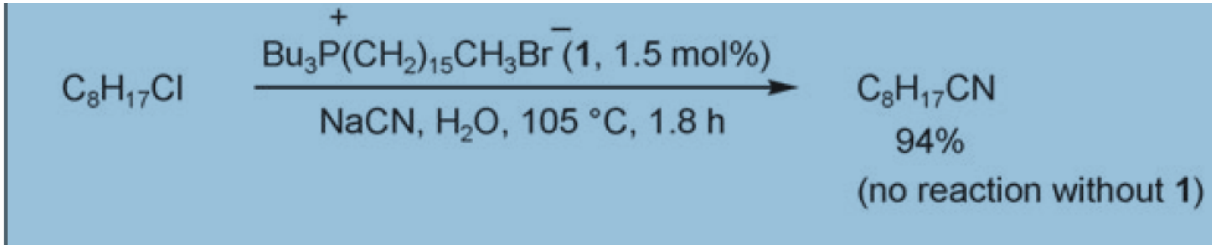
Asymmetric Phase-Transfer Catalysis

presented by Katharina M. Lippert

Contents

Review

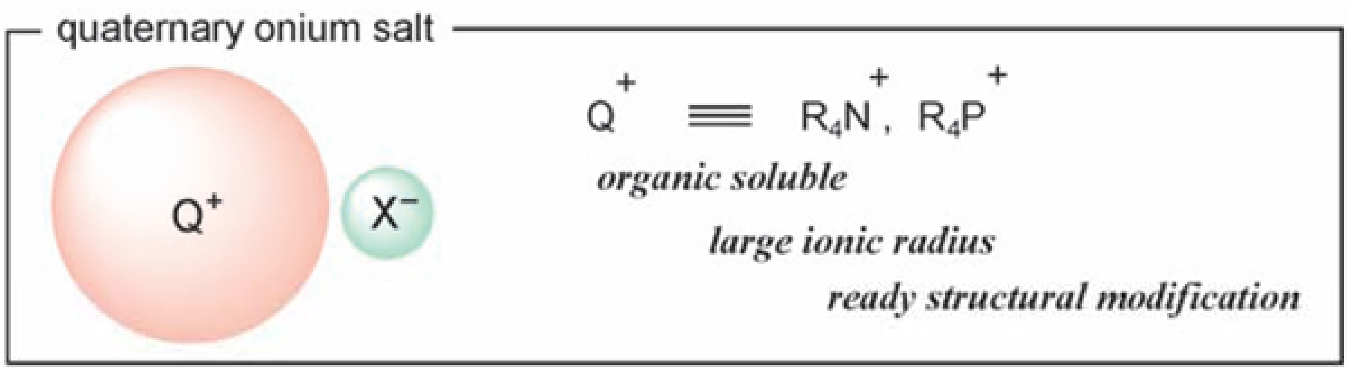
- 1960s Brändström, Makosza and Starks investigated characteristics of quaternary Onium salts
- 1971 Starks established “phase-transfer catalysis”

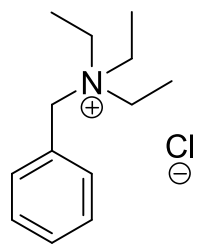


- Usually PTC-reactions between two phases: organic and solid or aqueous solution

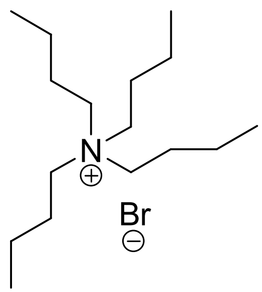
- C. M. Starks, *J. Am. Chem. Soc.* **1971**, *93,* 195-199. C. M. Starks and R. M. Owens, *J. Am. Chem. Soc.* **1973**, *95*, 3613-3617.

Onium salt

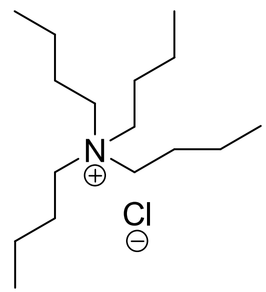




1a



1b

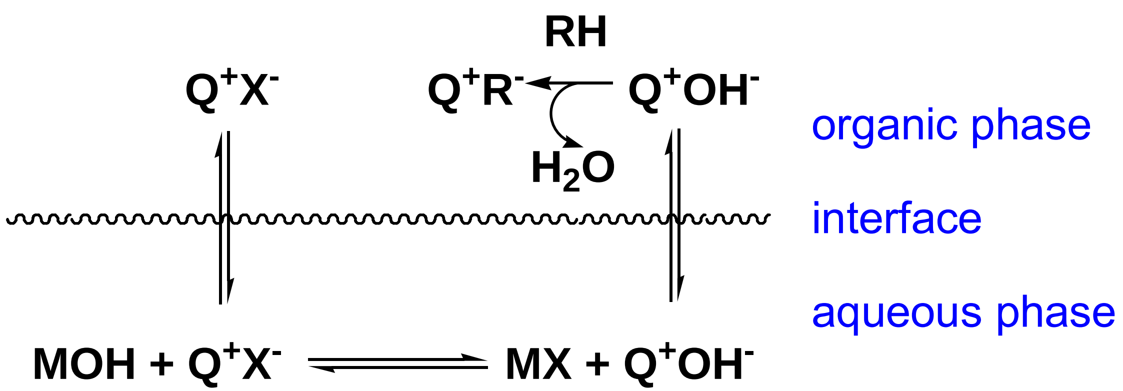


1c

K. Maruoka, Takashi Ooi, *Angew. Chem. Int. Ed.* **2007**, *46,* 4222-4266.

Mechanism

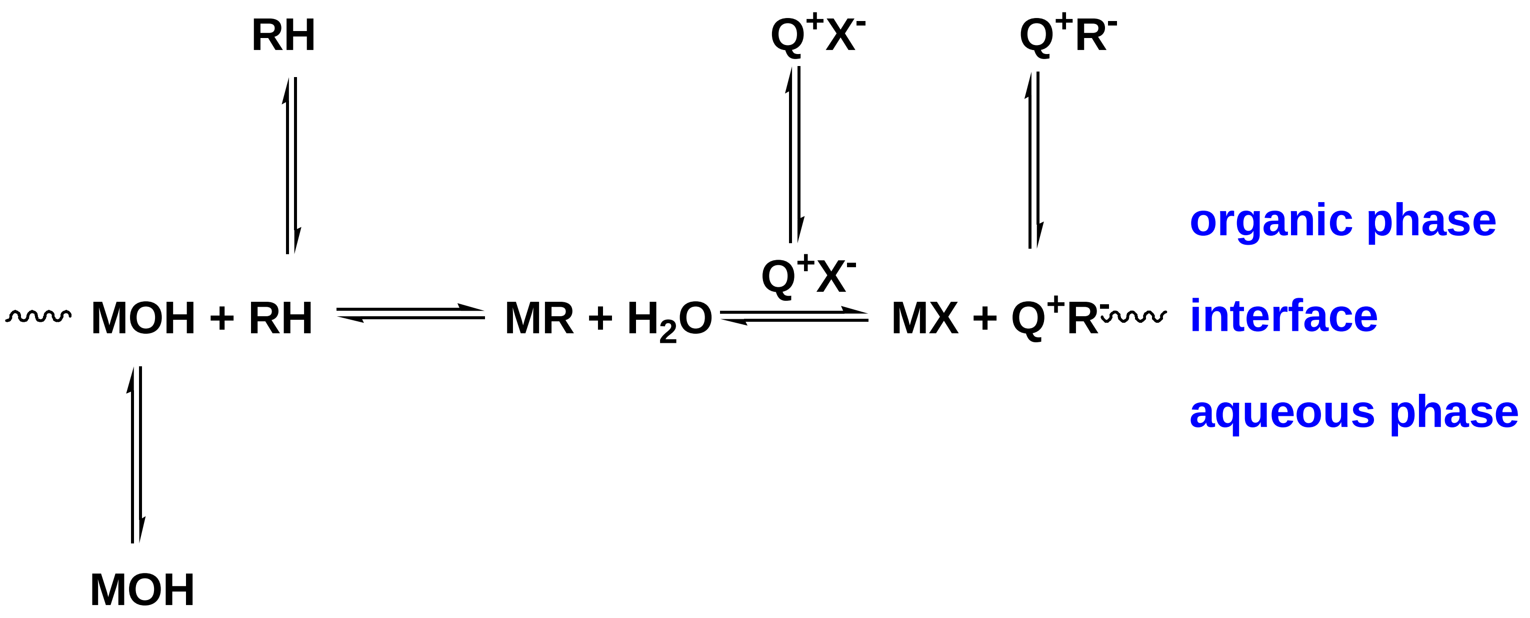
- Starks extraction mechanism



C. M. Starks, *J. Am. Chem. Soc.* **1971,** *93*, 195-199. C. M. Starks and R. M. Owens, *J. Am. Chem. Soc.* **1973,** *95*, 3613-3617.

Mechanism

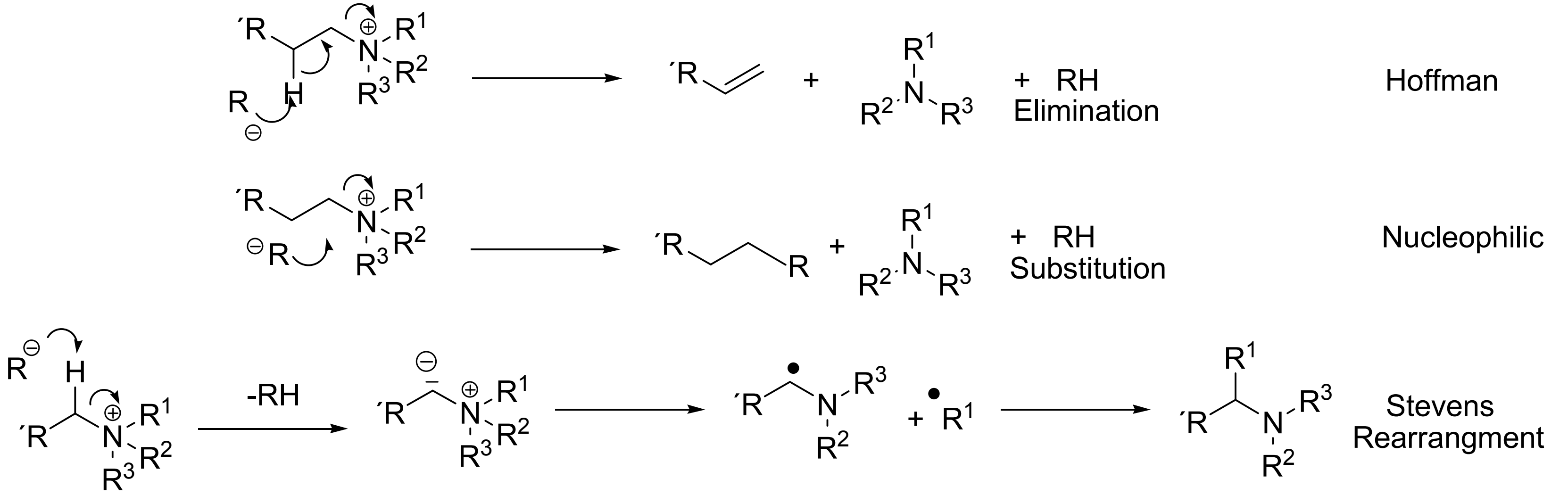
- Makosza Interface mechanism



M. Makosza, *Tetrahedron Lett.* **1966**, 4621-4624. M. Makosza, *Tetrahedron Lett.* **1966**, 5489-5492. M. Makosza, *Tetrahedron Lett.* **1969**, 673-676. M. Makosza, *Tetrahedron Lett.* **1969**, 677-678. M. Makosza and M. Wawrzyniewicz, *Tetrahedron Lett.* **1969**, 4659-4662.

Stability of the Onium Carbanion

- Absence of elektrophile: degradation



Influence of pH-value

- Decomposition of the catalyst
- Hydrolysis of the subsbstrate (imine- and/or Ester function)
- Racemization of the product
- Dialkylation of the product

➡ protection of acid function with *tert*-butylester

➡ benzoiminfunction facilates the α-C-H- abstraction protects for further α-C-H-abstraction

Reaction optimization

- **Base**

  Low lipophilic character of cation

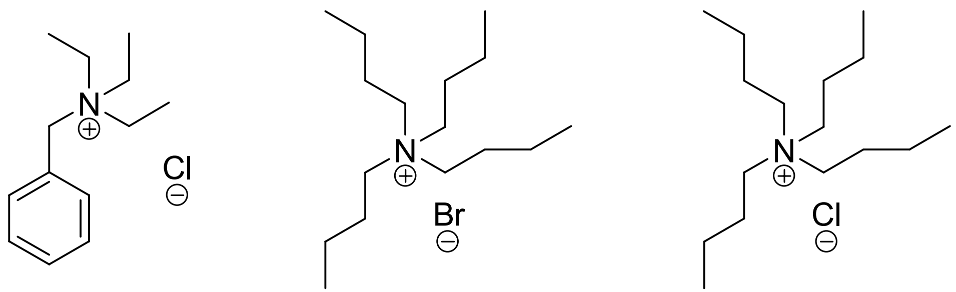
- **Solvent**
  - micell-formation at high catalyst concentration in unpolar solvents
  - polar protic character: Solvation of anions and cations
  - polar aprotic character: (DMSO, DMF) solvate cations
  - Low polar character: No solvating of salts
  - Immiscible with water

Reaction optimization

- **Temperature**
  - affects the interaction of onium ion and enolate
- **Substrate concentration**
- **stirring speed**
  - effects a bigger contact of surface areas
  - prohibition of concentration gradients

Requirement to the catalyst

- Solubility in organic solvent of Onium-Salt
  - high lipophilic character



1a 1b 1c

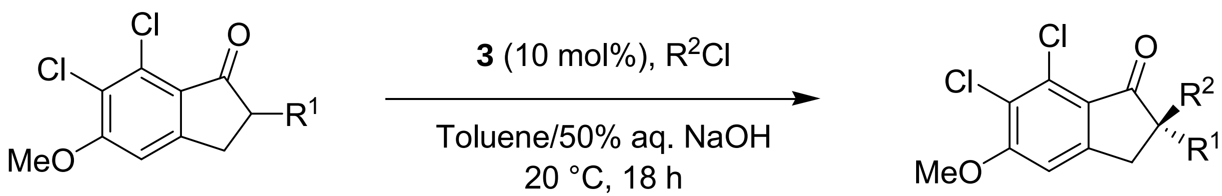
  - ionic radius: low electronic density + reduced hydration
- Easy exchange of hydroxide and carbanion
  - high reactive chiral onium carbanion
  - chiral catalyst shields one of the enantiotopic sides

Advantages of PTC

- Simple experimental procedures
- Generally more selective and less side reactions than homogeneous reactions
- Mild reaction conditions
- Cheap and biodegradable
- Environmental friendly reagents and solvents
- Commerically available starting substrates
- Useful for industry

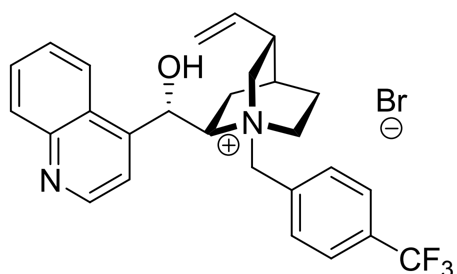
Innovative work

1984: Working Group of Merck



2 **4**

2a R^1 = Ph with **3** and R^2 = Me : **4a** 95 %, 92% *ee*
2b R^1 = Pr with **3** and R^2 = MeC(Cl)=CHCH$_2$: **4b** 99 %, 92% *ee*



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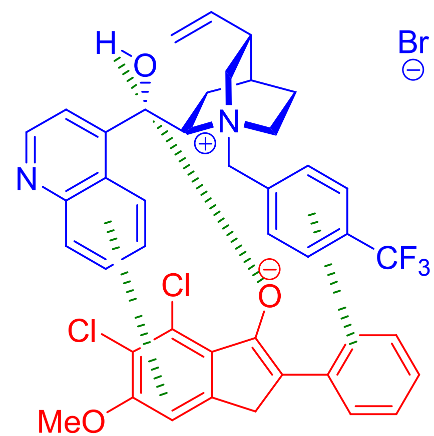
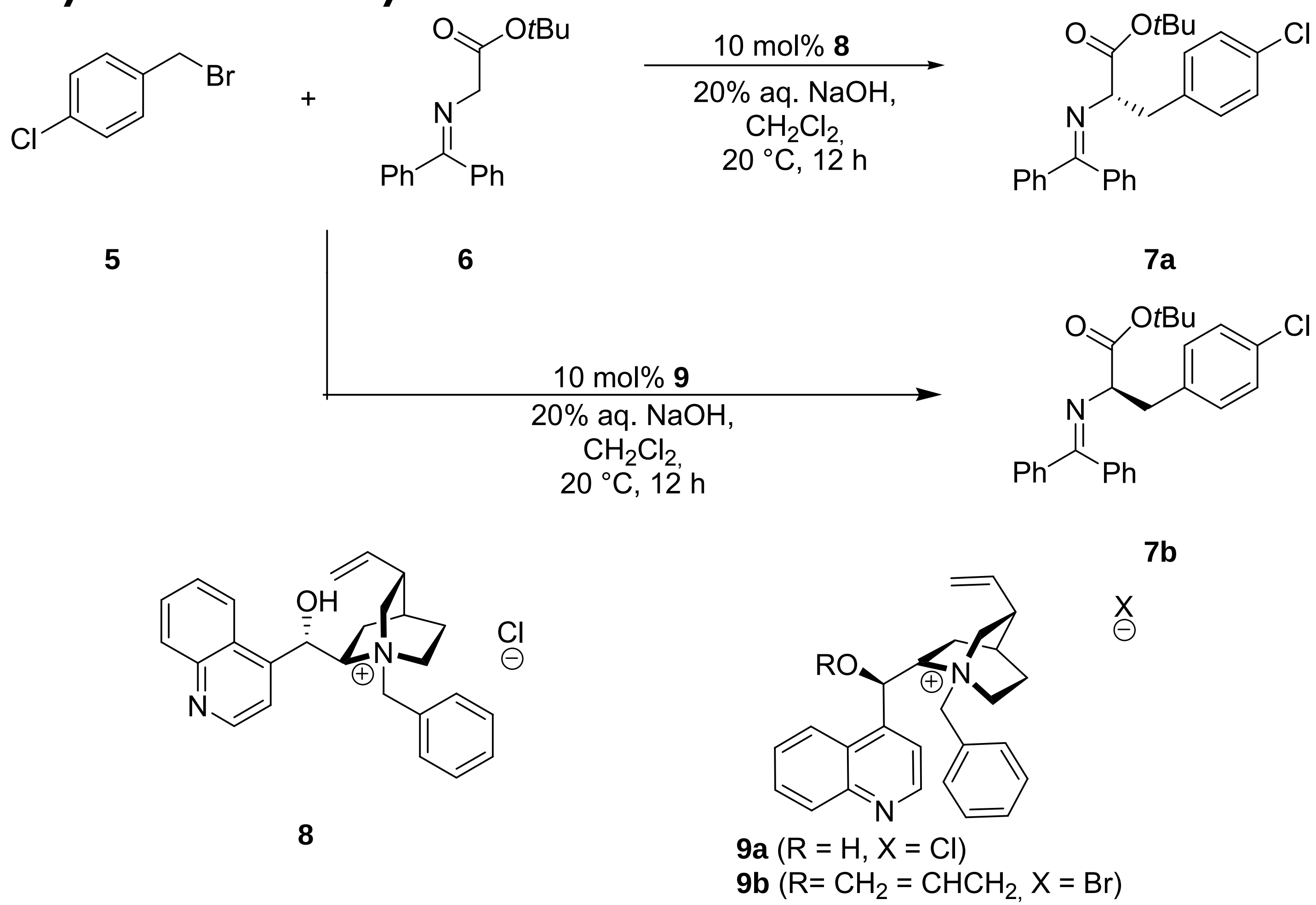


U. H. Dolling, P. Davis, E. J. J. Grabowski, *J. Am. Chem. Soc.* **1984**, *106*, 446-447. D. L. Hughes, U. H. Dolling, K. M. Ryan, E. F. Schoenewaldt, E. J. J. Grabowski, *J. Org. Chem.* **1987**, *52*, 4745-4752.

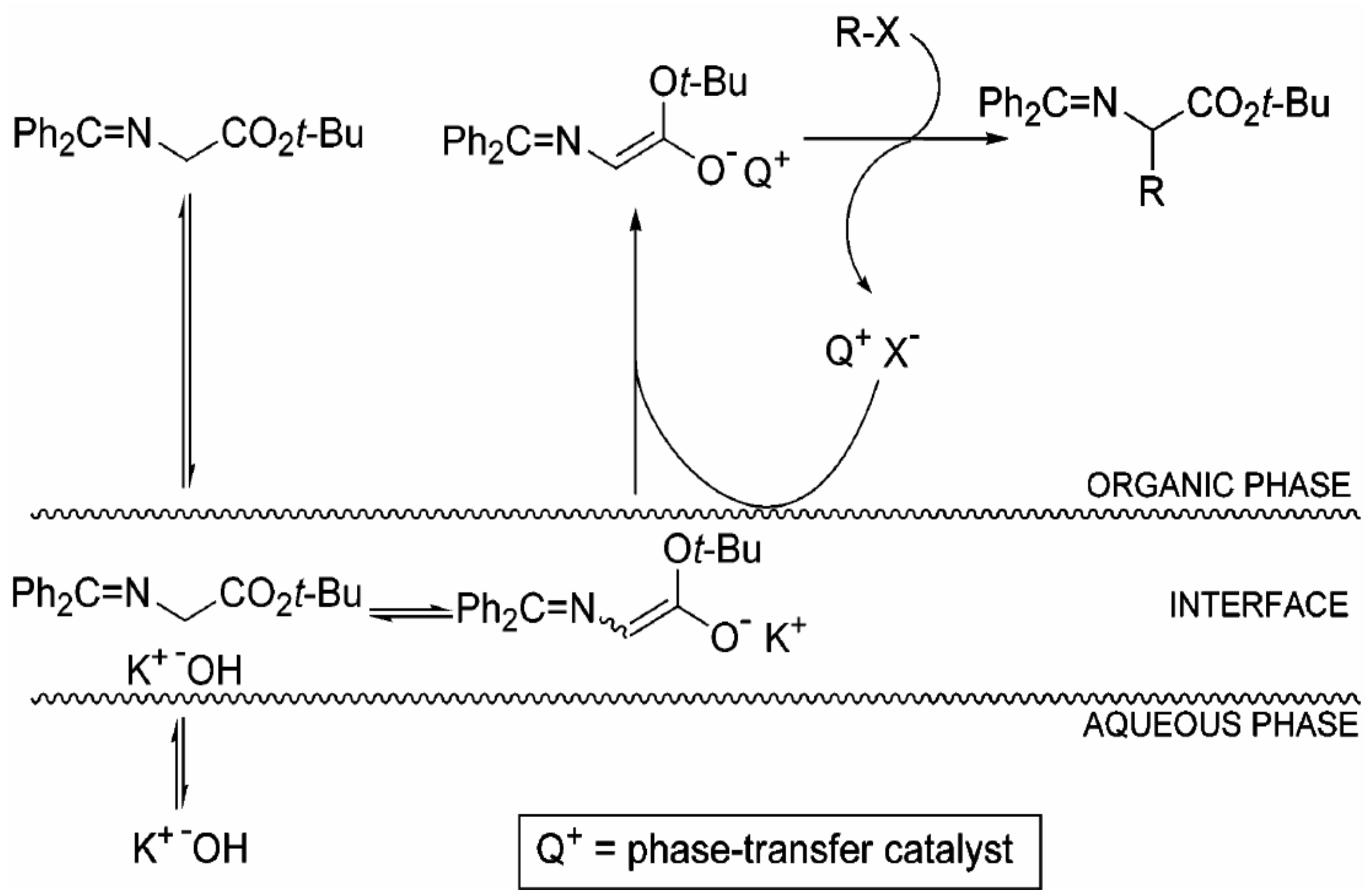
Asymmetric synthesis of α-amino acids

- Alkylation of Glycinate Schiff-Bases



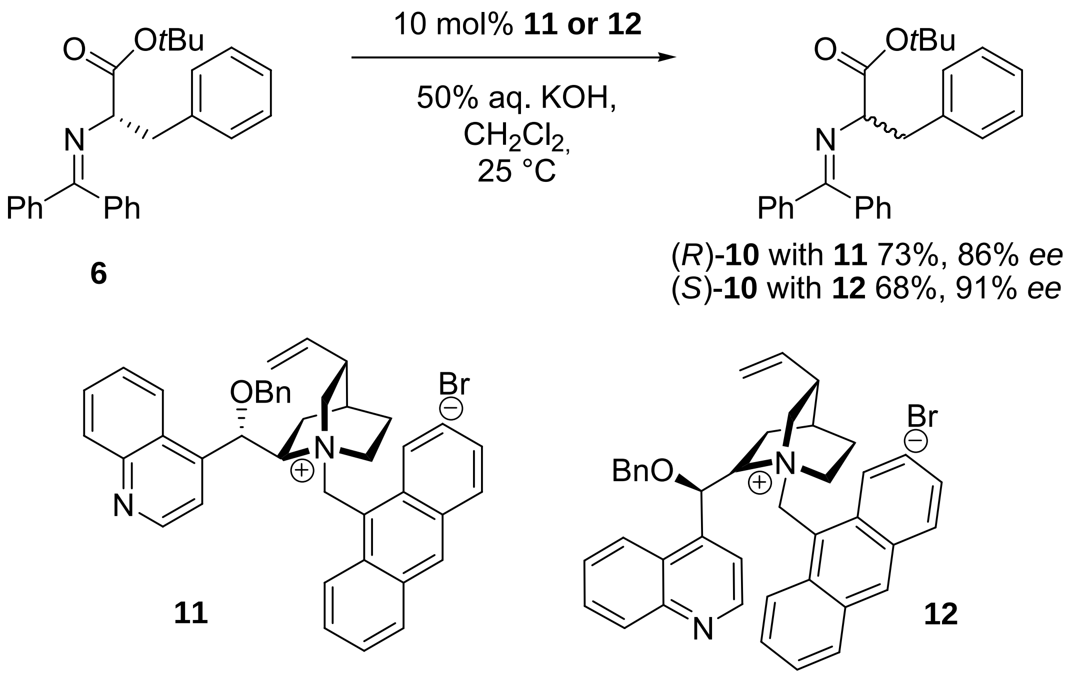
- M. J. O'Donnell, W. D. Bennett, S. Wu, *J. Am. Chem. Soc.* **1989**, *111*, 2353-2355. K. B. Lipkowitz, M. W. Cavanaugh, B. Baker, M. J. O'Donnell, *J. Org. Chem.* **1991**, *56*, 5181-5192.

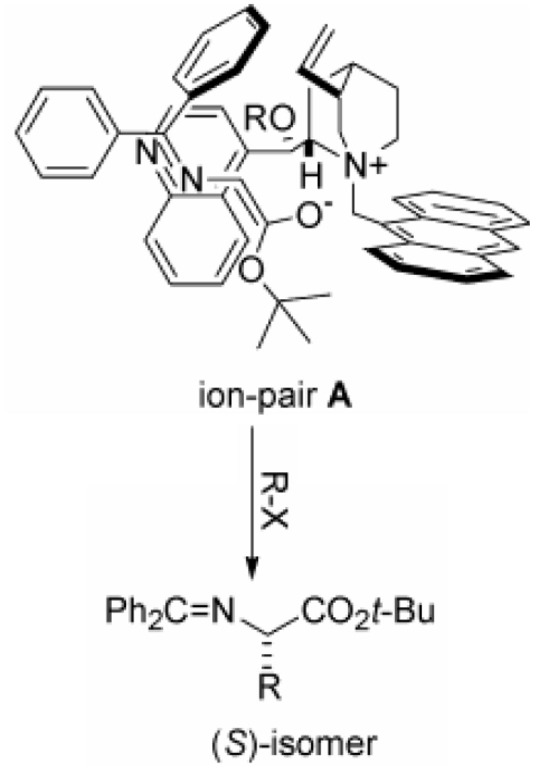
Mechanism



B. Lygo and B. I. Andrews, *Acc. Chem. Res.* **2004**, *37*, 518-525.

Arrangement of quaternary ammonium salt





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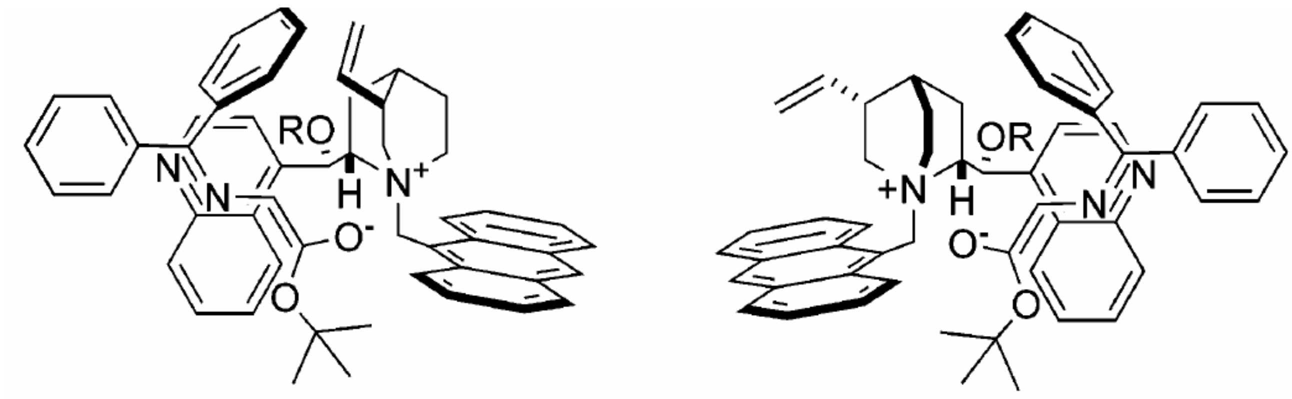
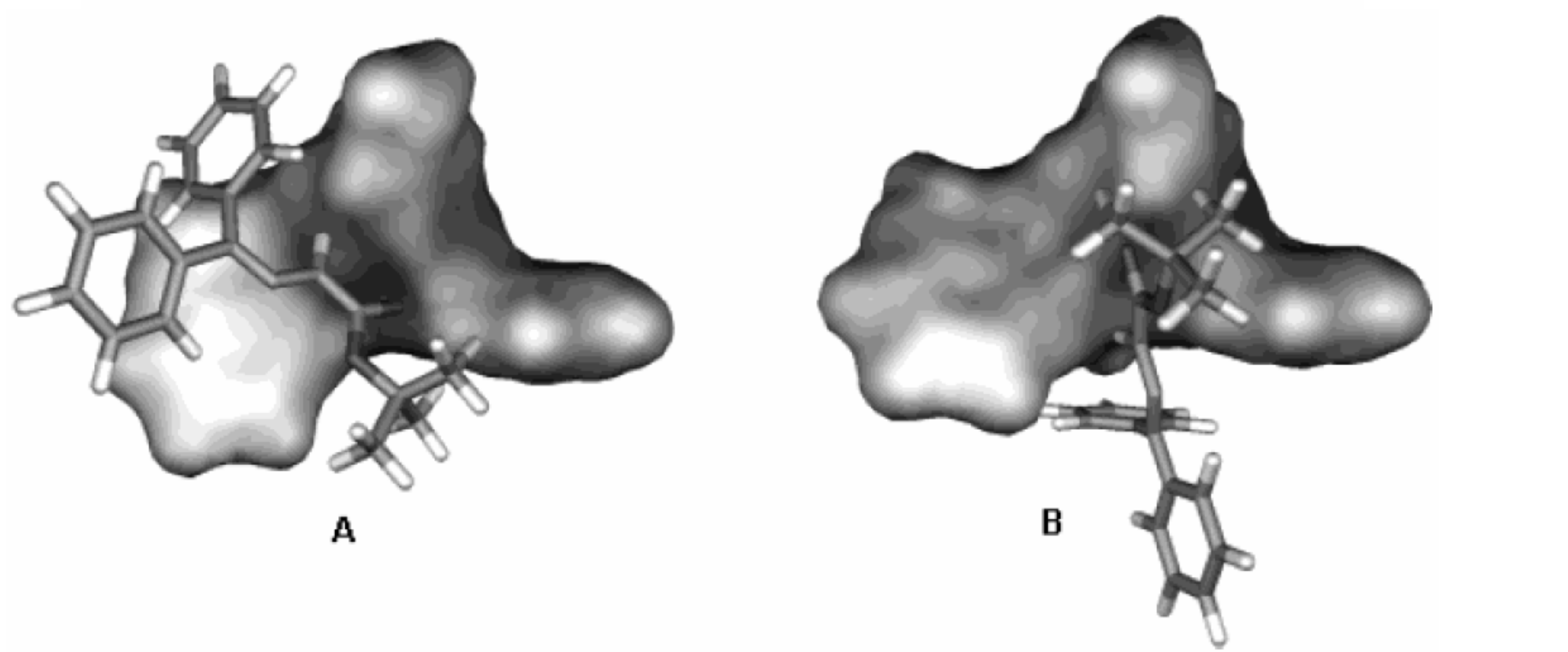
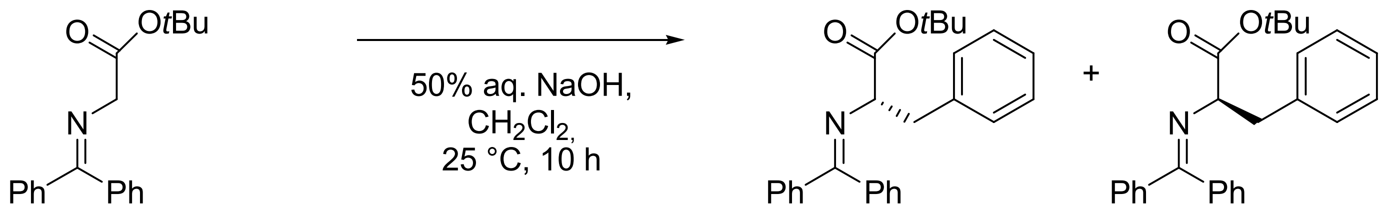




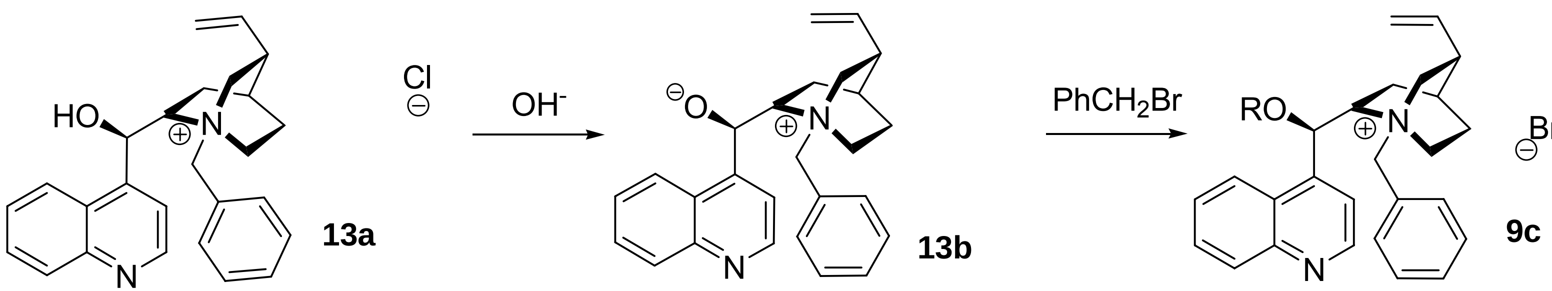
- B. Lygo and B. I. Andrews, *Acc. Chem. Res.* **2004**, 37, 518-525. F. Mohamadi, N. G. J. Richards, W. C. Guida, R. Liskamp, M. Lipton, C. Caufield, G. Chang, T. Hendrickson and W. C. Still, **1990**, *11*, 440-467.

Racemization studies of monoalkylated products



(S)-**10** *(S)*-**10** *(R)*-**10**

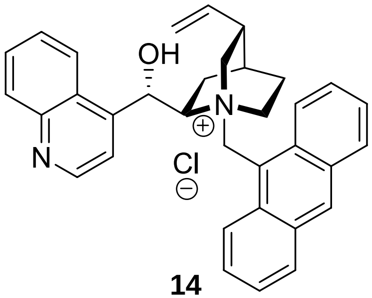
	(S)-**10**	*(R)*-**10**
without catalyst and alkylhalogenid	100%	0%
with Bu_4NBr (10 mol%)	100%	0%
with **13a**	65%	35%
with **13b** and $PhCH_2Br$ (1.2 eq.)	100%	0%
with **9c**	100%	0%



M. J. O'Donnell, W. D. Bennett, W. A. Bruder, W. N. Jacobsen, K. Knuth, B. LeClef, R. L. Polt, F. G. Bordwell, S. R. Mrozack, T. A. Cripe, *J. Am. Chem. Soc.* **1988**, *110*, 8520-8525. M. J. O'Donnell, S. Wu, J. C. Huffman, *Tetrahedron* **1994**, *50*, 4507-4518.

Asymmetric synthesis of α-amino acids and their derivates

- 1997: Lygo



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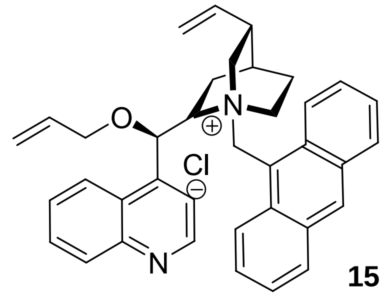
- 1997: Corey



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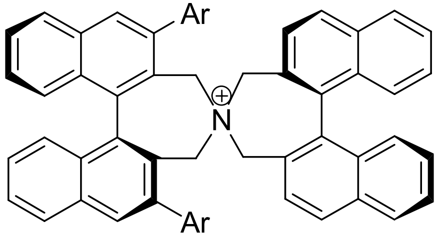
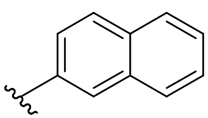
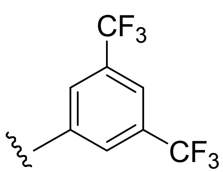
- 1999: Marouka



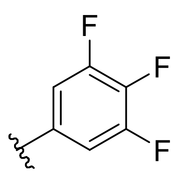
Ar = H (**16a**), Ph (**16b**),



16c



16d



16f

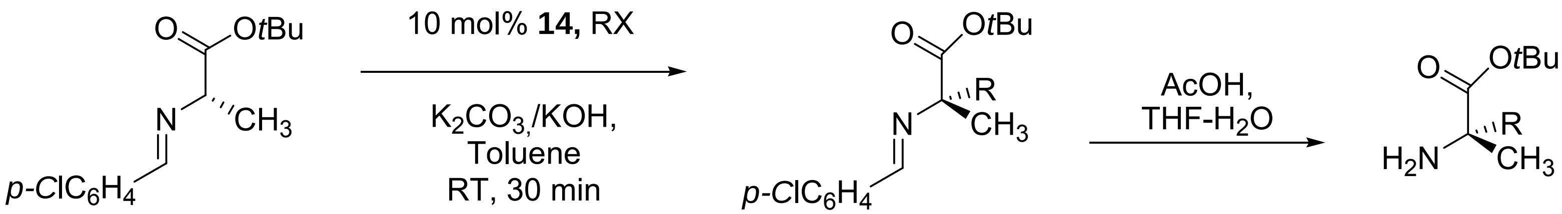
B. Lygo, B. I. Andrews, J. Crosby and J. A. Peterson, *Tetrahedron Lett.* **2002,** *43, 8015*-8018.

E. J. Corey, F. Xu and M. C. Noe, *J. Am. Chem. Soc.* **1997**, *119*, 12414-12415.

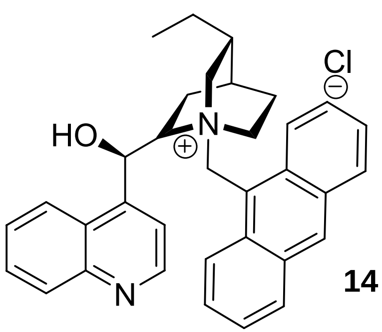
T. Ooi, M. Kameda and K. Maruoka, *J. Am. Chem. Soc.* **1999**, *121*, 6519-6520.

Second Alkylation of Schiff Base

- Lygo



17 **18** **19**



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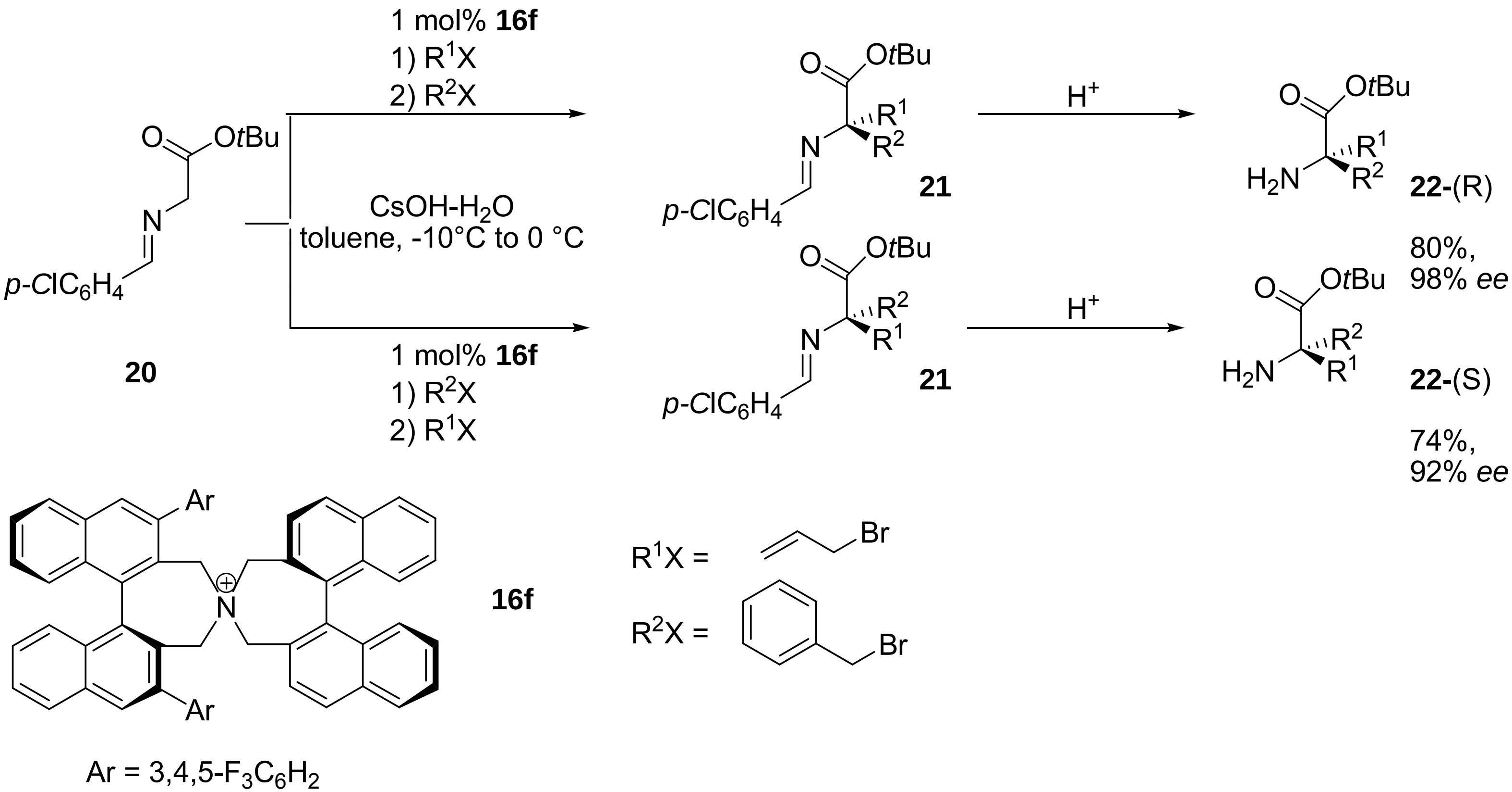
RX =	$PhCH_2Br$	: 95%, 87% *ee*
	p-$ClC_6H_4CH_2Br$	: 72% 77% *ee*
	n-BuI	: low yield 36% *ee*
	ICH_2CO_2*t*Bu	: 58%, 19% *ee*

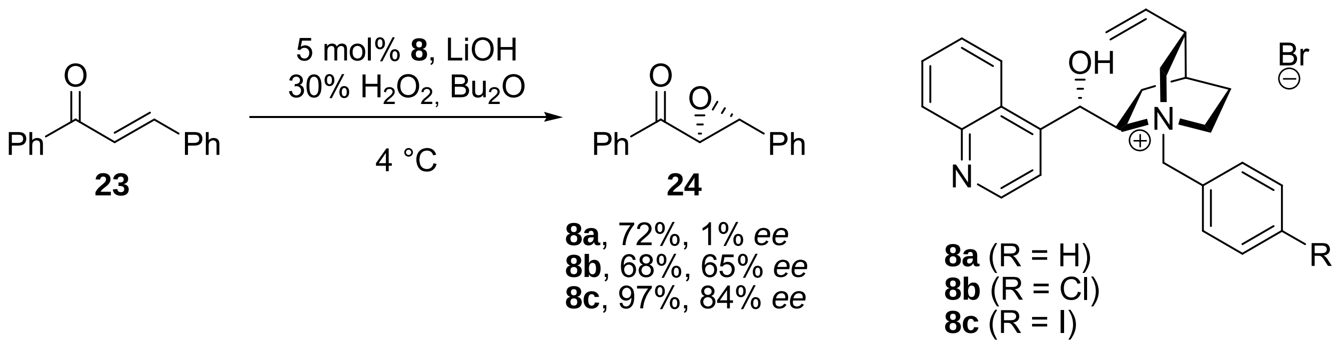
B. Lygo, B. I. Andrews, J. Crosby and J. A. Peterson, *Tetrahedron Lett.* **2002**, *43,* 8015-8018.

One Pot Double Alkylation



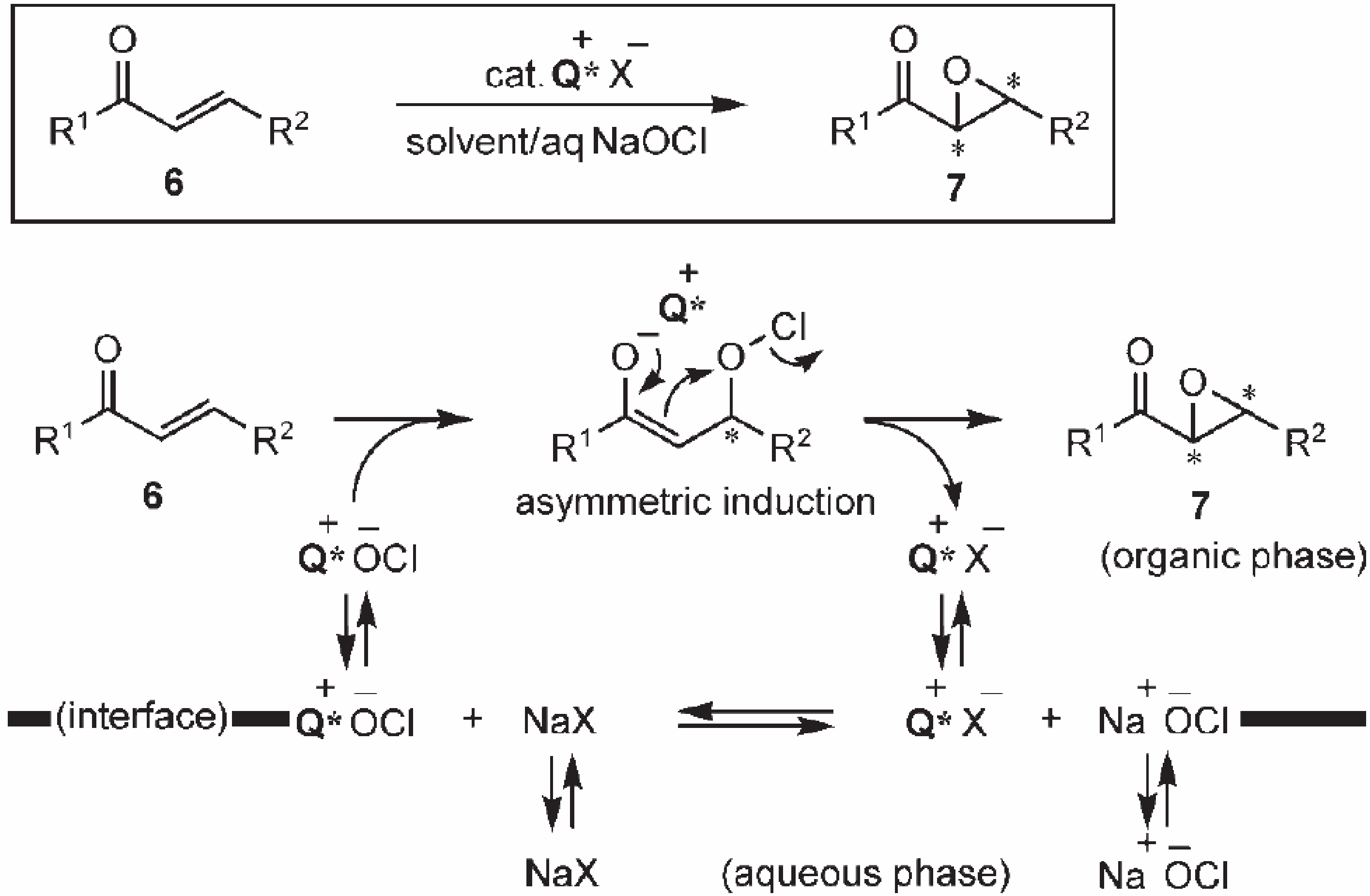
T. Ooi, M. Takeuchi, M. Kameda, K. Maruoka, *J. Am. Chem. Soc.* **2000**, *122*, 5228-5229.

Catalytic Epoxidation



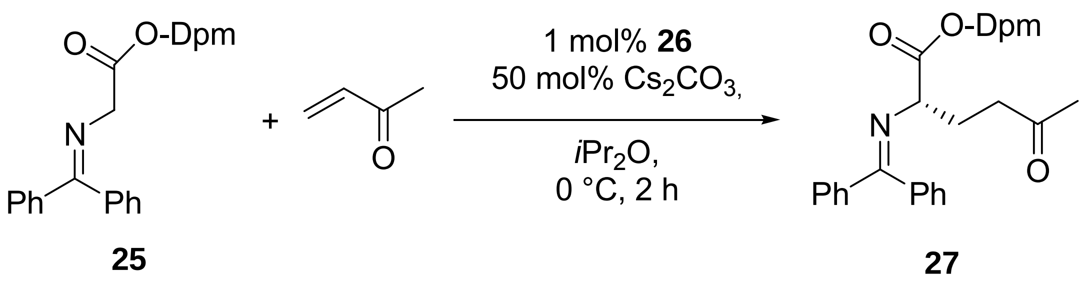
S. Arai, H. Tsuge and T. Shioiri, *Tetrahedron Lett.* **1998**, *39*, 7563-7566. S. Arai, H. Tsuge, M. Oku, M. Miura and T. Shioiri, *Tetrahedron* **2002**, *58*, 1623-1630.

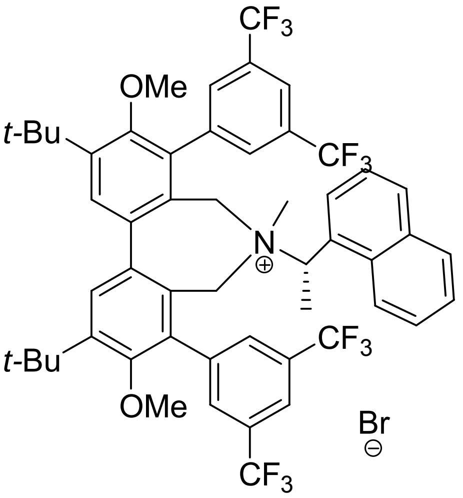
Mechanism



- S. Arai, H. Tsuge and T. Shioiri, *Tetrahedron Lett.* **1998**, *39*, 7563-7566. S. Arai, H. Tsuge, M. Oku, M. Miura and T. Shioiri, *Tetrahedron* **2002**, *58*, 1623-1630.

Asymmetric Michael-Addition





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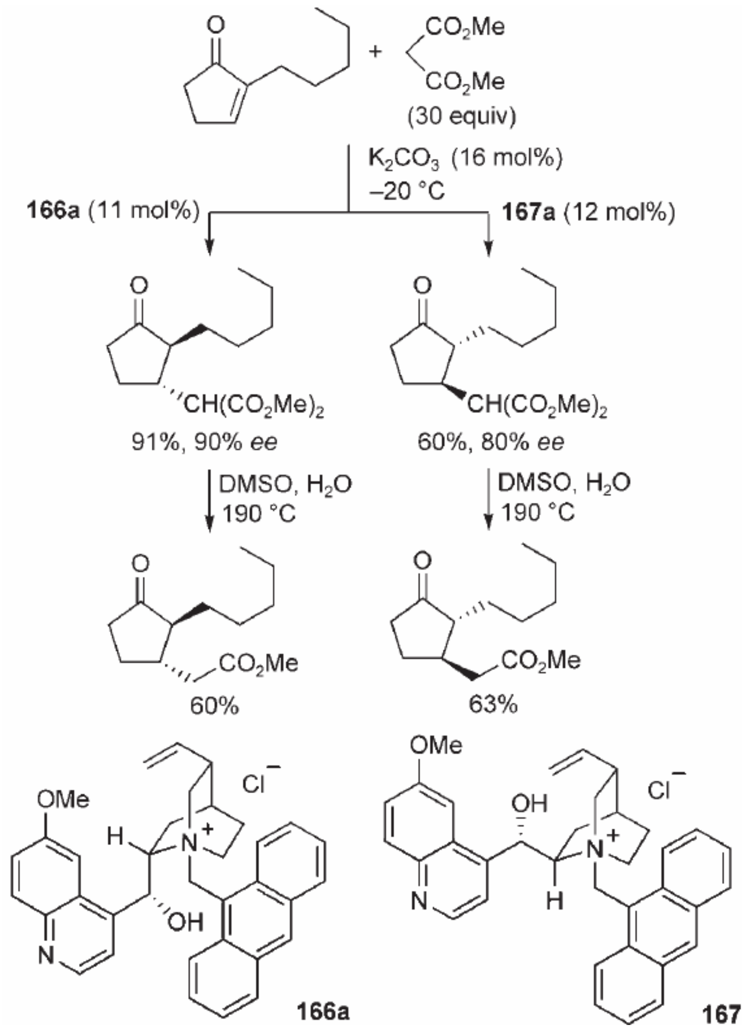
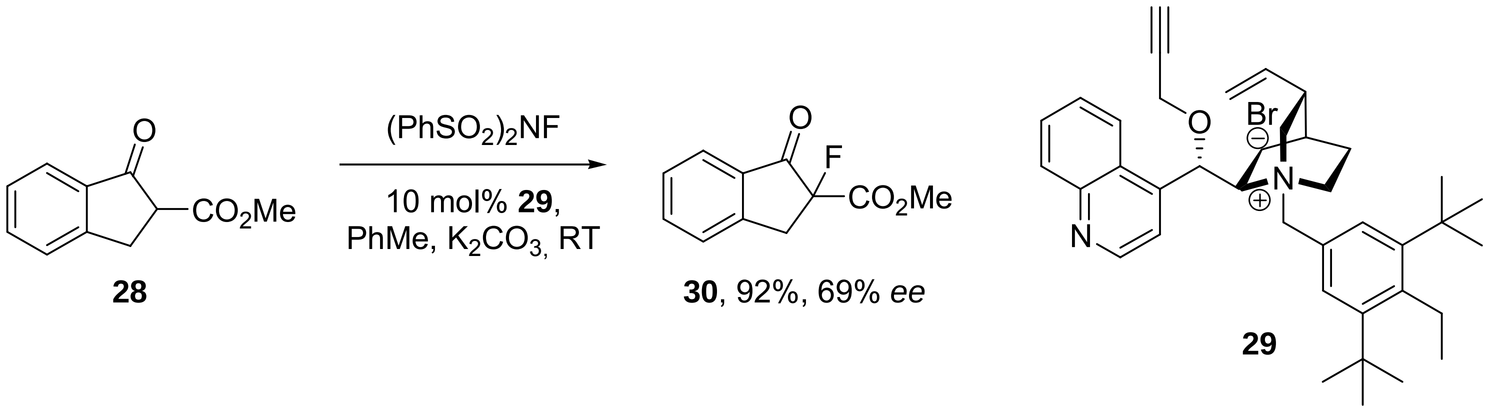
- B. Lygo, B. Allbutt, E. H. M. Kirton, *Tetrahedron Lett.* **2005**, *46*, 4461-4464.

Asymmetric Michael-Addition



- T. Perrard, J. C. Plaquevent, J. R. Desmurs and D. Hebrault, *Org. Lett.* **2000**, *2, 2959-2962.*

Enantioselective Fluorination



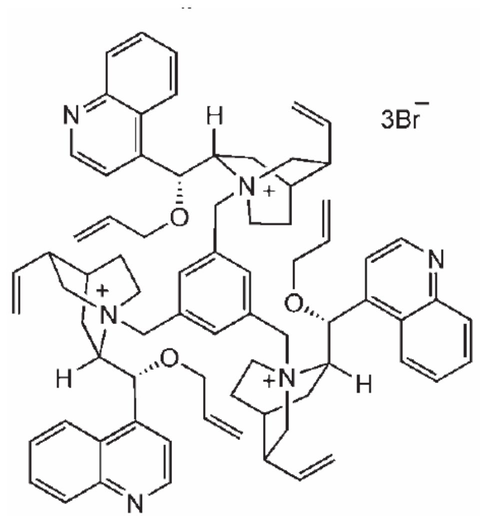
D. Y. Kim and E. J. Park, *Org. Lett.* **2002**, *4, 545-547.*

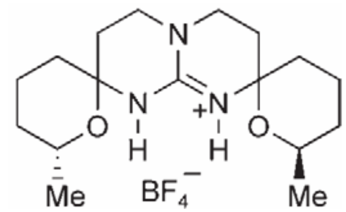
Other asymmetric PTC reactions

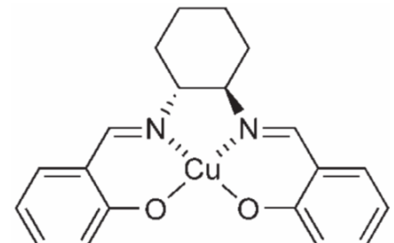
- Aldol reaction
- Strecker reaction
- Dihydroxylation
- Aziridination
- Neber Rearrangement
- Mannich Reaction
- Darzens Reaction

T. Hashimoto and K. Maruoka, *Chem. Rev.* **2007,** *107,* 5656-5682**.** Takashi Ooi and K. Maruoka, *Angew. Chem. Int. Ed.* **2007,** *46,* 4222-4266.

More catalysts







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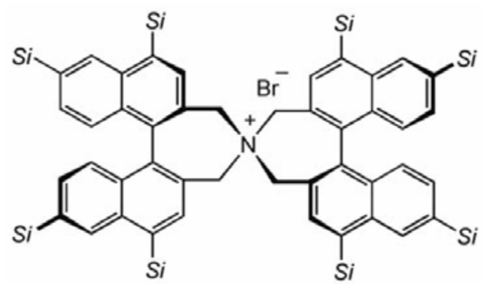
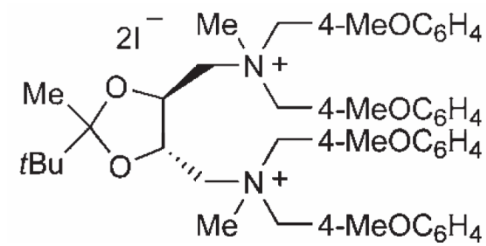


(R,R)-**71** [Si = $SiMe_2(CH_2CH_2C_8F_{17})$]



a. Siva and E. Murugan, *Journal of Molecular Catalysis A: Chemical* ***2006****, 248, 1-9.*

b. M. T. Allingham, A. Howard-Jones, P. J. Murphy, D. A. Thomas and P. W. R. Caulkett, *Tetrahedron Lett.* ***2003****, 44, 8677-8680.*

c. Y. N. Belokon, M. North, T. D. Churkina, N. S. Ikonnikov and V. I. Maleev, *Tetrahedron* ***2001****, 57, 2491-2498.*

d. S. Shirakawa, Y. Tanaka, K. Maruoka, *Org. Lett.* ***2004****, 6, 1429-1431.*

e. T. Ohshima, T. Shibuguchi, Y. Fukuta and M. Shibasaki, *Tetrahedron* ***2004****, 60, 7743-7754.*

Summary

- Many alkaloid derivatives act as phase-transfer catalysts
- Variety of new PTC-catalysts
- High reactivity
- High enantioselectivity
- New synthetic opportunities:
  - Synthesis of amino acids
  - Using environmentally friendly substrates
- Industrial use

- Thank you for your attention!