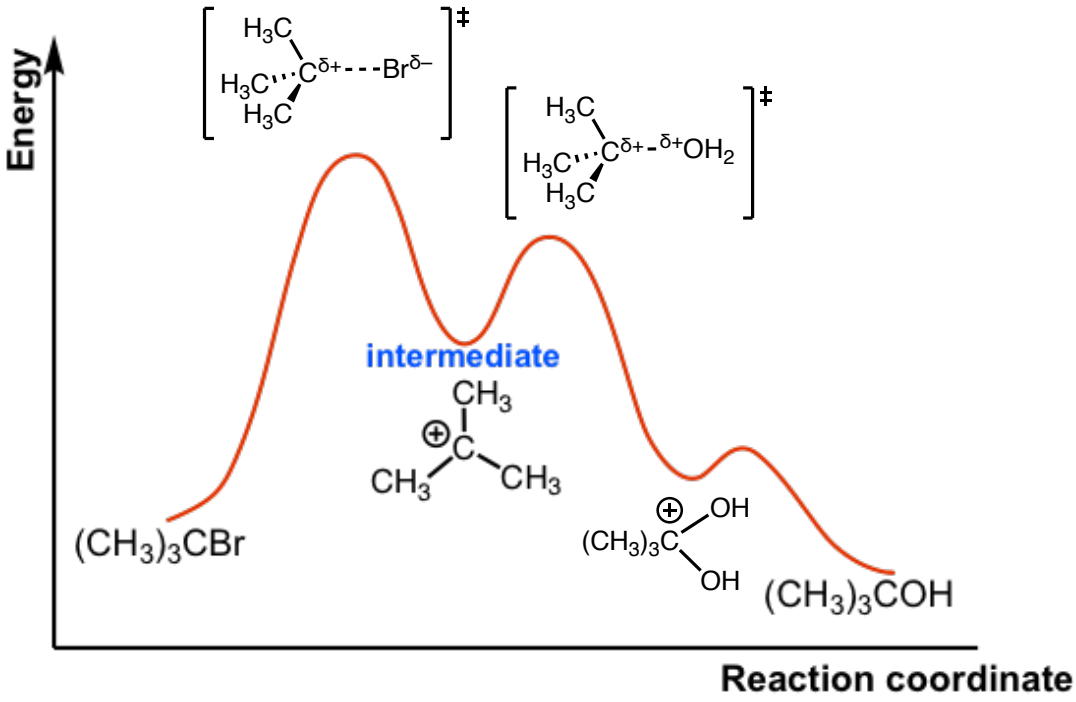
reaction rate = k[R_3C-X]

The S_N1 Mechanism



SN1 reactions happen in two steps:
1. The leaving group leaves, and the substrate forms a carbocation intermediate.
2. The nucleophile attacks the carbocation, forming the product.

Activation Energy and the S_N1 Reaction



Relative reactivity of substrates towards S_N1 reaction

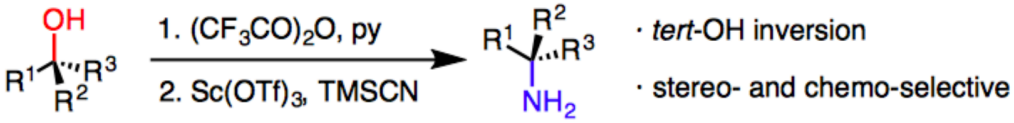
tertiary 3° > secondary 2° > primary 1° and methyl

1) Liu, X. *Organic Chemistry I* (Kwantlen Polytechnic University)
2) Ouellette, R. J. *et. al. Principles of Organic Chemistry*. **2015**, 189-208

2. S_N1 reaction

2-2. Stereoinvertive substitutions through cationic intermediates

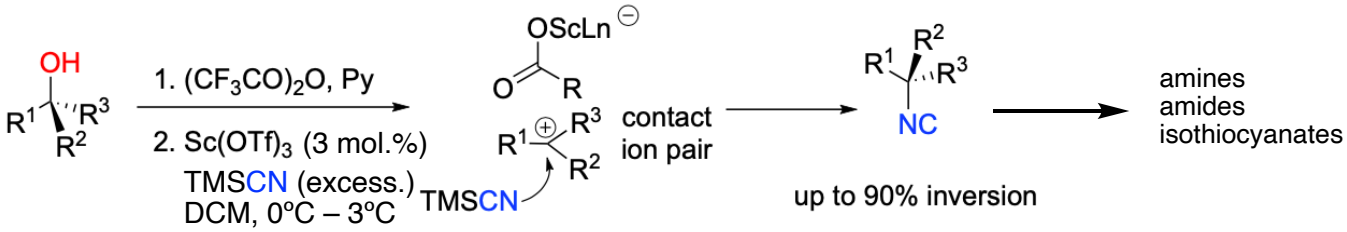
Stereoinversion of tertiary alcohols to tertiary-alkyl isonitriles and amines (Shenvi 2013)

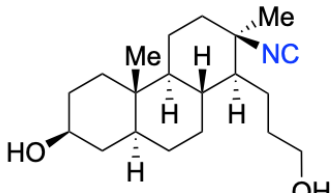


· *tert*-OH inversion

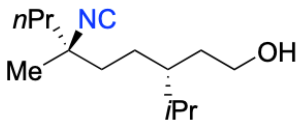
· stereo- and chemo-selective

Ryan A. Shenvi

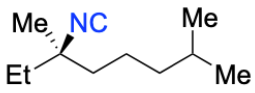




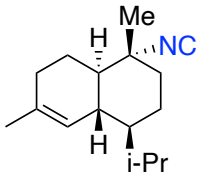
69% yield, 91:9 dr



71% yield, 90:10 dr



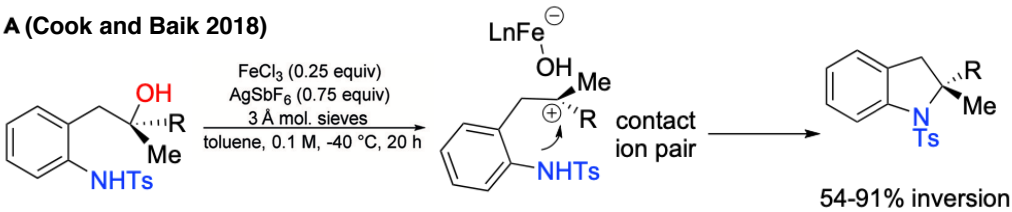
78% yield, 68% ee
(from 86% ee)



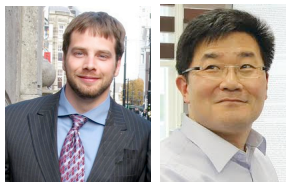
59% yeild, 91:9 dr

Intramolecular substitution of tertiary alcohols

A (Cook and Baik 2018)

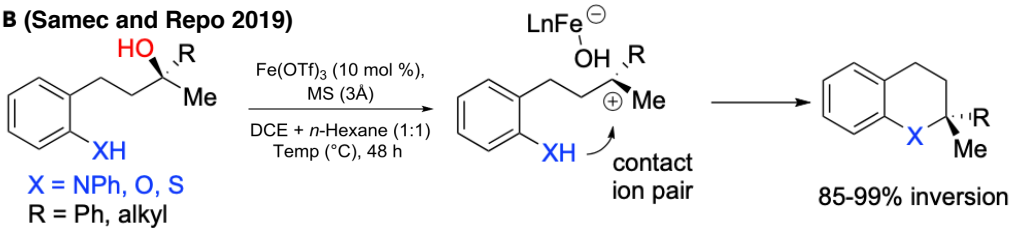


54-91% inversion

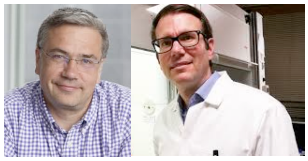


Silas P. Cook **Mu-Hyun Baik**

B (Samec and Repo 2019)



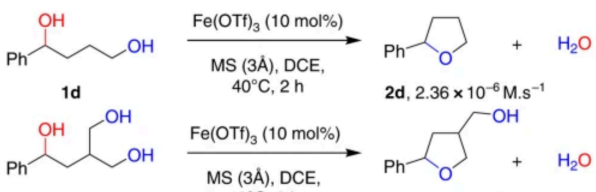
85-99% inversion



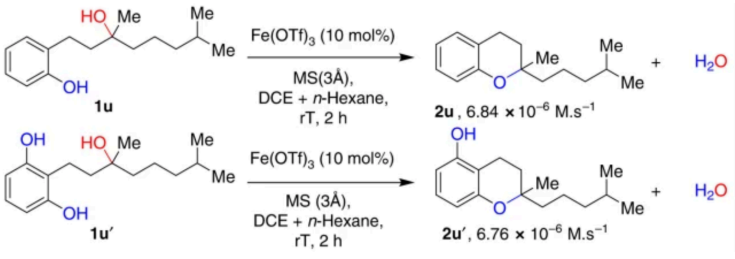
Timo Repo **Joseph S.M. Samec**

B (Samec and Repo 2019) Kinetic Studies

Secondary Alcohols



Tertiary Alcohols

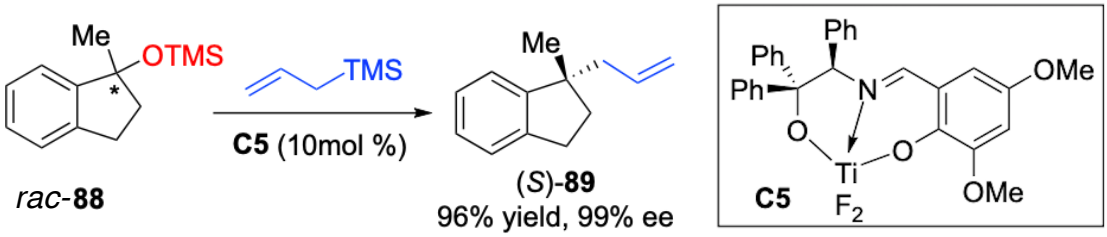


1) Shenvi, R. A. *et. al. Nature.* **2013**, *501*, 195-199
2) Cook, S. P *et. al. Angew. Chem. Int. Ed.* **2019**, *58*, 1727 –1731
3) Samec. J. S. M. *et. al. Nature Communications.* **2019**, *10*, 3826.

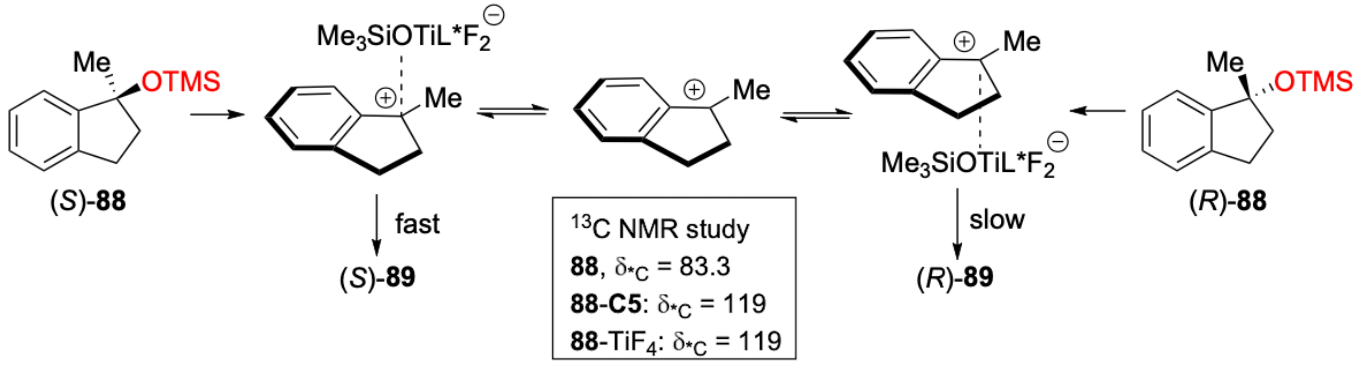
2. S_N1 reaction

2-3. Stereoconvergent substitutions through cationic intermediates

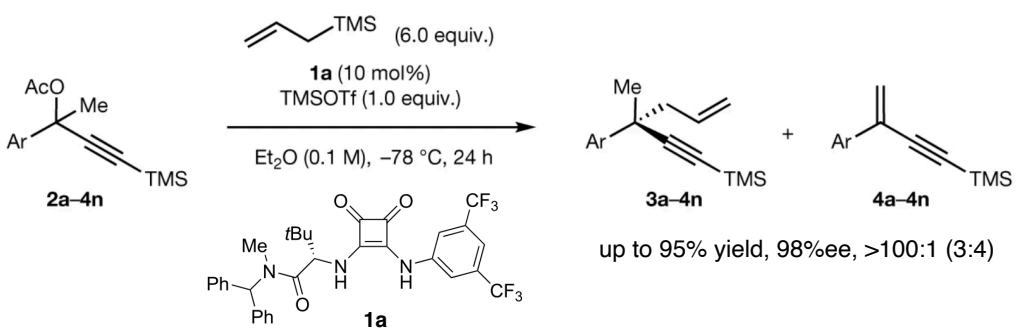
Chiral metal-complex-mediated substitution (Braun 2004)



Manfred Braun

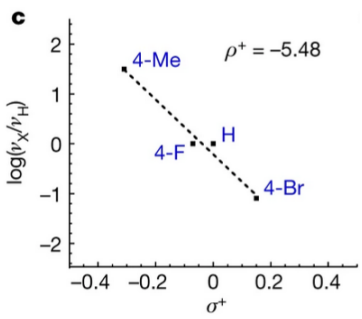


Chiral metal-complex-mediated substitution (Braun 2004)

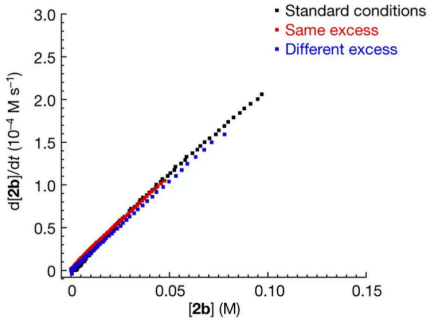


Eric Jacobsen

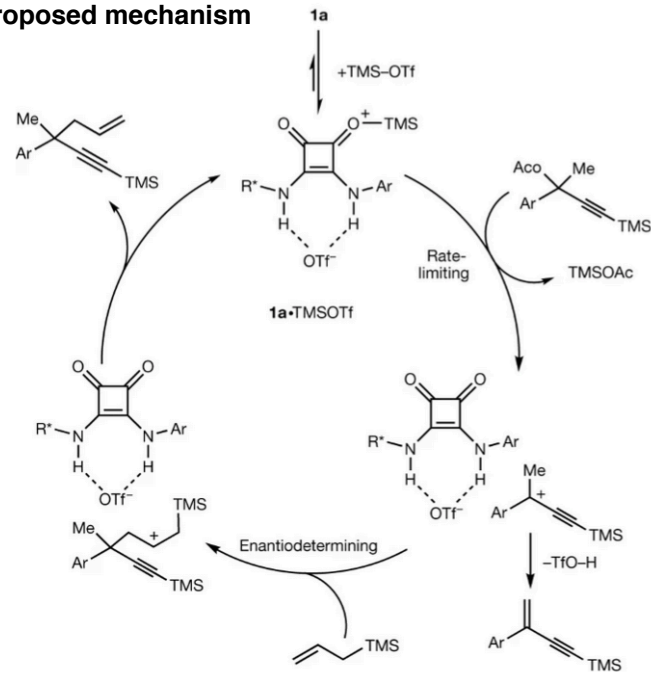
Hammett plot



Kinetic data



Proposed mechanism



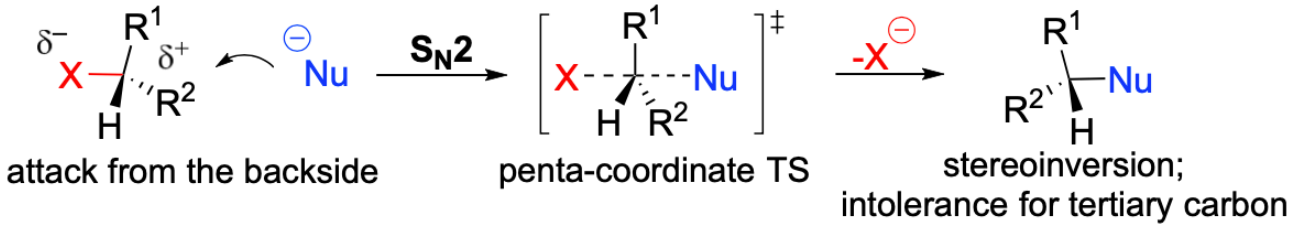
1) Braun, M. *et. al. Angew. Chem. Int. Ed.* **2004**, *43*, 534 –517

2) Jacobsen, E. N *et. al. Nature.* **2018**, *556*, 447-451.

3. S_N2 reaction

3-1. About S_N2 reaction

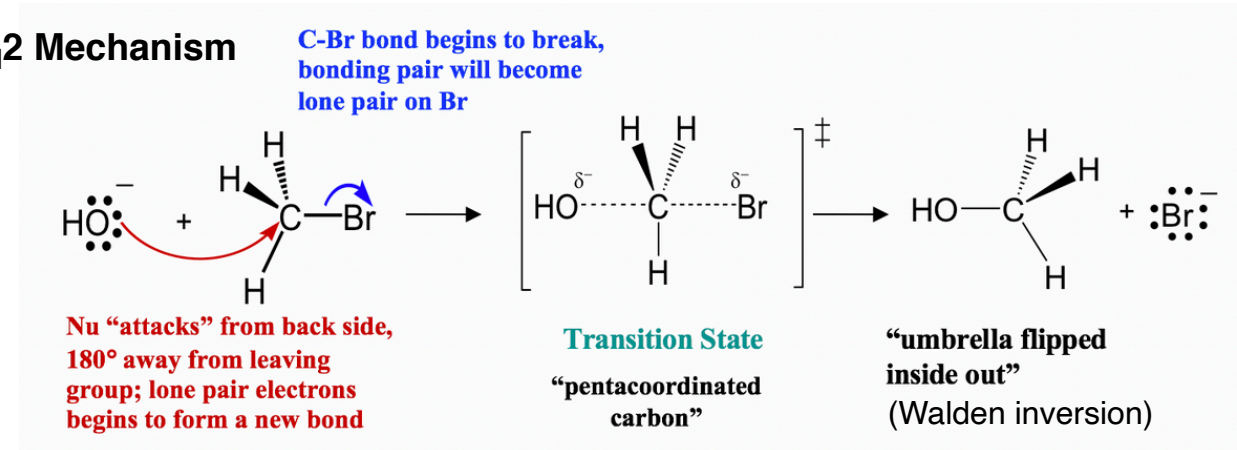
S_N2 reaction, meaning Substitution, Nucleophilic and Bimolecular.



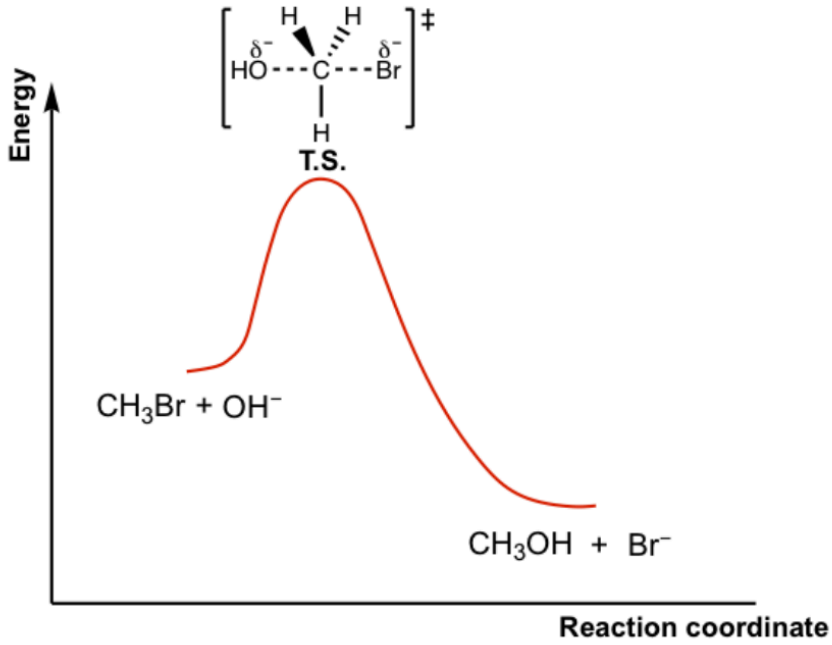
attack from the backside — penta-coordinate TS — stereoinversion; intolerance for tertiary carbon

reaction rate = $k[Nu^-][R_3C\text{-}X]$

The S_N2 Mechanism



Energy Diagram of S_N2 Mechanism



Relative reactivity of alkyl halides towards S_N2 reaction

methyl > primary 1° > secondary 2° >> tertiary 3°

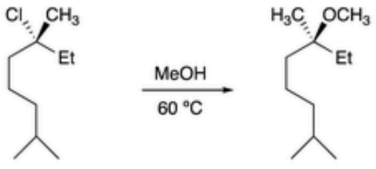
1) Liu, X. *Organic Chemistry I* (Kwantlen Polytechnic University)
2) Ouellette, R. J. *et. al. Principles of Organic Chemistry*. **2015**, 189-208
3) Walden, P. *Berichte der deutschen chemischen Gesellschaft*. **1896**, *29*, 133-138

3. S_N2 reaction

3-2. Stereoinvertive S_N2 substitutions at tertiary carbon centers

1. HIstory

(Steavens and McNiven 1939)

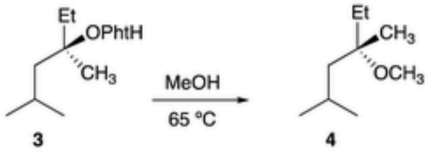


1 2

Original report by Hughes and Ingold (methanolysis at 60 °C)
34% optical activity

Same transformation with precise analytical tools by Müller and Rossier
(methanolysis at 25°C)
78% inversion of configuration

(Doering and Zeiss 1953)



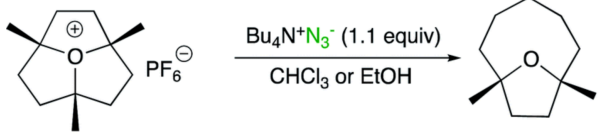
3 4

Original report by Doering and Weiss (methanolysis at 60 °C)
54% inversion of configuration

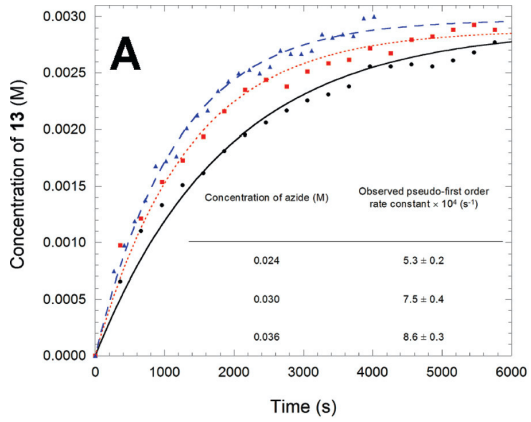
Same type of transformation with precise analytical tools by Müller and Rossier
(methanolysis at 25°C)
87% inversion of configuration

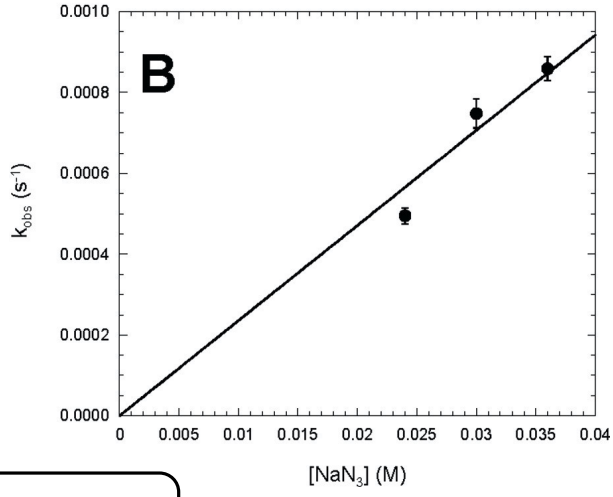
2. S_N2 nucleophilic ring-opening reactions at tertiary carbon centers

(Mascal 2010)

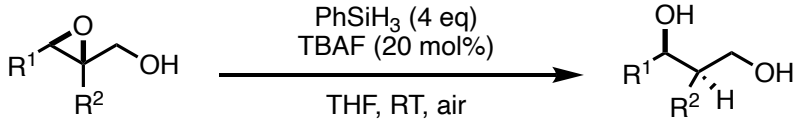


Kinetic Data

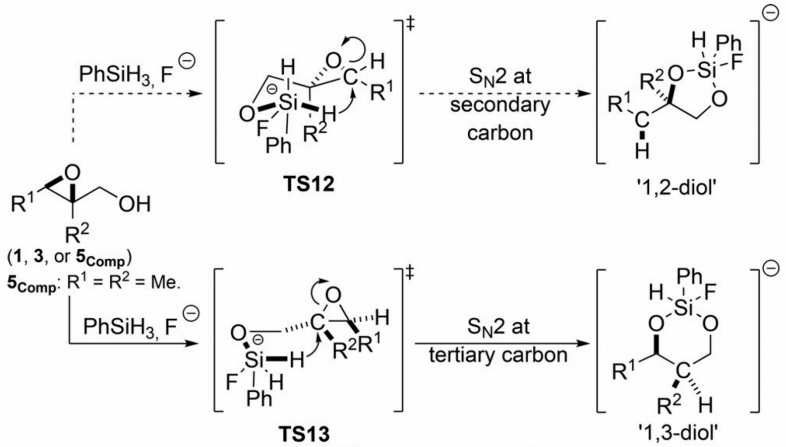


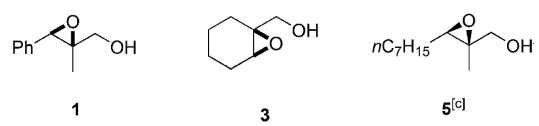


(Gansäuer 2017)



70–88% yield





1 3 5[c]

		ΔG‡298	ΔΔ G‡298	∠ HCO [°]
1	TS12	27.3	5.9	146.4
	TS13	21.4		153.0
3	TS12	24.1	7.0	81.7
	TS13	17.1		89.0
5Comp	TS12	26.3	5.4	147.4
	TS13	20.9		152.6

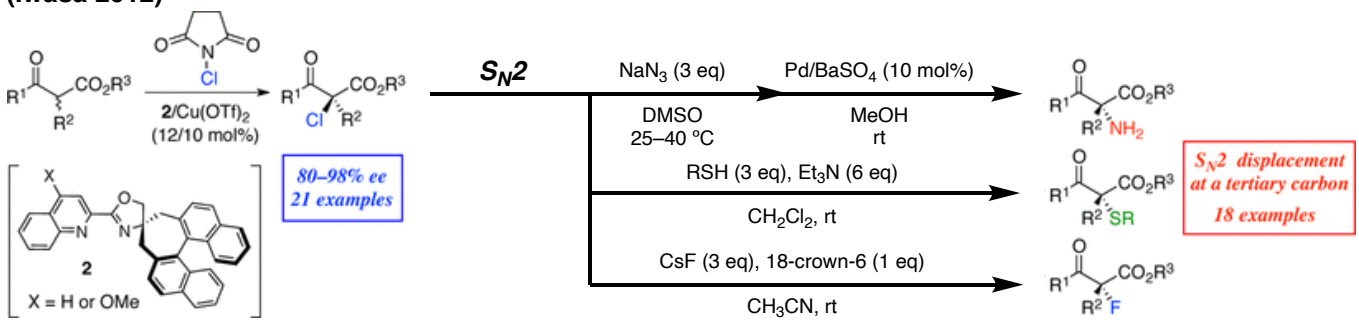
1) Hughes, E. D. *et. al. Nature*, **1950**, *166* , 679 **2)** Zeiss, H. H. *et. al. J. Am. Chem. Soc.*, **1953**, *75* , 4733
3) Müller, P. *et. al. J. Chem. Soc., Perkin Trans. 2***000**, *2*, 2232 **4)** Mascal, M. *et. al. J. Am. Chem. Soc.* **2010**, *132*, 10662
5)Gansäuer, A. *Angew. Chem. Int. Ed.* **2017**, *56*, 9719–9722 **6)**Steven, P. G. *et. al. J. Am. Chem. Soc.*, **1939**, *61*, 1295.

3. S_N2 reaction

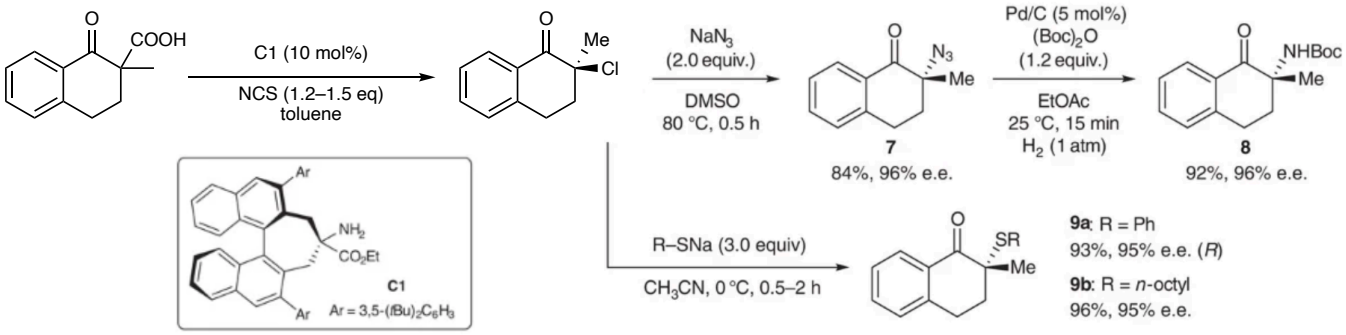
3-2. Stereoinvertive S_N2 substitutions at tertiary carbon centers

3. S_N2 reaction of chiral tertiary halides

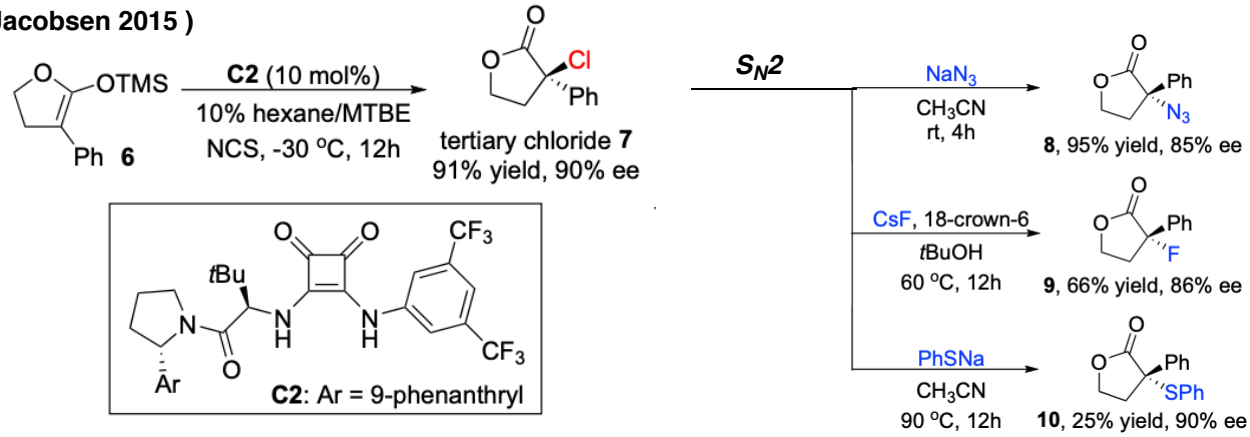
(Iwasa 2012)



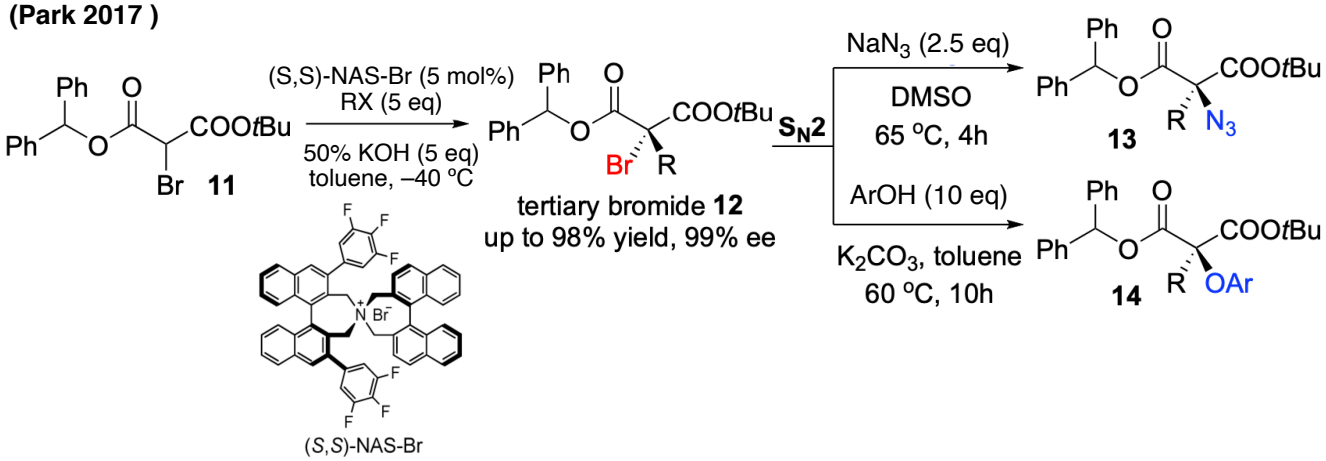
(Iwasa 2017)



(Jacobsen 2015)



(Park 2017)



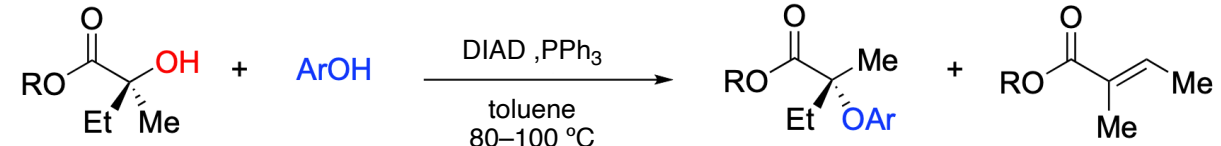
1) Iwasa, S. *et. al.* J. Am. Chem. Soc. **2012,** *134*, 9836–9839
2) Iwasa, S. *et. al. Nature Communications.* **2017**, *5*, 15600
3) Jacobsen. E. N. *et. al. Tetrahedron Letters.* **2015,** *56, 3248-3430*
4) Park, H-G. *et. al. J. Org. Chem.* **2017**, *82*, 4936–4943

3. S_N2 reaction

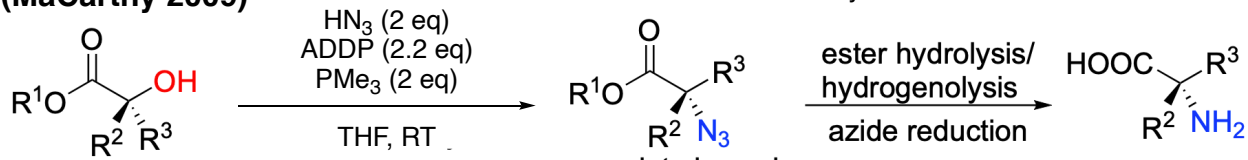
3-2. Stereoinvertive S_N2 substitutions at tertiary carbon centers

4. S_N2 Reactions of tertiary alchohol

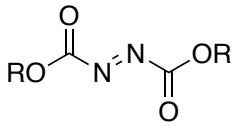
Mitsunobu type reaction
(Shi 2003)



(MaCarthy 2009)

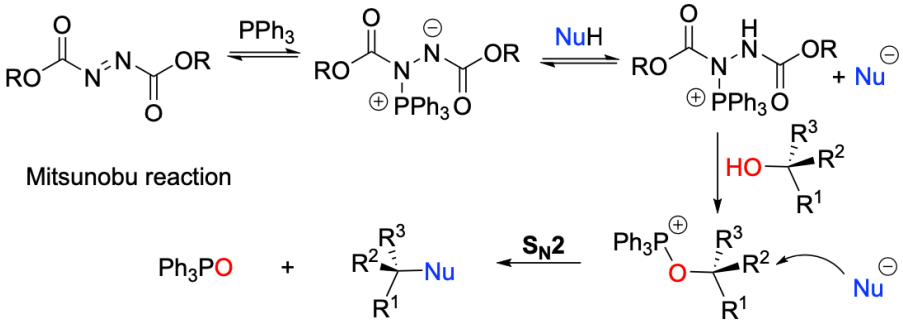


Mitsunobu Reagent

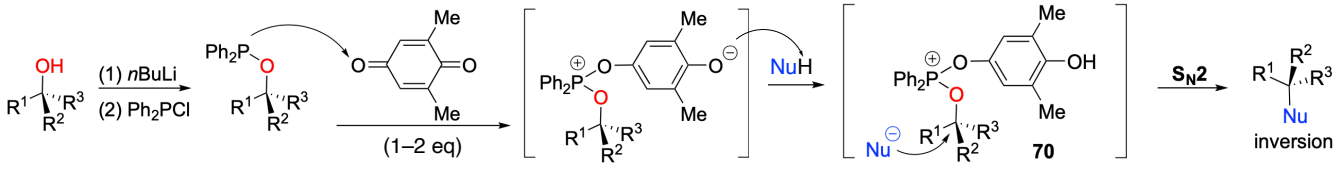


R = Et (DEAD)
R = i-Pr (DIAD)
R = Cy (ADDP)

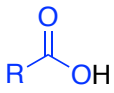
Mechanism



(Mukaiyama 2003 – 2007)

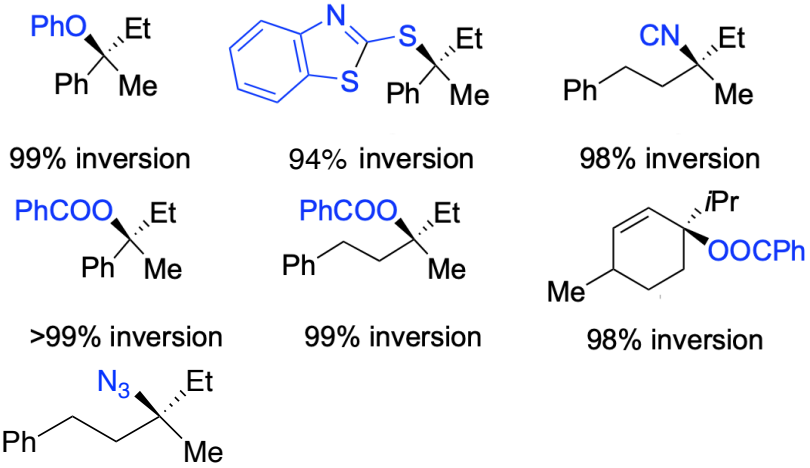


Nucleophiles



ROH
RSH
$(EtO)_2POCN$
$TMSN_3$

Selected examples



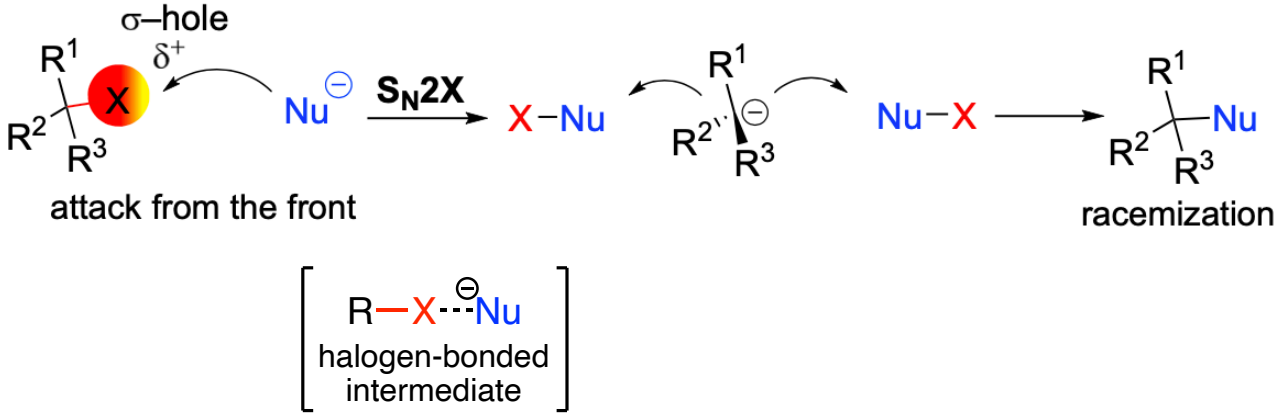
etc.

1) Shi, Y-J. *et. al. Tetrahedro Letters* **2003,** *44*, 3609–3611 **2)** MaCarthy, J. R. *et. al. Org. Lett.* **2009**, *11*, 807–810
3) Mukaiyama, T. *et. al. J. Am. Chem. Soc.* **2003**, *125*, 10538-10539 **4)** Mukaiyama, T. *et. al. J. Am. Chem. Soc.* **2004**, *126*, 7359-7367
5) Mukaiyama, T. *et. al. Chem. Lett.* **2004**, *33*, 1522-1523 **6)** Mukaiyama, T. *et. al. Bull. Chem. Soc. Jpn.* **2006**, *79*, 1106–1117
7) Mukaiyama, T. *et. al. Chem. Lett.* **2007**, *36*, 2-7 **8)** Mukaiyama, T. *et. al. Tetrahedron.* **2007,** *63*, 6358–6364
9) Mukaiyama, T. *et. al. Chem. Lett.* **2005**, *34*, 638-639 **10)** Mukaiyama, T. *et. al. Bull. Chem. Soc. Jpn.* **2006**, *79*, 780–790

4. S_N2X reaction

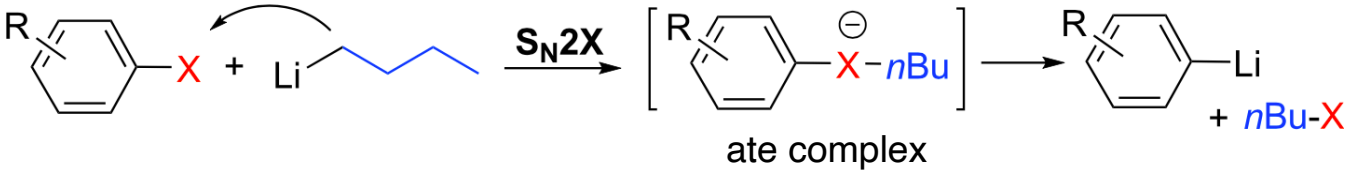
4-1. About S_N2X reaction

"S_N2X" or "S_N2Hal" reactions means "halogenophilic nucleophilic substitution reactions"



1.History

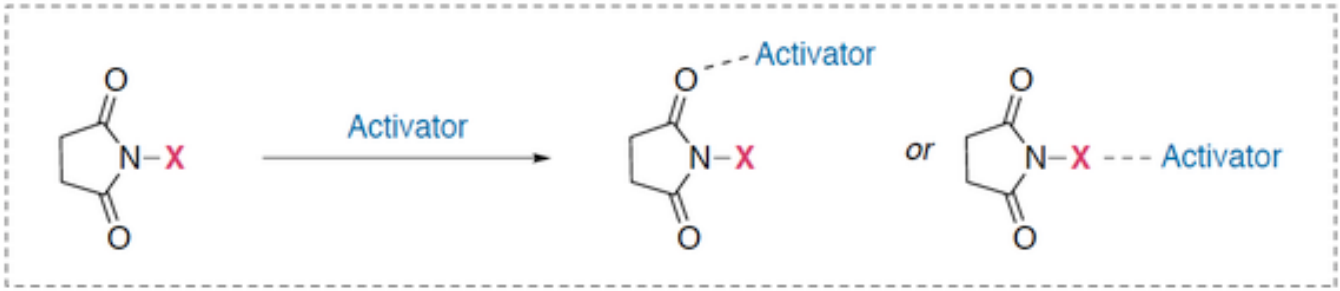
Lithium-halogen exchange (Witting and Gilman 1930s)



X-ray crystal structure of "ate complex" (Farnham 1986)

2.Halogenating agents

Alkyl halides activated by adjacent EWGs are also known as electrophilic halogenating agents, typically containing N–X bonds; for example, NCS, NBS, and NIS.

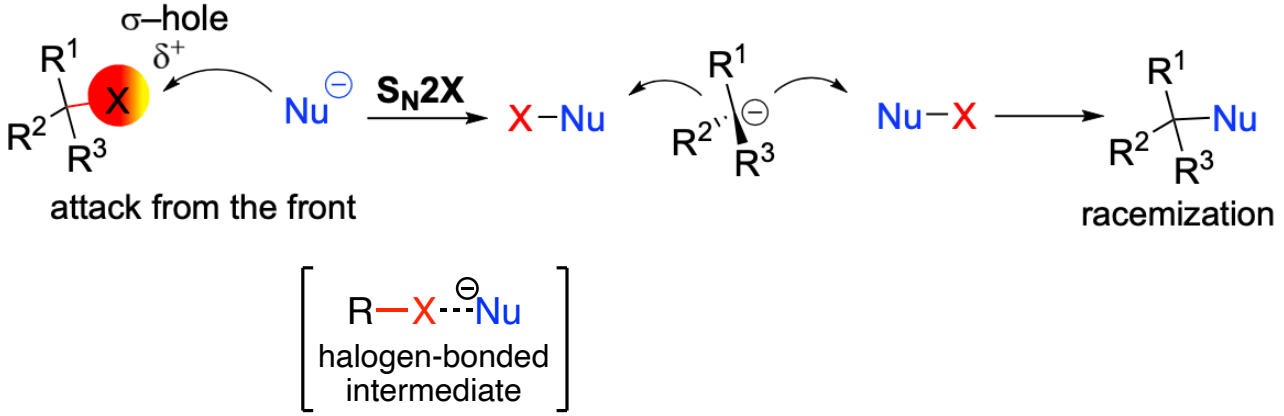


1) Witting, G. *et. al.*Ber. Dtsch. Chem. Ges. A/B. **1938**, *71*, 1903–1912.
2) Gilman, H. *et. al.* J. Am. Chem. Soc. **1939,** *61*, 106–109.
3) Farnham, W. B. *et. al.*J. Am. Chem. Soc. 108, 2449–2451.

4. S_N2 reaction

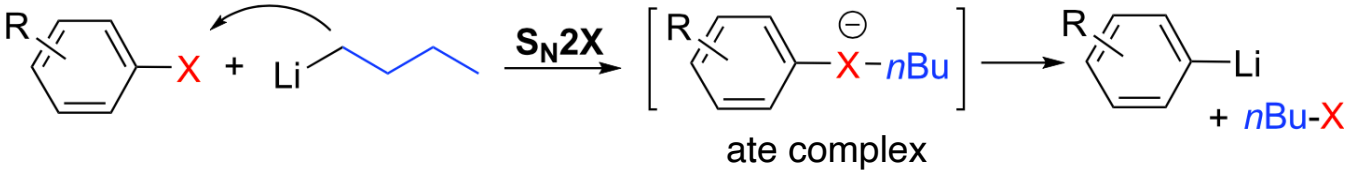
4-1. About S_N2X reaction

"S_N2X" or "S_N2Hal" reactions means "halogenophilic nucleophilic substitution reactions"



1.History

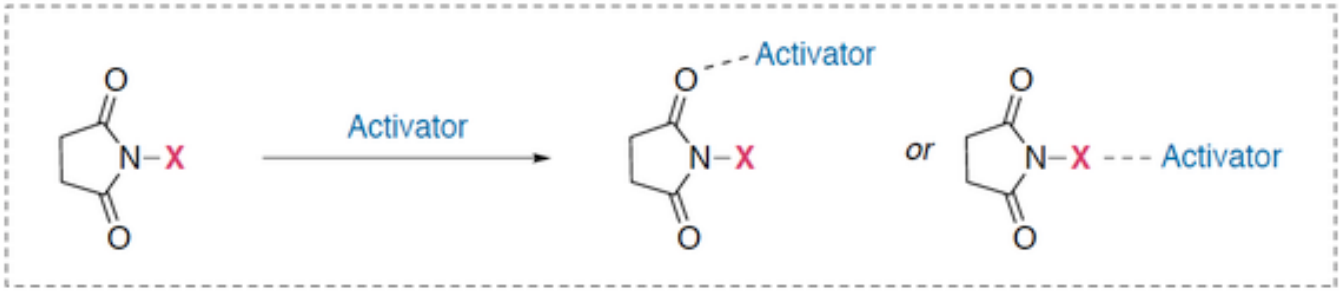
Lithium-halogen exchange (Witting and Gilman 1930s)



X-ray crystal structure of "ate complex" (Farnham 1986)

2.Halogenating agents

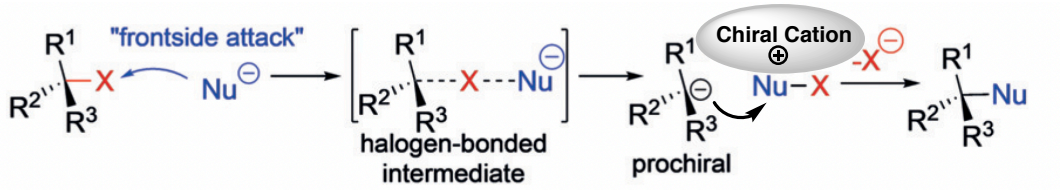
Alkyl halides activated by adjacent EWGs are also known as electrophilic halogenating agents, typically containing N–X bonds; for example, NCS, NBS, and NIS.



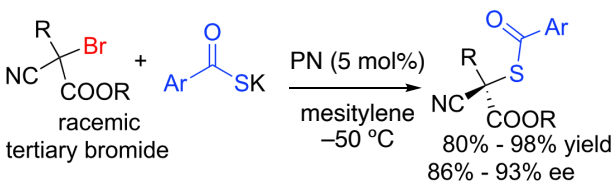
1) Witting, G. *et. al.*Ber. Dtsch. Chem. Ges. A/B. **1938**, *71*, 1903–1912.
2) Gilman, H. *et. al.* J. Am. Chem. Soc. **1939,** *61*, 106–109.
3) Farnham, W. B. *et. al.*J. Am. Chem. Soc. 108, 2449–2451.

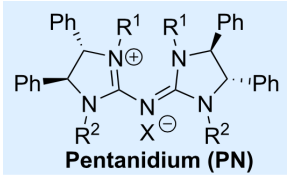
4. S_N2X reaction

Enantioconvergent S_N2X reactions of tertiary halides (Tan 2019)



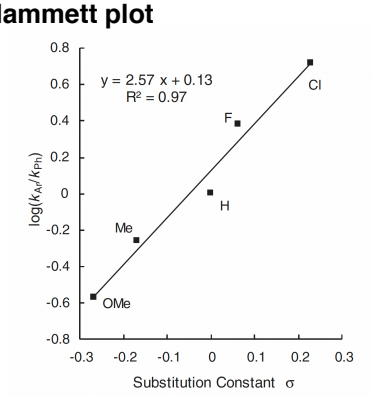
Choon-Hong Tan



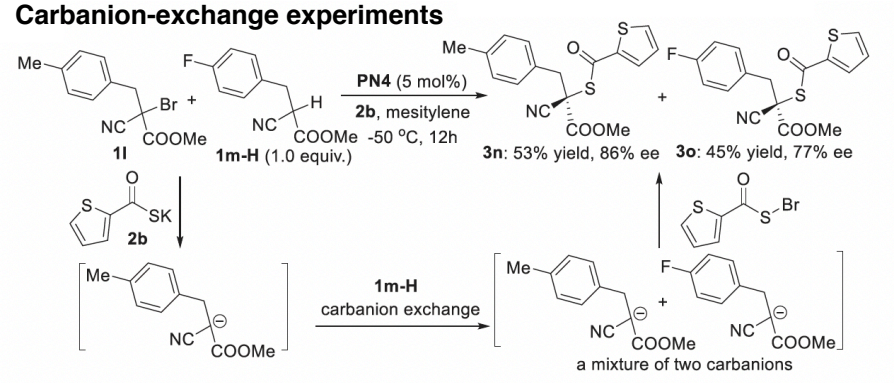


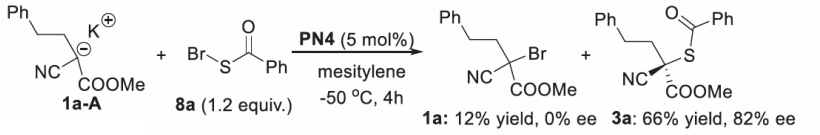
Pentanidium (PN)

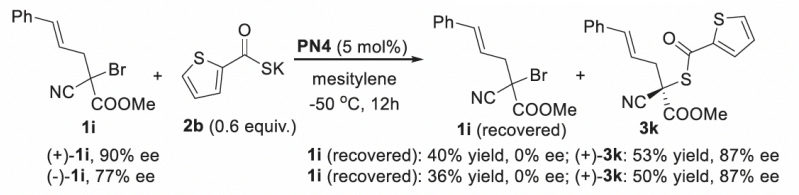
Hammett plot



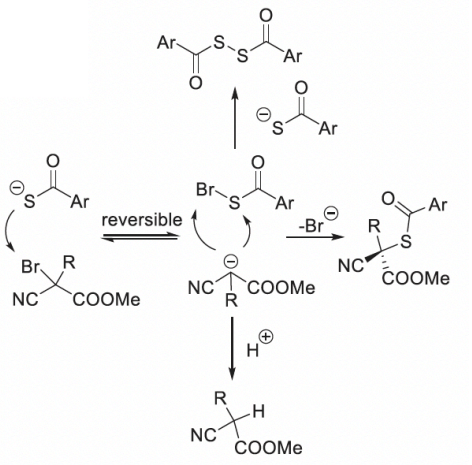
Carbanion-exchange experiments

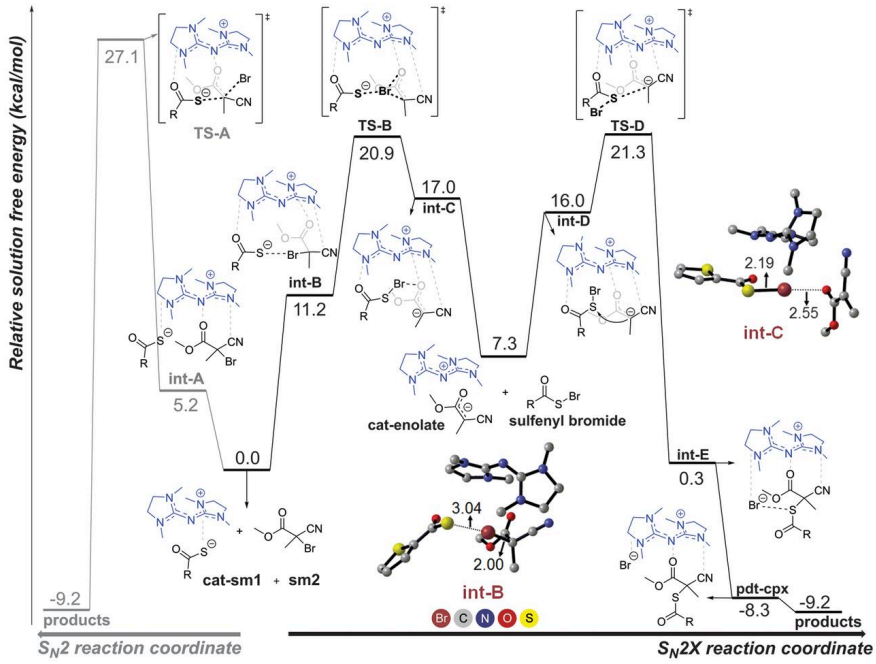






Proposed S_N2X pathway

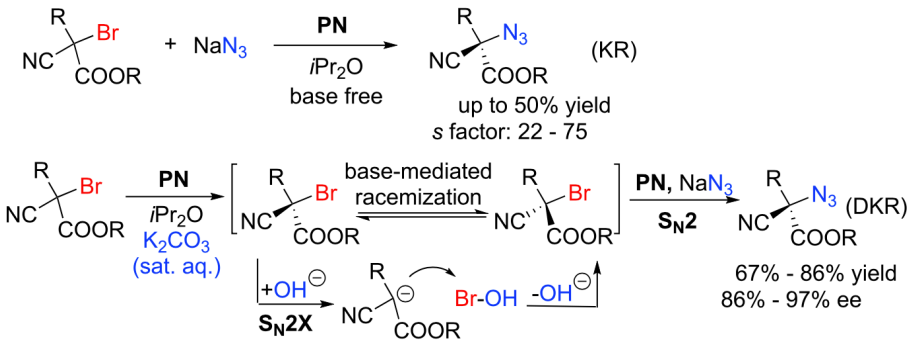




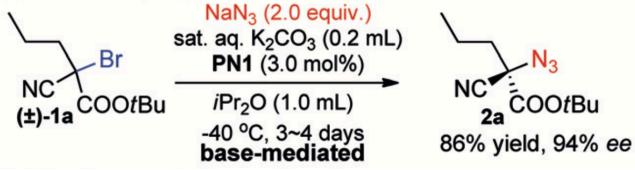
1) Tan, C-H. *et. al. Science*, **2019**, *363* , 400-404

4. S_N2X reaction

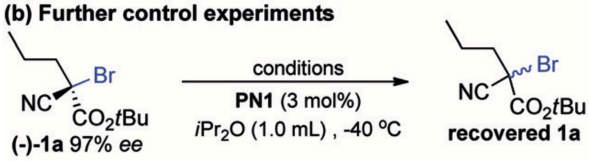
Enantioconvergent S_N2X reactions of tertiary halides (Tan 2020)



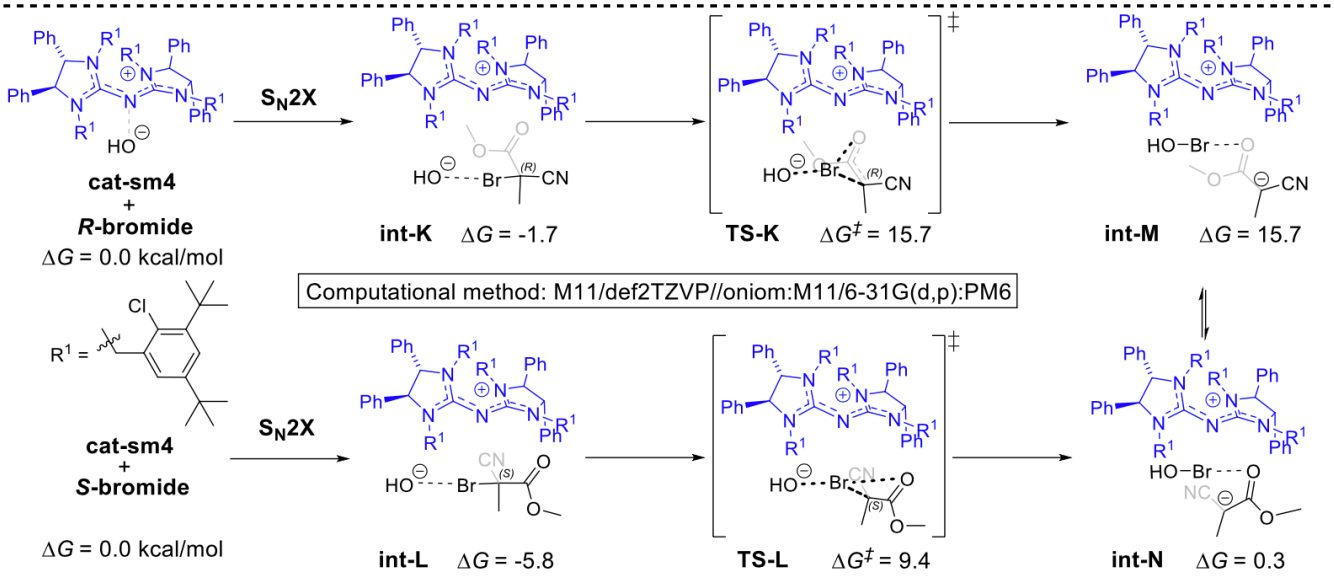
(a) Previously reported basic conditions (Tan 2019)

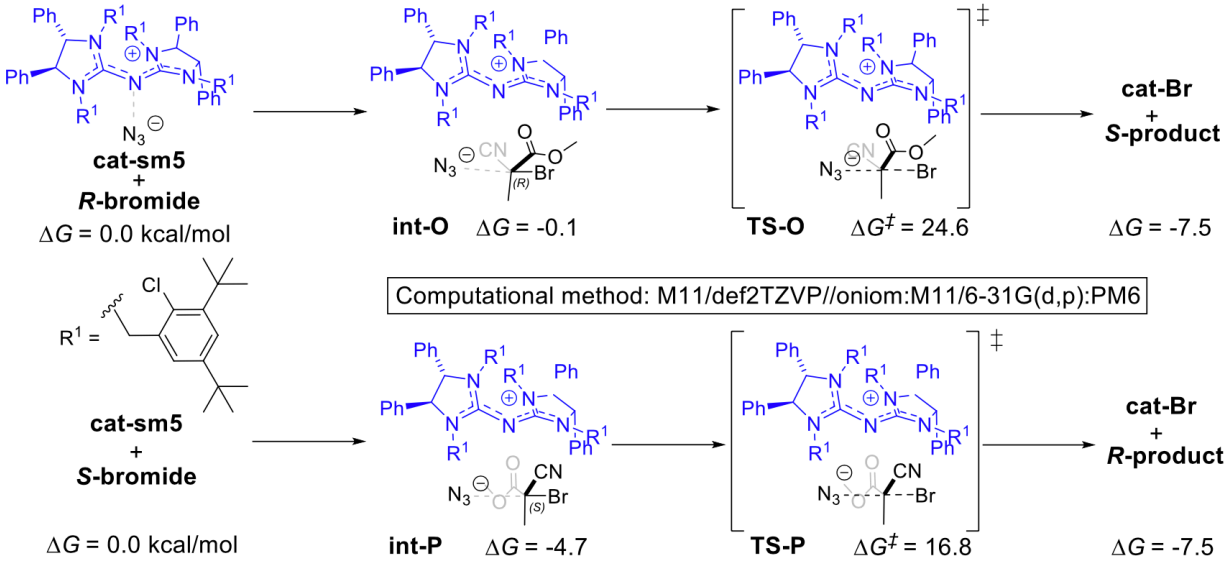


(b) Further control experiments



Conditions: (1) add nothing: after 10 h, *ee* value of **(-)-1a** maintained
(2) H_2O (0.2 mL): after 10 h, *ee* value of **(-)-1a** maintained
(3) sat. aq. K_2CO_3 (0.2 mL): < 10 min, racemic **1a** obtained
(4) solid K_2CO_3 (0.2 g): 2h, racemic **1a** obtained

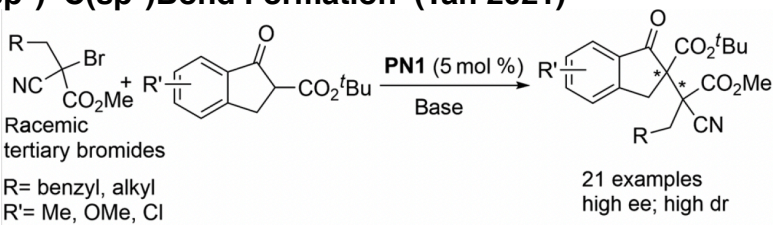


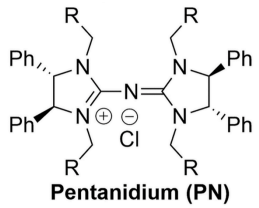


1) Tan, C-H. *et. al. Angew. Chem*, **2020**, *132* , 9140-9143

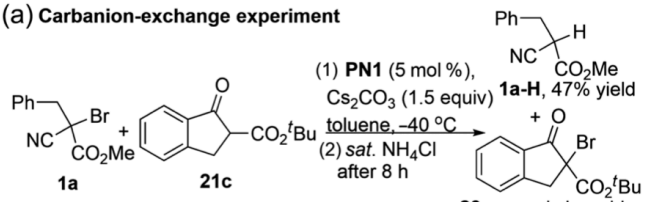
4. S_N2X reaction

C(sp^3)–C(sp^3)Bond Formation (Tan 2021)

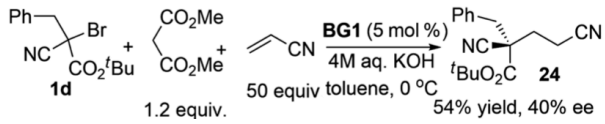




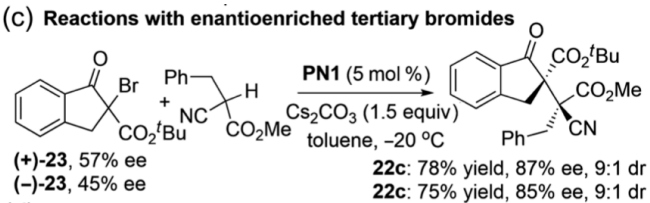
(a) **Carbanion-exchange experiment**



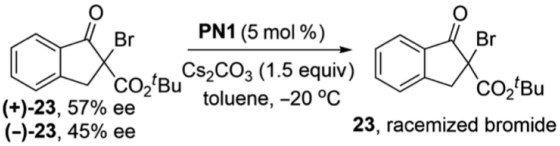
(b) **Carbanion-trapping experiment**



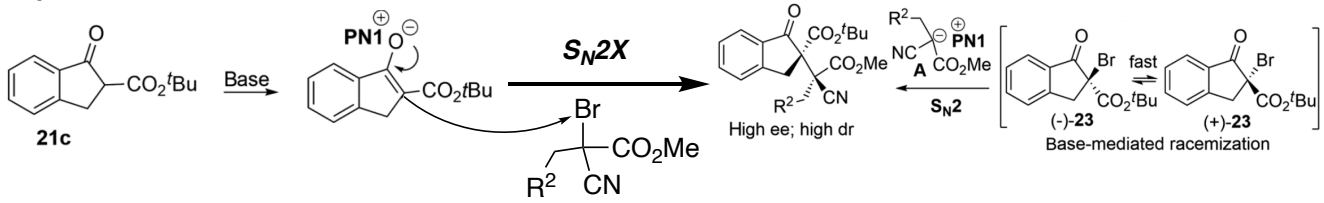
(c) **Reactions with enantioenriched tertiary bromides**

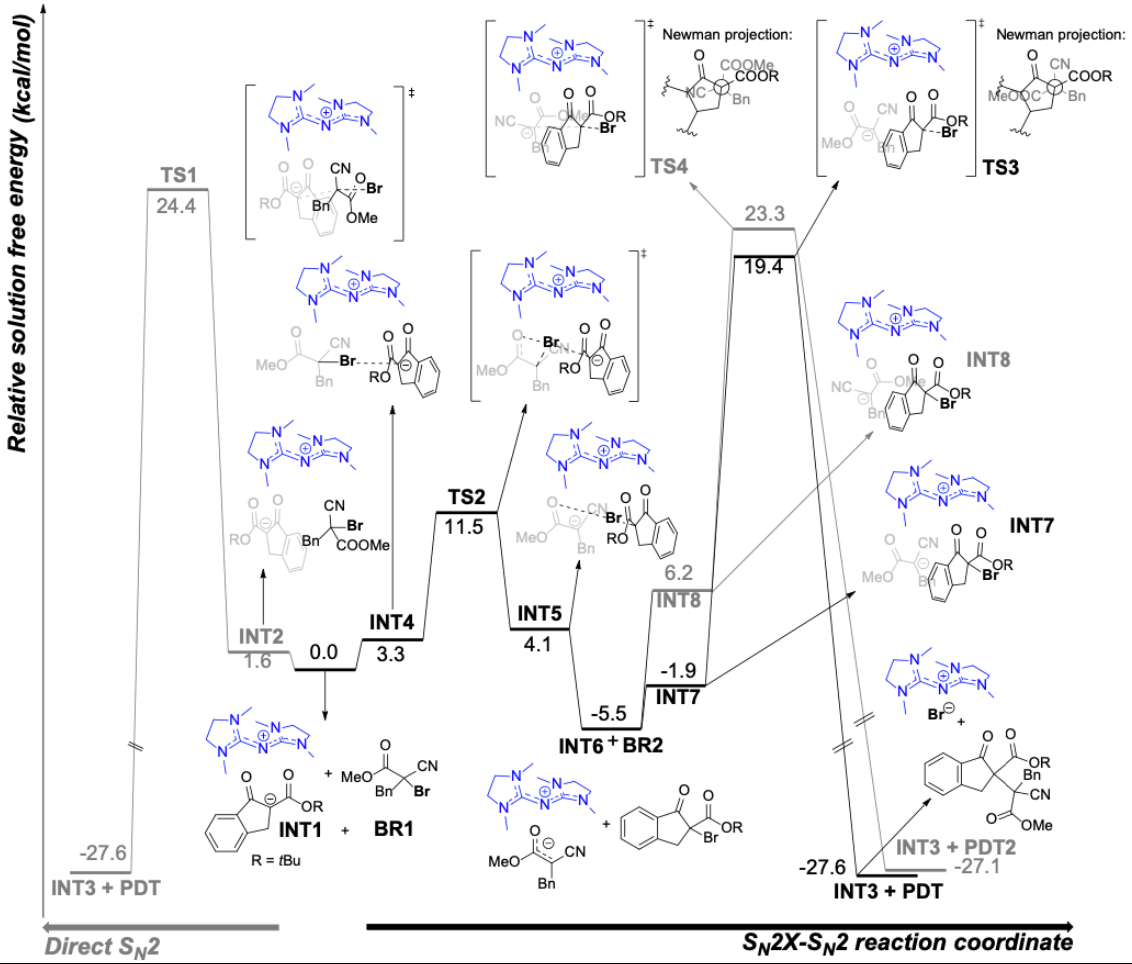


(d) **Base-mediated racemization**



Proposed mechanism



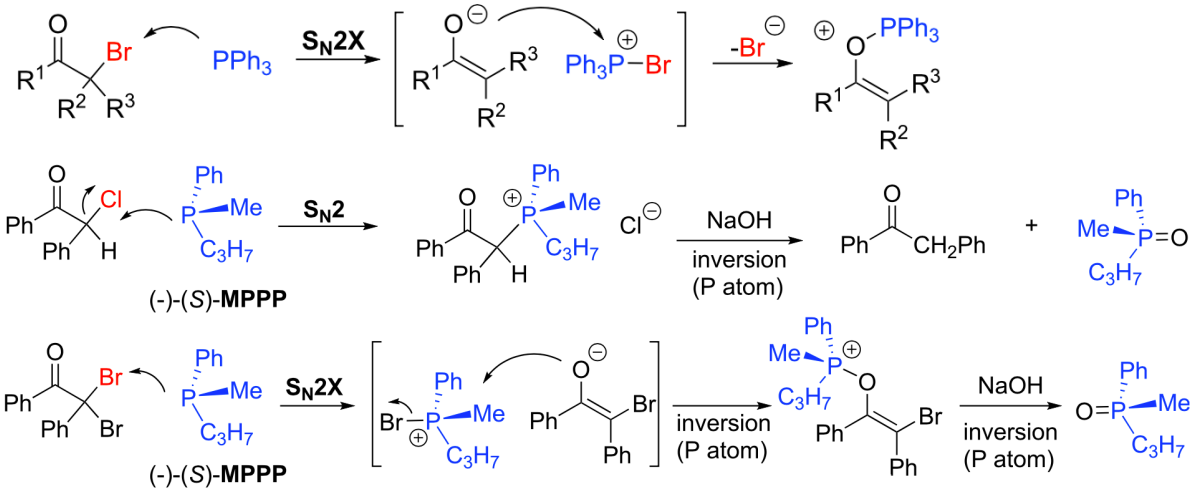


1) Tan, C-H. *et. al. CCS. Chem*, **2021**, *3* , 2192-2200. **2)** Tan, C-H. *et. al. ChemRxiv*. **2021**

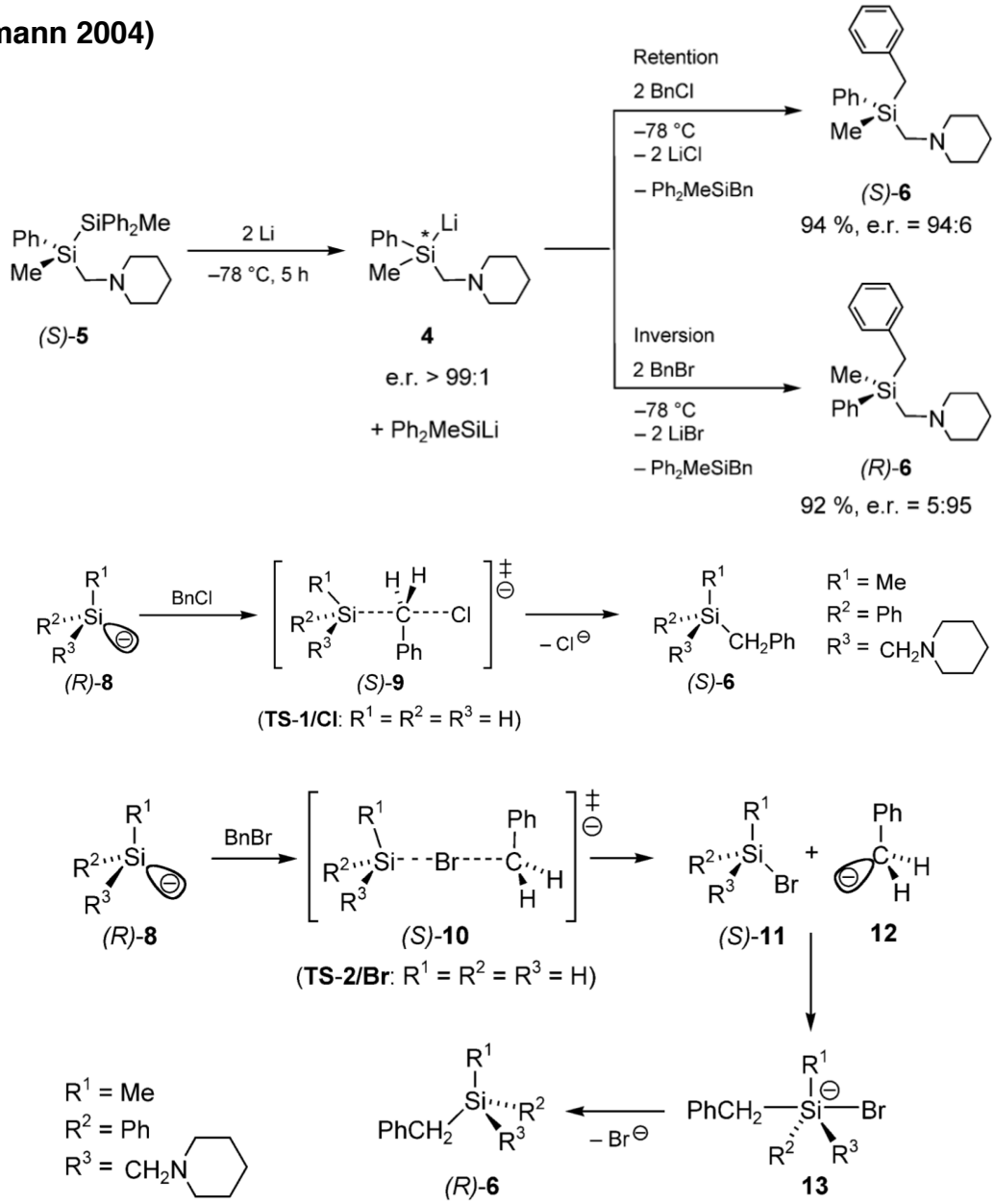
5. Mechanistic Aspects

5-1. S_N2 vs S_N2X

(Borowitz 1971)



(Strohmann 2004)



1) Borowitz, I. J. *et. al. J. Org. Chem.* **1971**, *36*, 88-97.
2) Strohman, C. *Angew. Chem. Int. Ed.* **2004**, *43*, 1011–1014.

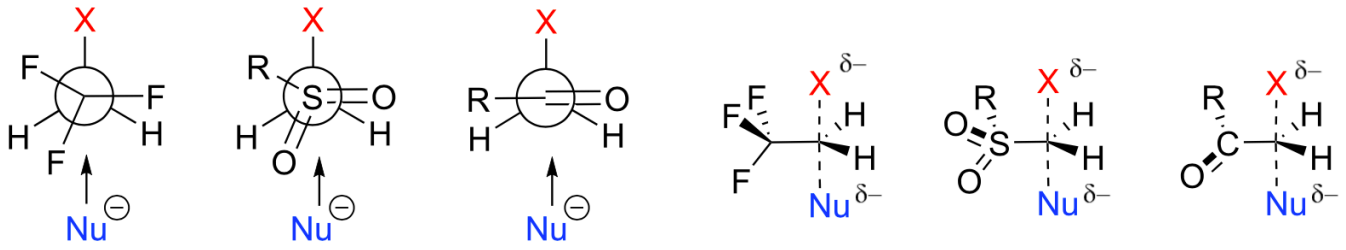
5. Mechanistic Aspects

5-2. Nucleophilies

Nucleophile	Halides (S_N2X rate constant in $1 \cdot mol^{-1} \cdot s^{-1}$)		
	Ar-C≡C-Cl	Ar-C≡C-Br	Ar-C≡C-I
S^{2-}	C + X (2.3×10^{-4})	X (47.7)	X (9×10^{4})
EtS^-	C + X (9×10^{-3})	X (23.5)	X (3×10^{4})
SO_3^{2-}	C	X (0.355)	X (40)
HS^-	C	X (0.101)	X (19)
PhS^-	–	X (0.040)	X (15)
CN^-	–	X (8.1×10^{-5})	X (0.023)
$(RO)_2PO^-$	–	X	X
$S_2O_3^{2-}$	–	C + X (2.3×10^{-6})	X (2.56×10^{-4})
OH^-	C	C + X	X
I^-	–	no reaction	X
CNS^-	–	no reaction	no reaction
N_3^-	–	no reaction	no reaction

Summary of attack on carbon (**C**) or on halogen (**X**) and the rate constants in the S_N2X reactions. Originally reported by the Verploegh and Drenth group.

5-3. EWGs on S_N2 reaction



5-4. Conclusion

S_N2X

- **Relative reactivity of alkyl halides towards S_N2X reaction** $I^- > Br^- > Cl^- > F^-$
- **Halogenophilic SN2X reaction prefers soft nucleophile and a highly polarizable soft halogen. (HSAB)**

S_N2X and S_N2

- **SN2X and SN2 reactions can be promoted by adjacent EWGs**

(1) the inductive effect of EWGs makes the carbon atoms more electron deficient
(2) EWGs can suppress potential competing SN1 reaction by destabilization of carbocation intermediates;
(3) tertiary carbons bonded to carbonyl or cyanide carbons, which are sp2 or sp-hybridized, are less sterically hindered for nucleophilic attack than sp3-hybridized alkyl groups.

1) Drenth, W. *et. al.* Recl. Trav. Chim. Pays-Bas **1971**, *90*, 765–778.
2) Brannen,W. T. *et. al.* J. Am. Chem. Soc. **1964**, *86,* 4645–4650.
3) Tan, C-H. *et. al. ChemRxiv.* **2021**