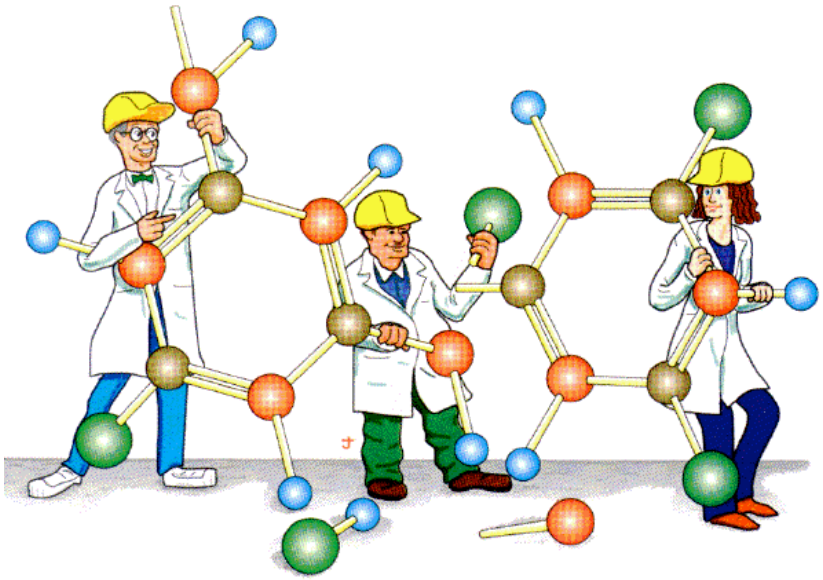
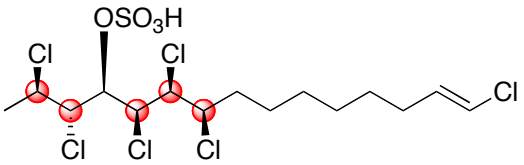
Frontiers in Chemistry Seminar

A Formidable Challenge: Asymmetric Halogenation in Organic Synthesis



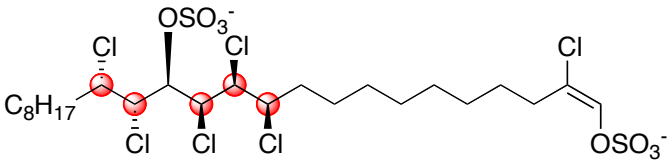
Filip R. Petronijević
The Wipf Group
December 10th, 2011

Highlights in Asymmetric Halogenation



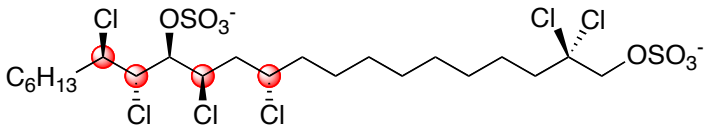
Chlorosulpholipid cytotoxin

Nilewski, C.; Geisser, R.W.; Carreira, E.M.
Nature **2009**, *457*, 573.



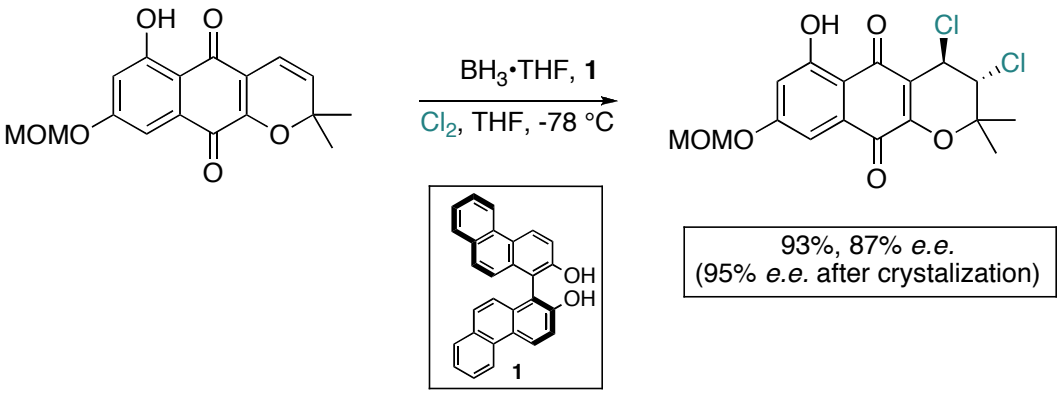
Malhamensilipin A

Shibuya, G.M.; Kanady, J.S.; Vanderwal, C.D.
J. Am. Chem. Soc. **2008**, *130*, 12514.

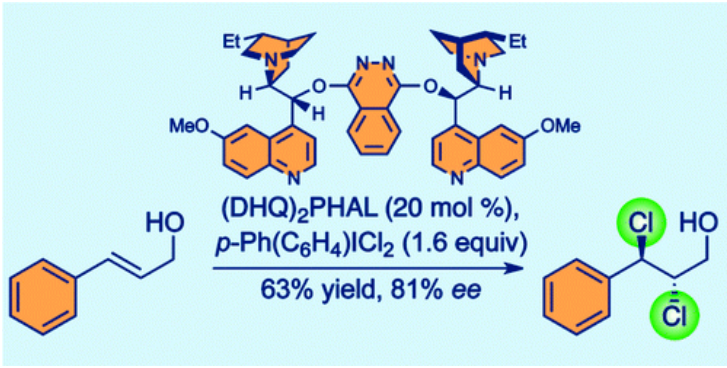


Danicalipin A

Yoshimitsu, T.; Nakatani, R.; Kobayashi, A.; Tanaka, T.
Org. Lett. **2011**, *13*, 908.

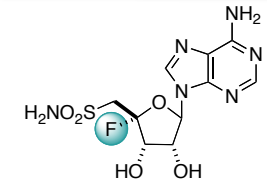


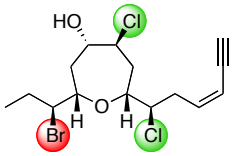
Snyder, S.A.; Tang, Z.-Y.; Gupta, R.
J. Am. Chem. Soc. **2009**, *131*, 5744.

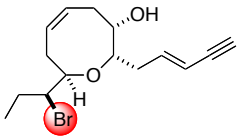


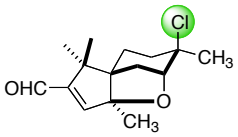
Nicolaou, K.C.; Simmons, N.L.; Ying, Y.; Heretsch, P.M.; Chen, J.S.
J. Am. Chem. Soc. **2011**, *133*, 8134.

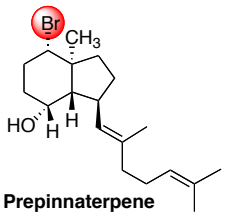
The Need for Halogenated Compounds


Nucleocidin


Rogioloxepane C


(*E*)- Prelauretin


Laurencial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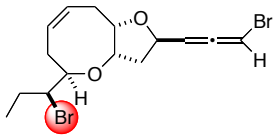
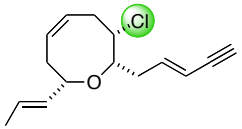
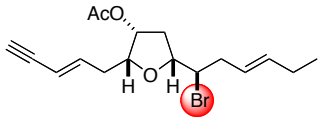
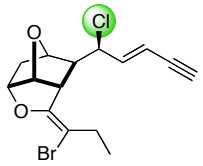
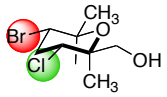
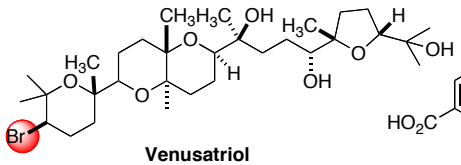

Laurallene

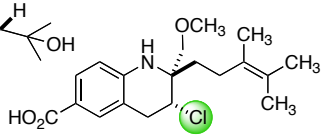

Laurenyne

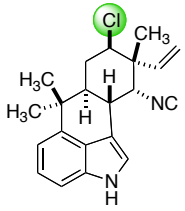

Kumausyne

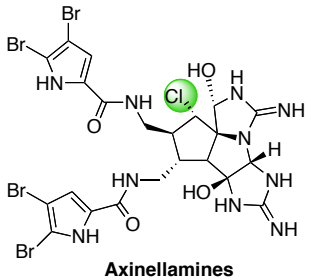

Maneonene B

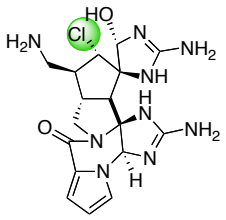

Aplysiapyranoid D


Venusatriol


Virantmycin


Hapalindole G


Axinellamines


Palau'amine

"Many organisms use organohalogens in chemical defense, in food gathering, or as regulatory hormones.

…

The chlorine atoms in the clinical antibiotic vancomycin are crucial in enforcing the requisite conformation for receptor binding.

…

Not counting terrestrial organisms, the 500.000 species of marine animals, plants, and bacteria guarantees that thousands of new organohalogen compounds are awaiting discovery. Of the 4.000 species of bryozoans, fewer than 20 have been examined for their chemical content.

…

Chlorine – once called the "devil's element" – and the other halogens play an important role in natural processes, both biogenic and abiogenic …

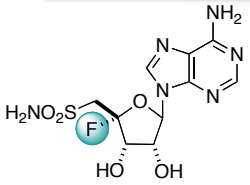
…

As organohalogen natural products research unfolds, new antibiotics, anticancer and antifungal agents, pesticides, herbicides, and other important medicinal drugs will be discovered"

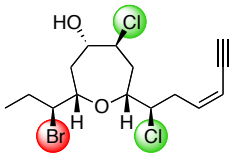
Gribble, G. W. *Acc. Chem. Res.* **1998**, *31*, 141-152.

1. For general reviews, see: a) Gribble, G.W. *Acc. Chem. Res.* **1998**, *31*, 141-152. b) Gribble, G.W. *Progress in the Chemistry of Organic Natural Products* **1996**, *68*, 1-498. 2. For review on fluorinated natural products, see: Harper, D.B.; O'Hagan, D.O. *Nat. Prod. Rep.* **1994**, *11*, 123-133.

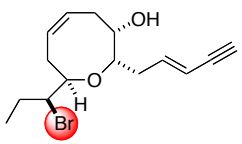
Halogenated Compounds in Nature



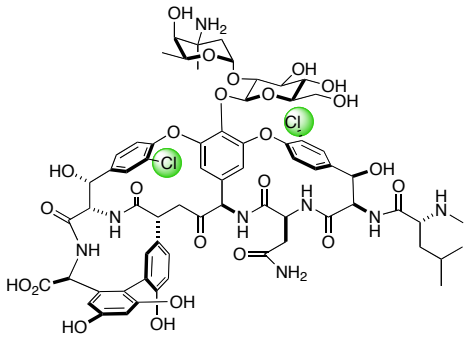
Nucleocidin



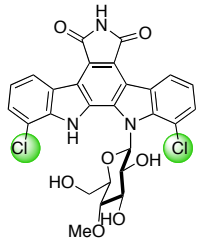
Rogioloxepane C



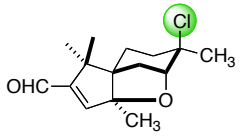
(*E*)- Prelauretin



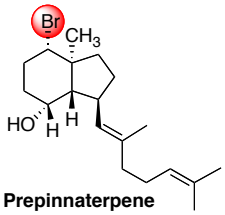
Vancomycin



Rebeccamycin



Laurencial



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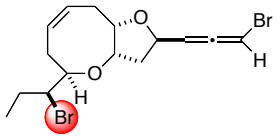

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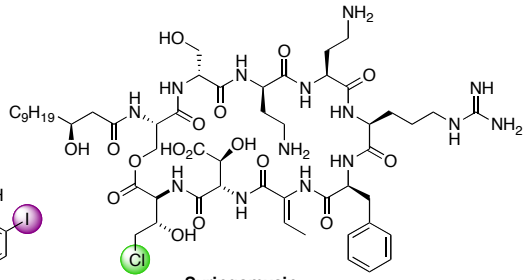
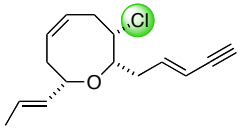
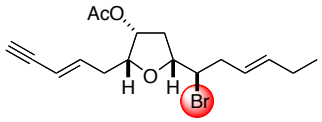


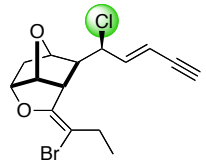
Syringomycin



Laurenyne



Kumausyne



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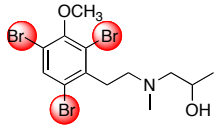
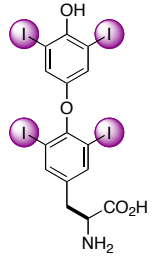
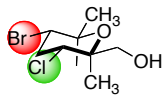


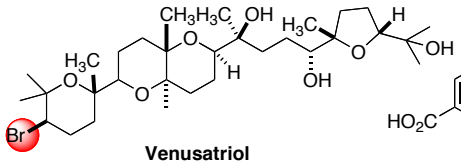
Convolutamine A



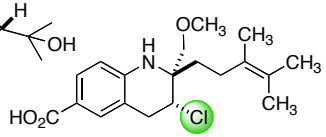
Thyroxine



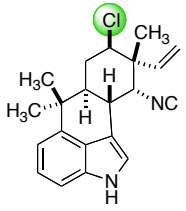
Aplysiapyranoid D



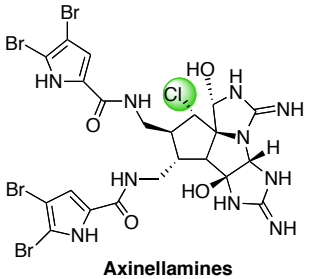
Venusatriol



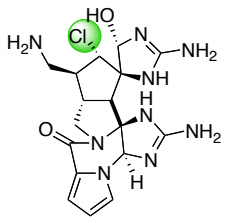
Virantmycin



Hapalindole G



Axinellamines

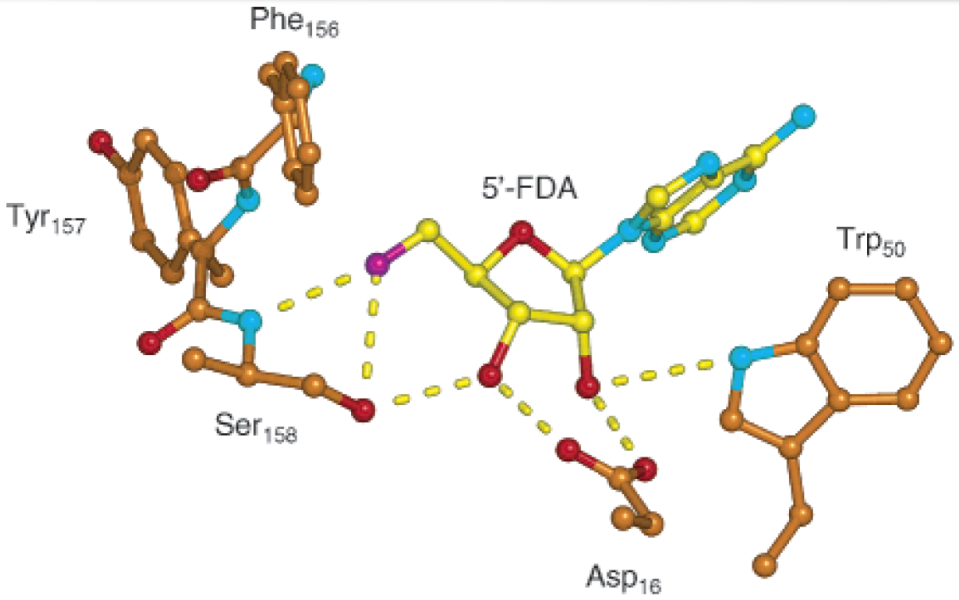


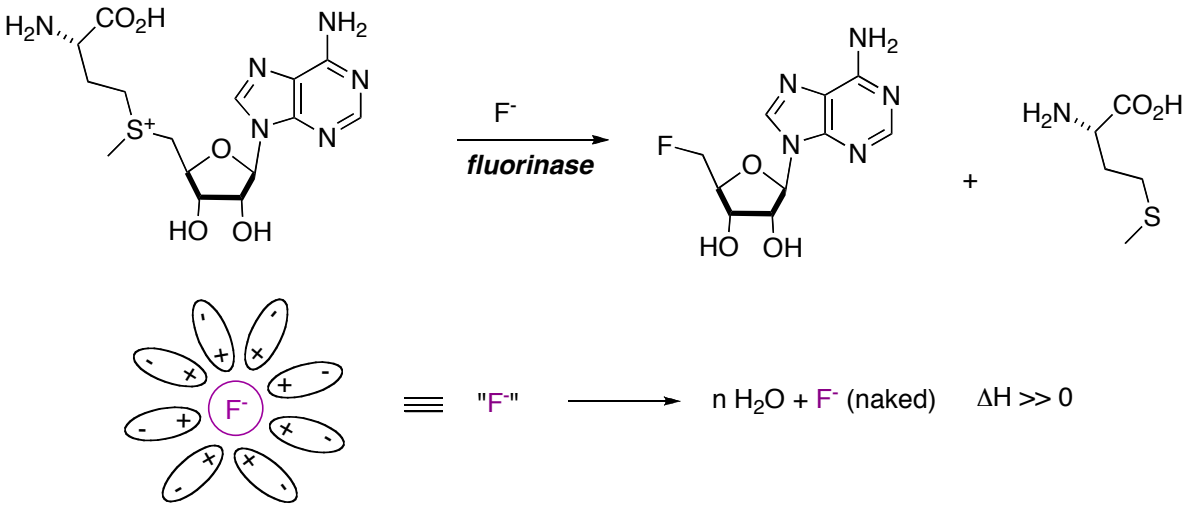
Palau'amine

- To date, more than 4500 halogenated natural products have been discovered
- 2300 organochlorines, 2100 organobromines, 120 organoiodines, and 30 organofluorines

Vaillancourt, F. H.; Yeh, E.; Vosburg, D. A.; Garneau-Tsodikova, S.; Walsh, C. T. *Chem. Rev.* **2006**, *106*, 3364-3378.

Nature's Inventory of Halogenation Catalysts
Fluorinating Enzymes: Nonoxidative Construction of the C-F Bond

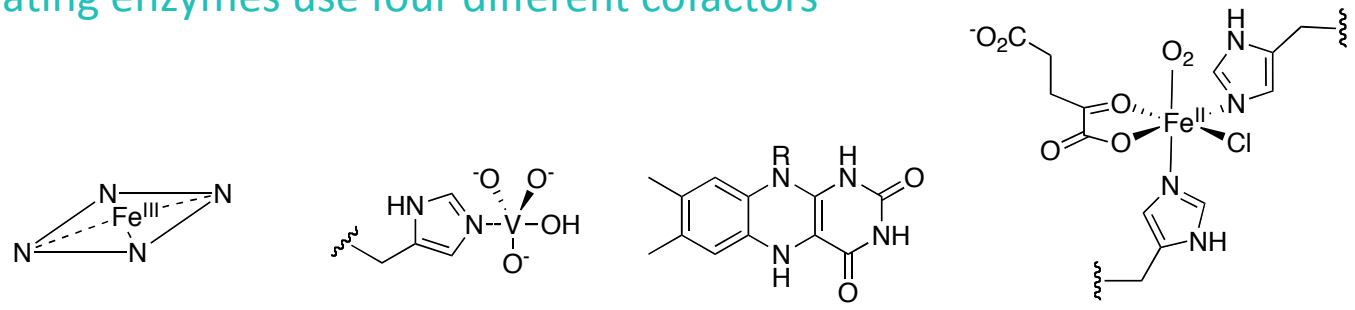




1. Dong, C.; Huang, F.; Deng, H.; Schaffrath, C.; Spencer, J. B.; O'Hagan, D.; Naismith, J. H. *Nature* **2004**, *427*, 561-565. 2. Vaillancourt, F. H.; Yeh, E.; Vosburg, D. A.; Garneau-Tsodikova, S.; Walsh, C. T. *Chem. Rev.* **2006**, *106*, 3364-3378.

Nature's Inventory of Halogenation Catalysts
Oxidative Logic in Chlorinating, Brominating and Iodinating Enzymes

Halogenating enzymes use four different cofactors



H_2O_2 as cosubstrate

haloperoxidases

O_2 as reducible cosubstrate

O_2-dependent halogenases

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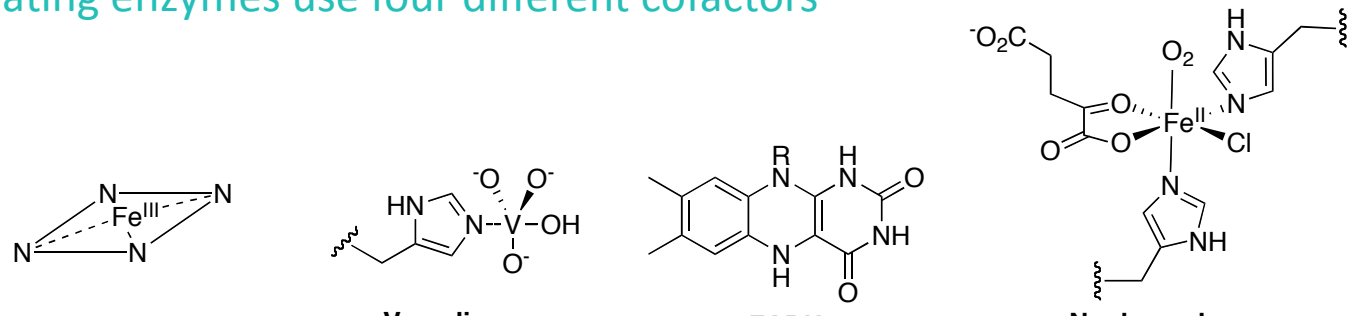
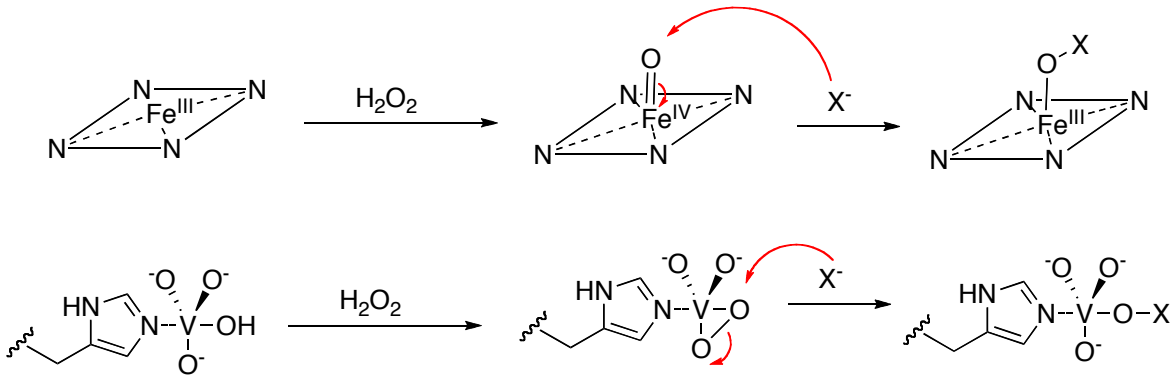


H_2O_2 as cosubstrate

haloperoxidases

O_2 as reducible cosubstrate

O_2-dependent halogenases



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Nature's Inventory of Halogenation Catalysts
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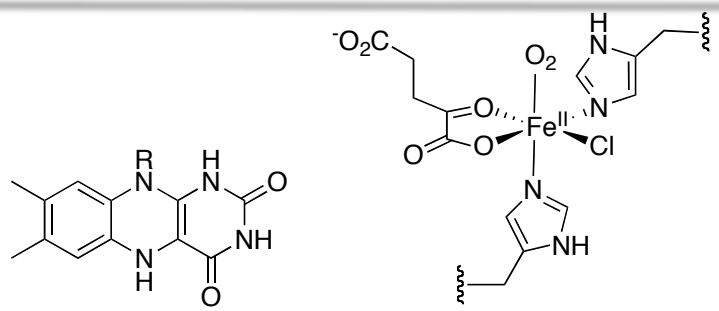
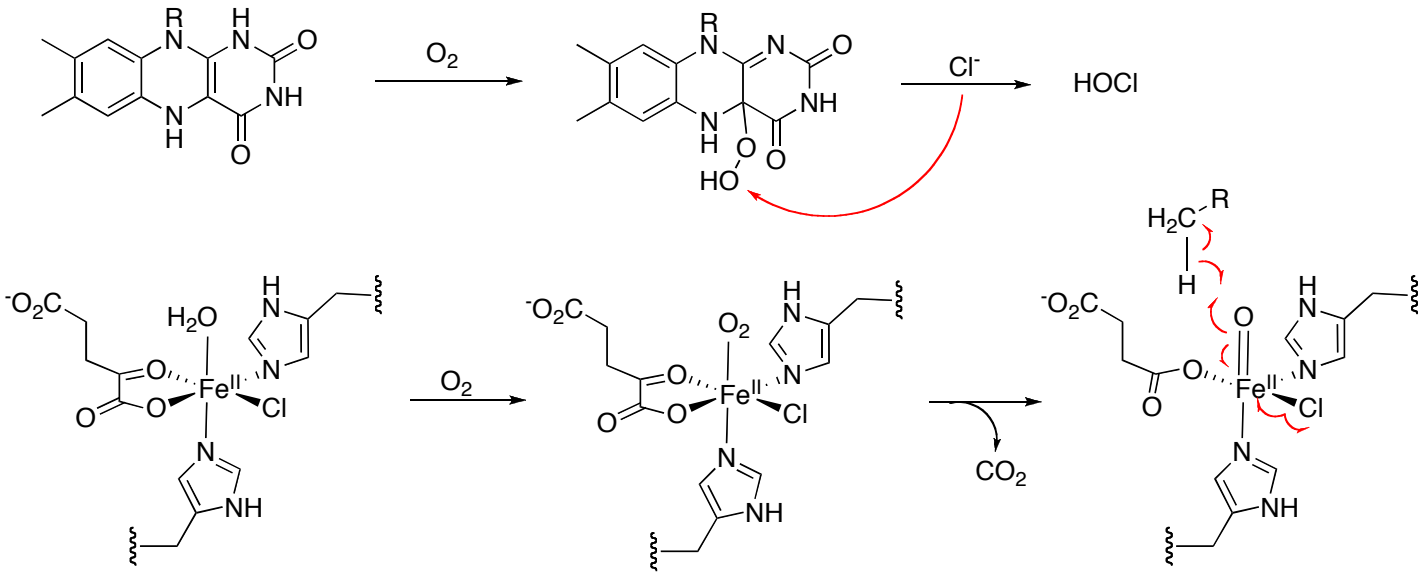


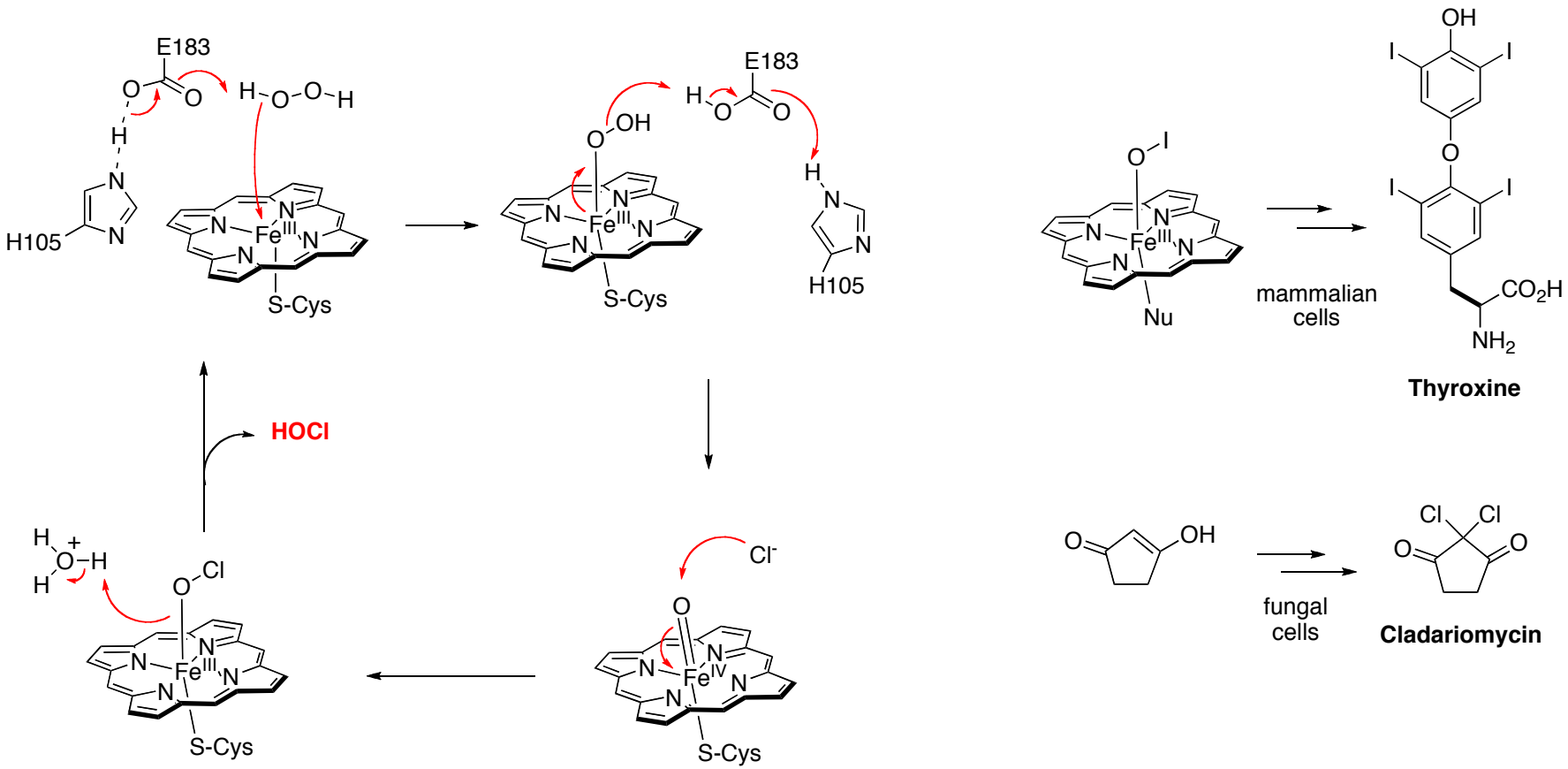
O_2 as reducible cosubstrate

O_2-dependent halogenases



Vaillancourt, F. H.; Yeh, E.; Vosburg, D. A.; Garneau-Tsodikova, S.; Walsh, C. T. *Chem. Rev.* **2006**, *106*, 3364-3378.

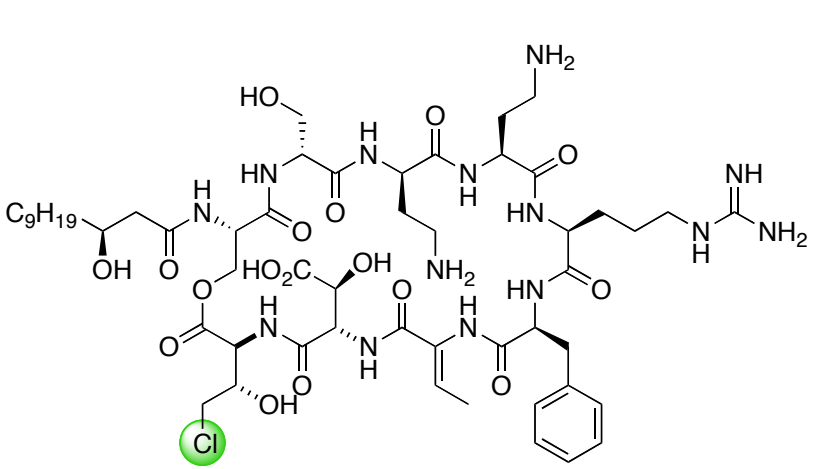
Heme-Dependent Haloperoxidases

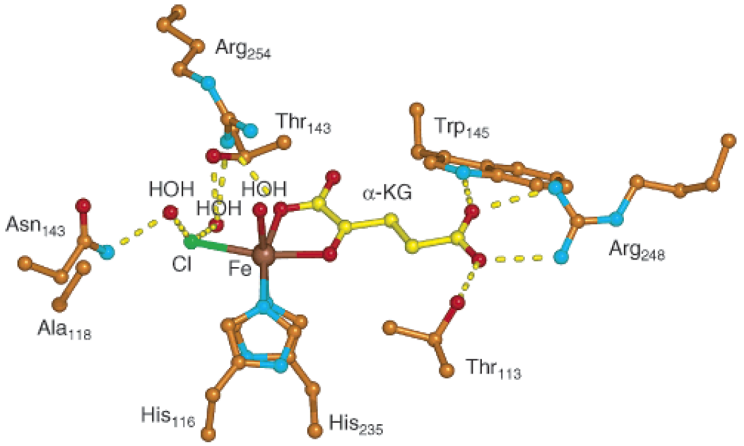


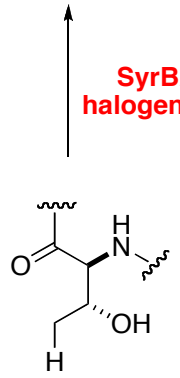
- the halogenating species are electropilic
- formation of these species is rate-determining steps
- HOCl is the electrophilic agent
- Cl_2 and HOCl could be detected in the absence of substrate

1. Vaillancourt, F. H.; Yeh, E.; Vosburg, D. A.; Garneau-Tsodikova, S.; Walsh, C. T. *Chem. Rev.* **2006**, *106*, 3364-3378. 2. Morrison, M.; Schonbaum, G. R. *Annu. Rev. Biochem.* **1976**, *45*, 861-888. 3. Corbet, M. D.; Chipko, B. R.; Baden, D. G. *Biochem. J.* **1978**, *175*, 353-360.

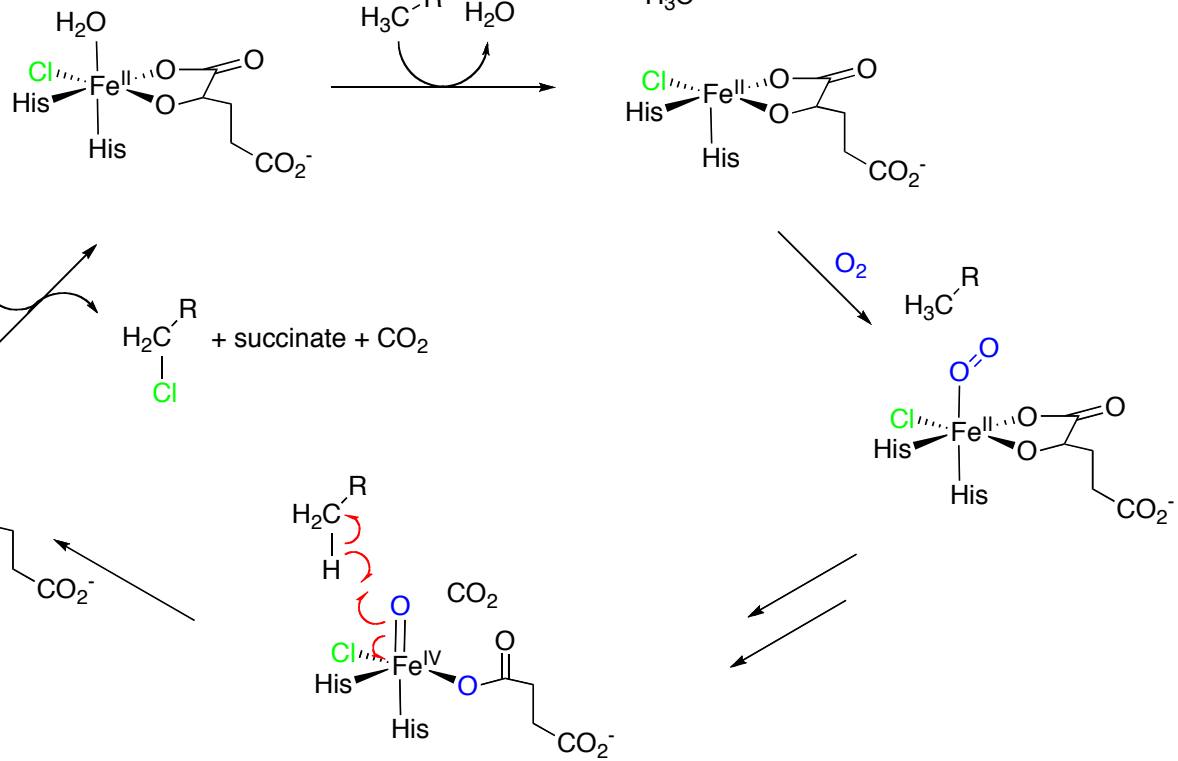
Non-heme Iron Halogenases for Unactivated Carbon Sites





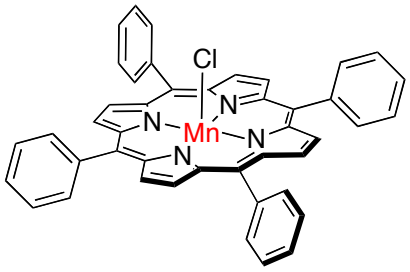


SyrB2 halogenase

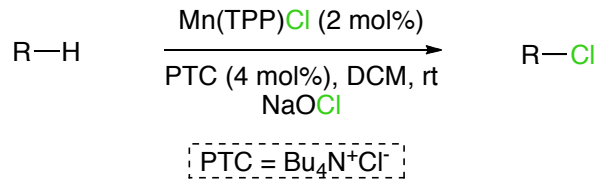


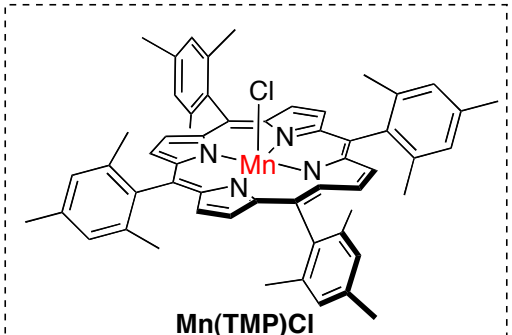
1. Vaillancourt, F. H.; Yeh, E.; Vosburg, D. A.; Garneau-Tsodikova, S.; Walsh, C. T. *Chem. Rev.* **2006**, *106*, 3364-3378. 2. Krebs, C.; Fujimori, D. G.; Walsh, C. T.; Bollinger, Jr., J. M. *Acc. Chem. Res.* **2007**, *40*, 484.

Manganese Porphyrins Catalyze Selective C-H Bond Halogenations

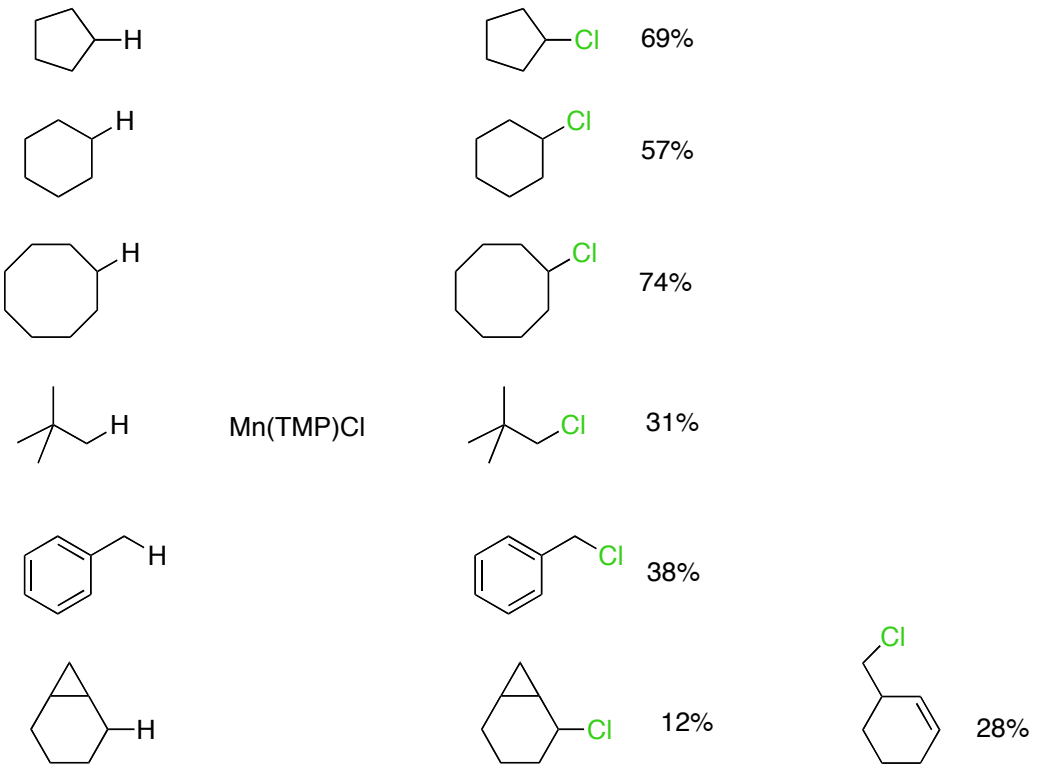


Mn(TPP)Cl



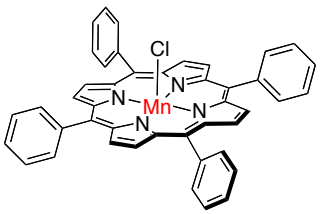


Mn(TMP)Cl



Liu, W.; Groves, J. T. *J. Am. Chem. Soc.* **2010**, *132*, 12847-12849.

Manganese Porphyrins Catalyze Selective C-H Bond Halogenations



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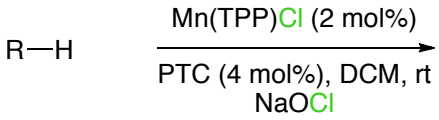
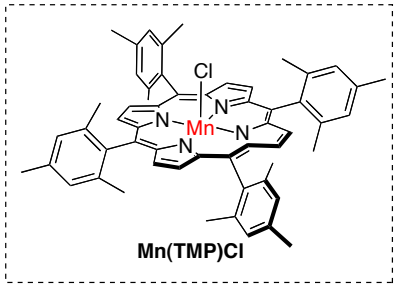
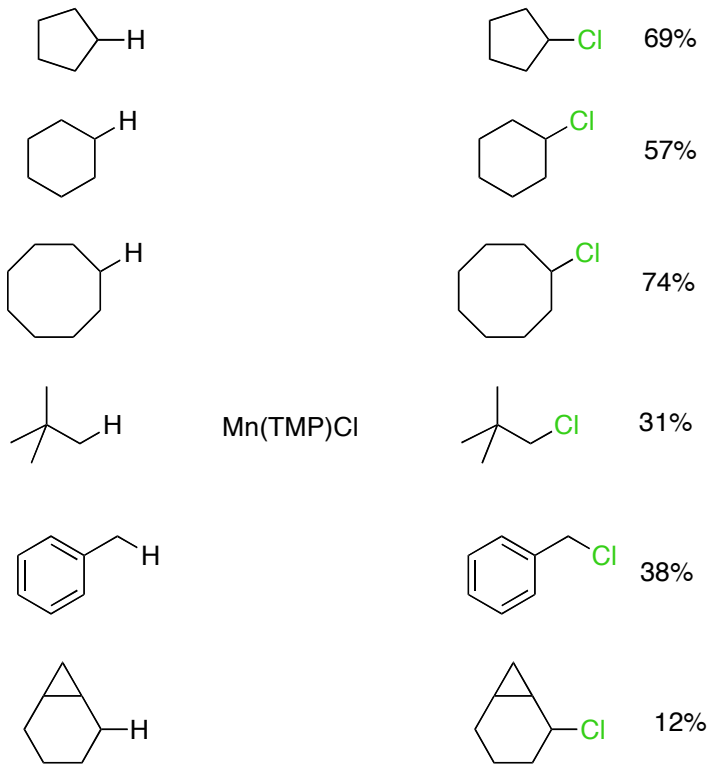


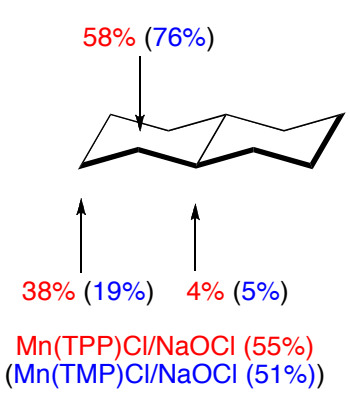
PTC = $Bu_4N^+Cl^-$



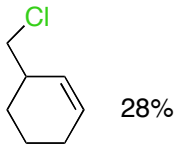
Mn(TMP)Cl

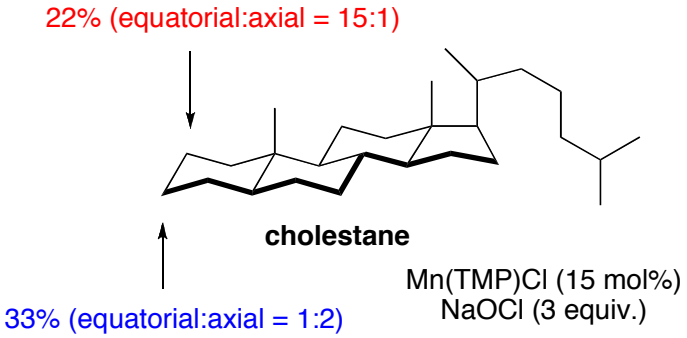


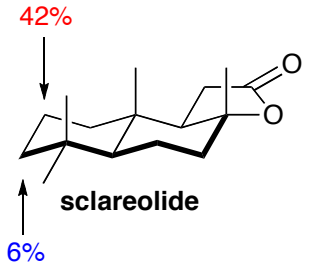
Steric effects lead to selective chlorination



Mn(TPP)Cl/NaOCl (55%)
(Mn(TMP)Cl/NaOCl (51%))







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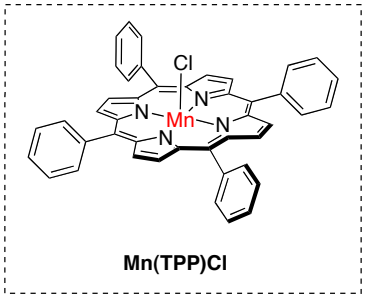
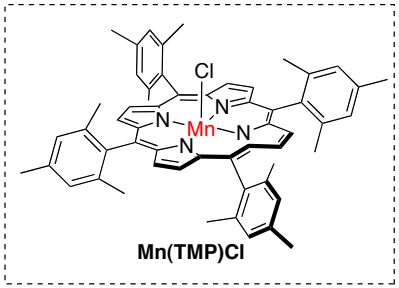
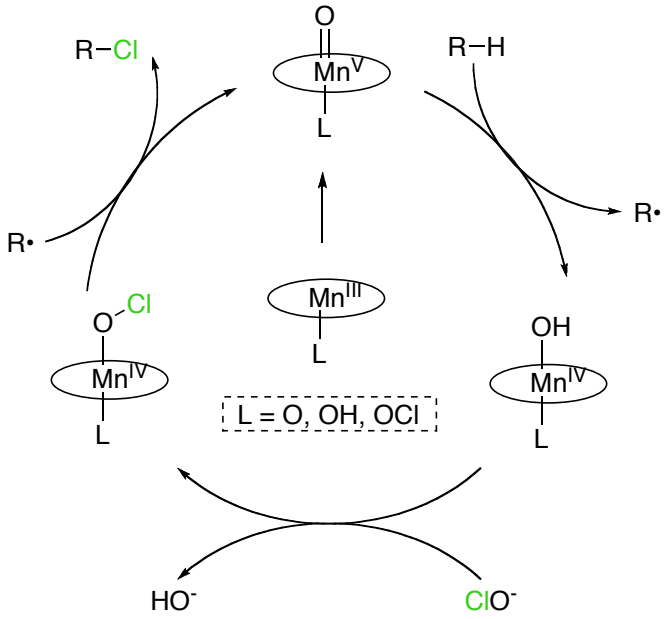
Manganese, Iron or Nickel: Site-Selective Halogenations



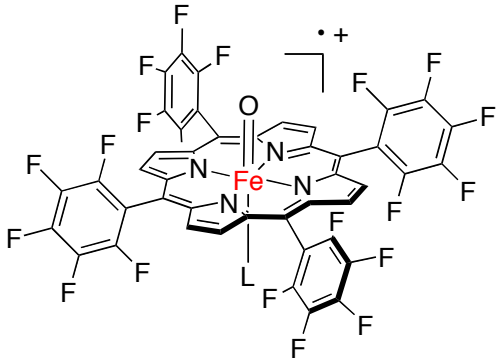
Mn(TPP)Cl



Mn(TMP)Cl



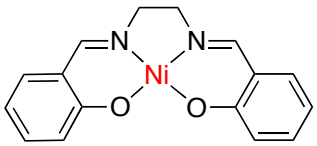
Liu, W.; Groves, J. T. *J. Am. Chem. Soc.* **2010**, *132*, 12847-12849.



((TPFPP$^{+\bullet}$)Fe^{IV}O(L))

L = $C_6F_5CO_2$
L = NO_3

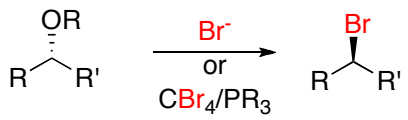
Cong, Z.; Kurahashi, T.; Fuijii, H. *Angew. Chem. Int. Ed.* **2011**, *50*, 1-6.

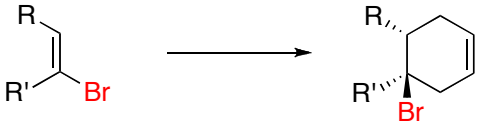


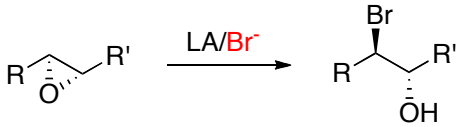
Ni(salen)

Querci, C.; Strologo, S.; Ricci, M. *Tetrahedron Lett.* **1990**, *31*, 6577-6580.

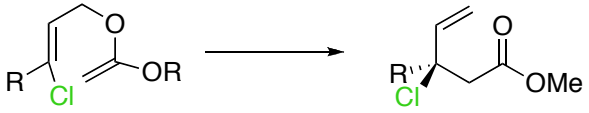
Conventional Halogenation Methods



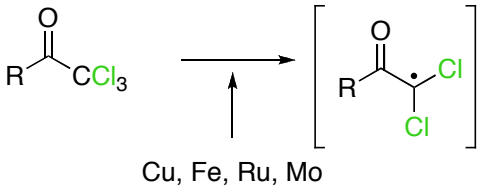


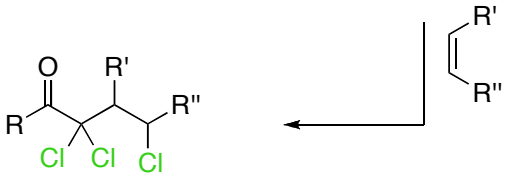


Nucleophilic Displacement

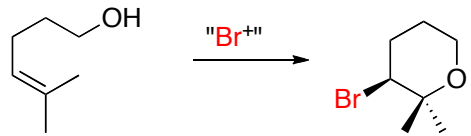


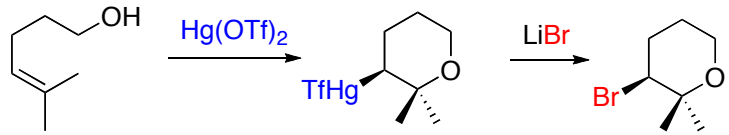
Cycloaddition/Sigmatropic Rearrangement



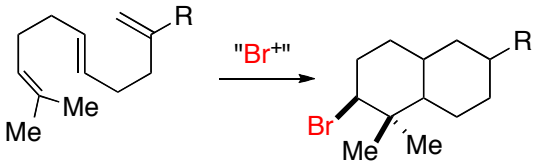


Karasch Reaction



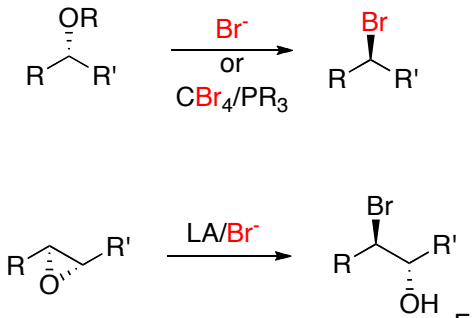


Bromoetherification
Oxymercuration-Bromination

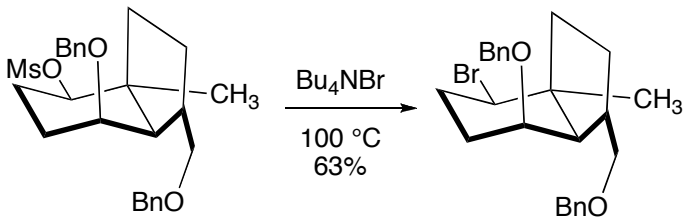


Polyene Cyclization

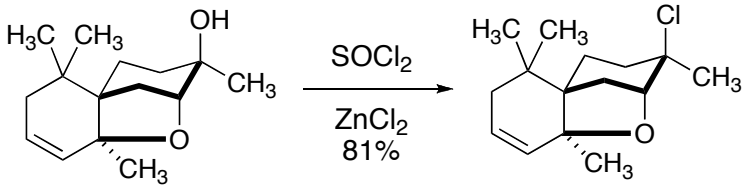
Conventional Halogenation Methods



Nucleophilic Displacement

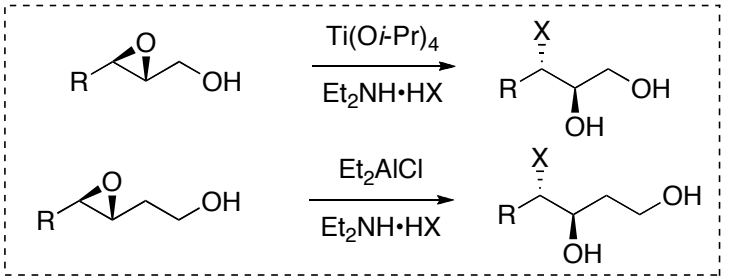


Fukuzawa, A.; Sato, H.; Masamune, T. *Tetrahedron Lett.* **1987**, *28*, 4303-4306.

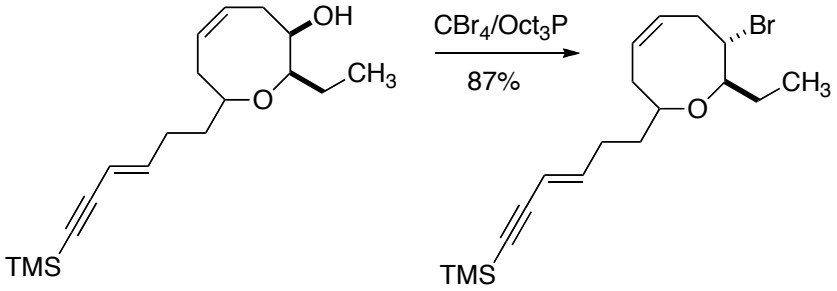


Miyashita, K; Tanaka, A.; Shintaku, K.; Iwata, C. *Tetrahedron* **1998**, *54*, 1395-1406.

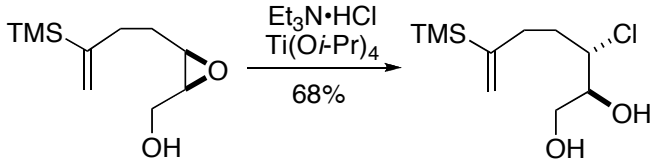
Murai's Regioselective Epoxy Alcohol Opening.



Gao, L. –X.; Murai, A. *Tetrahedron Lett.* **1992**, *33*, 4349-4352.

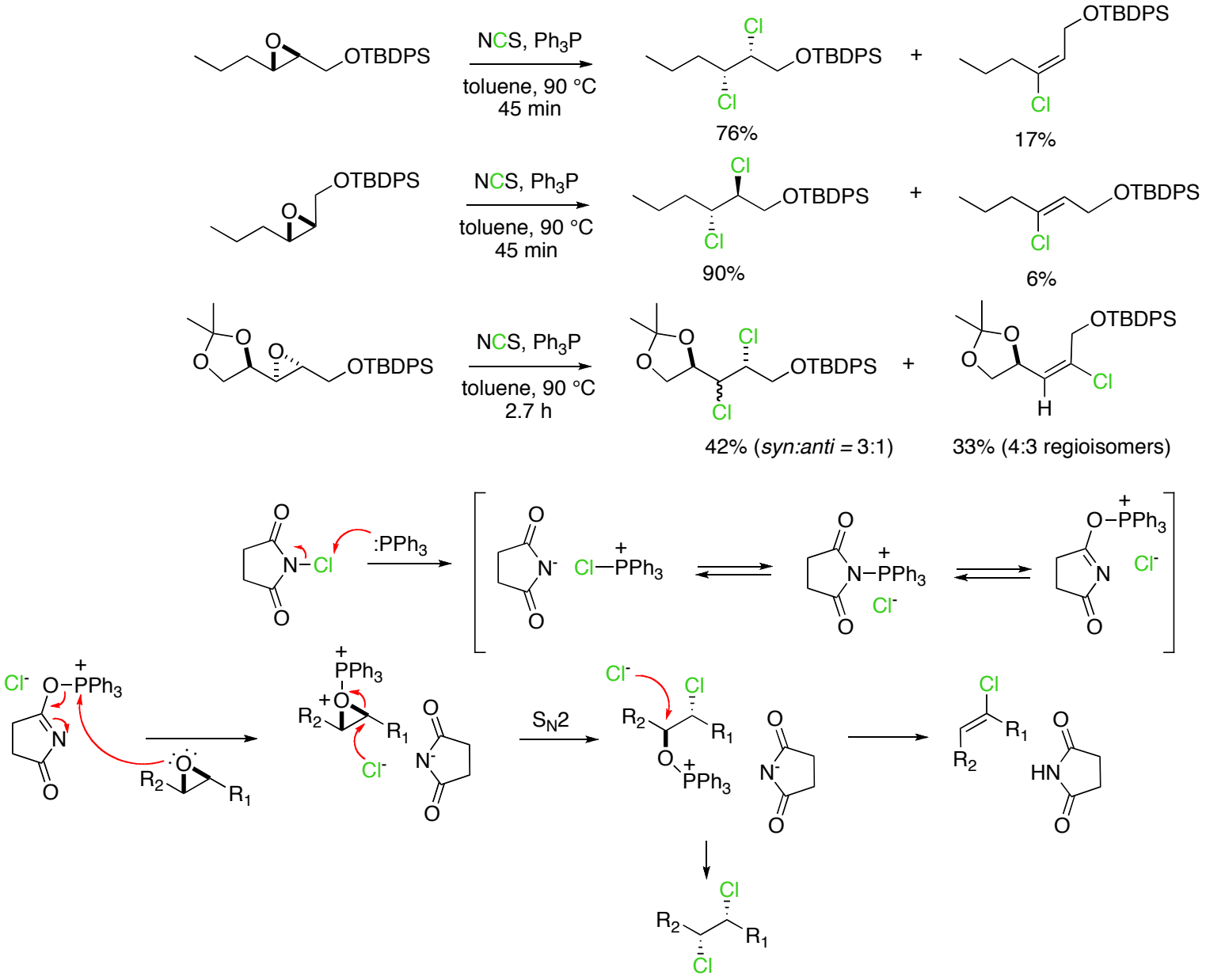


Tsushima, K.; Murai, A. *Tetrahedron Lett.* **1992**, *30*, 4345-4348.



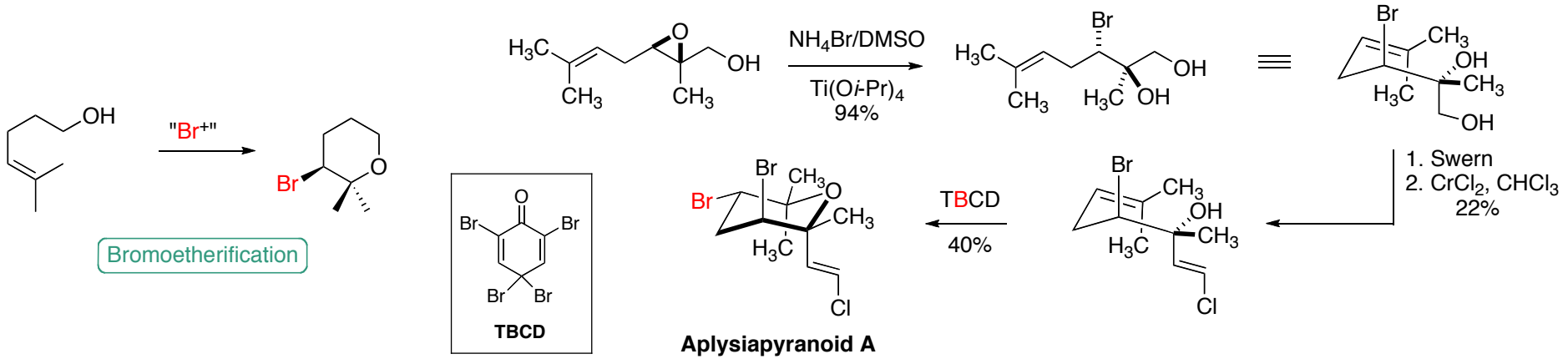
Overman, L. E.; Thompson, A. S. *J. Am. Chem. Soc.* **1988**, *110*, 2248-2256.

Chiral Epoxides as Substrates for Dichlorination

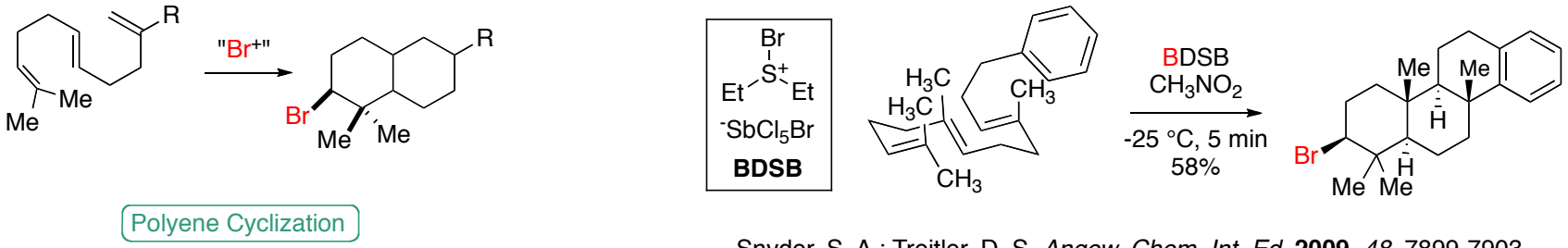


Yoshimitsu, T.; Fukumoto, N.; Tanaka, T. *J. Org. Chem.* **2009**, *74*, 696-702.

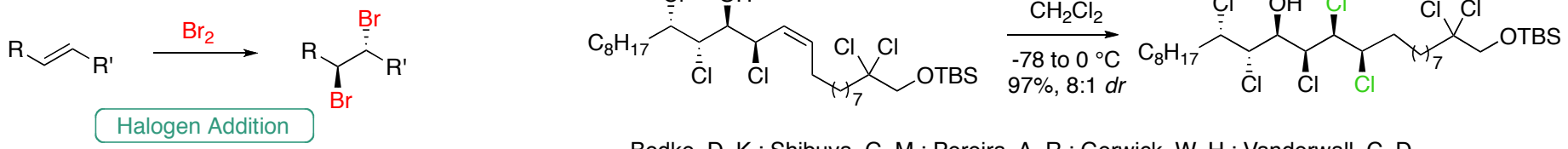
Halonium-Induced Cyclizations



Jung, M. E.; D'amico, D. C.; Lew, W. *Tetrahedron Lett.* **1993**, *34*, 923-926.

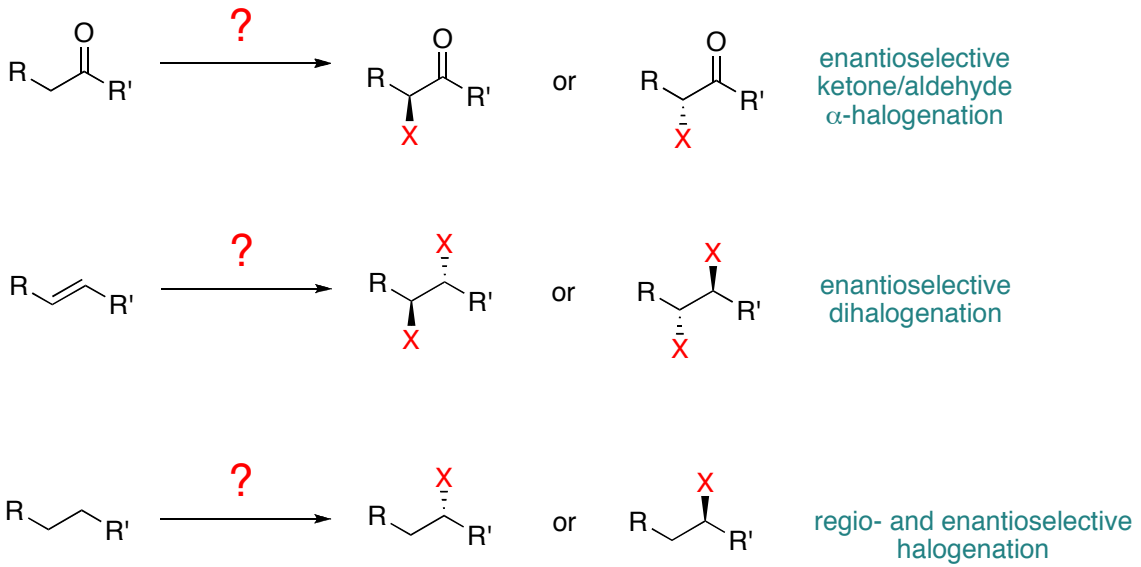


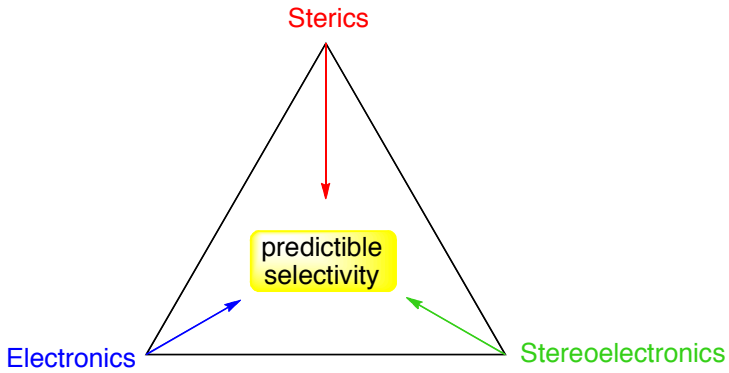
Snyder, S. A.; Treitler, D. S. *Angew. Chem. Int. Ed.* **2009**, *48*, 7899-7903.



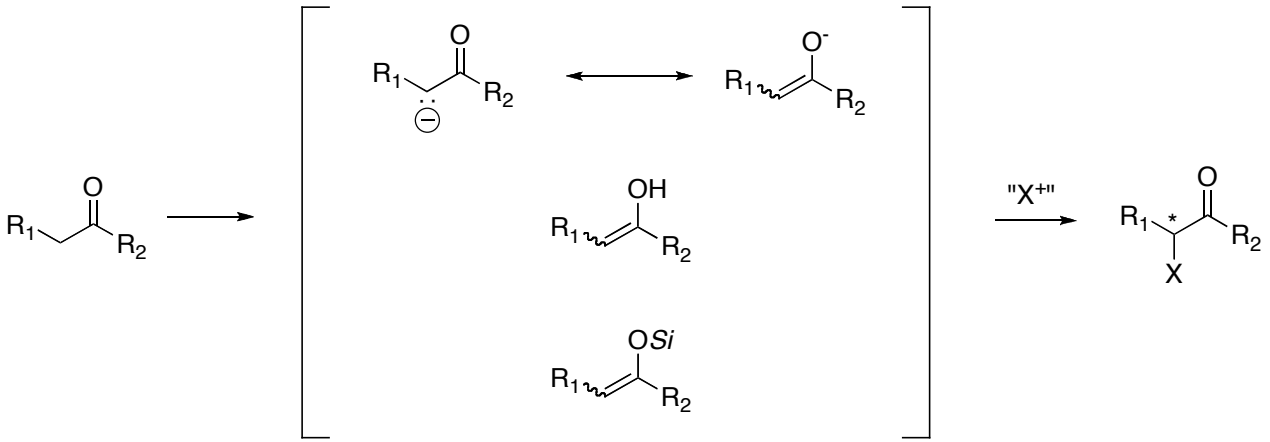
Bedke, D. K.; Shibuya, G. M.; Pereira, A. R.; Gerwick, W. H.; Vanderwall, C. D. *J. Am. Chem. Soc.* **2010**, *132*, 2542-2543.

To Do or Not to Do Enantioselectively

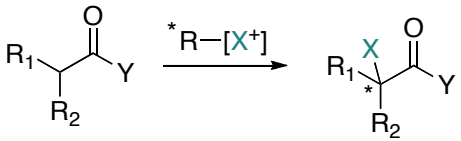




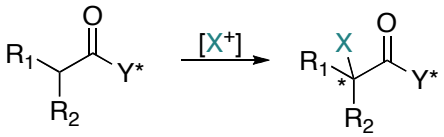
Logic behind Halogenation of Carbonyl Compound



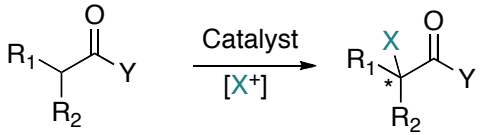
Reagent-controlled halogenation



Substrate-controlled halogenation

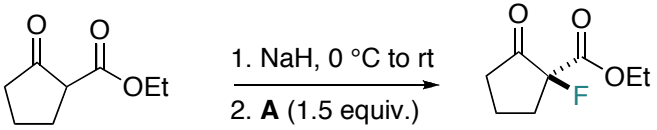


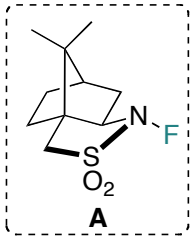
Catalytic asymmetric halogenation



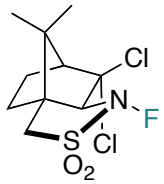
1. For general reviews on carbonyl compounds halogenations, see: a) Ibrahim, H.; Togni, A. *Chem. Commun.* **2004**, 1147-1155. b) Oestreich, M. *Angew, Chem. Int. Ed.* **2005**, *44*, 2324-2327. 2. For the review about fluorination of the organic compounds, see: Taylor, S. D.; Kotoris, C. C.; Hum, G. *Tetrahedron* **1999**, *55*, 12431-12477.

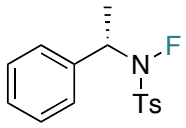
Enantioselective Fluorination of Ketones

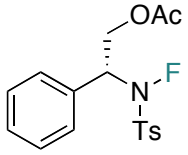


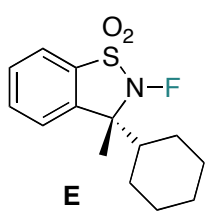


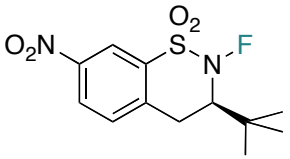
Differding, E.; Lang, R. W. *Tetrahedron Lett.* **1998**, *29*, 6087-6090.

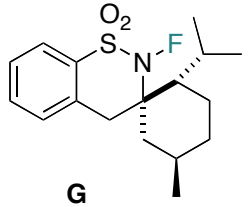


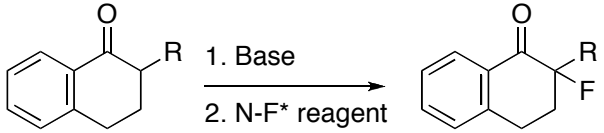




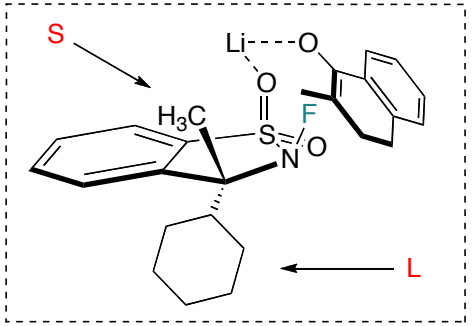






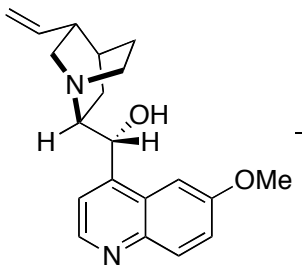


N-F*	Base	Product	Yield (%)	*ee* (%)	Config.
B	NaHMDS	a	53	76	*S*
E	LDA	a	67	74	*S*
G	LiHMDS	a	65	70	*S*
F	LiHMDS	a	79	62	*R*
E	LDA	b	79	88	*S*
C	KHMDS	b	53	48	-

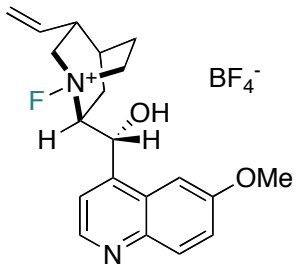


1. Davis, F. A.; Zhou, P.; Murphy, C. K. *Tetrahedron Lett.* **1993**, *34*, 3971-3974. 2. Davis, F. A.; Zhau, P.; Murphy, C. K.; Sundarababu, G.; Qi, H.; Han, W.; Przeslawski, R. M.; Chen, B. –C.; Carroll, P. J. *A J. Org. Chem.* **1998**, *63*, 2273-2280. 3. Takeuchi, Y.; Suzuki, T.; Satoh, A.; Shiragami, T.; Shibata, N. *J. Org. Chem.* **1999**, *64*, 5708-5711. 4. Liu, Z.; Shibata, N.; Takeuchi, Y. *J. Org. Chem.* **2000**, *65*, 7583.

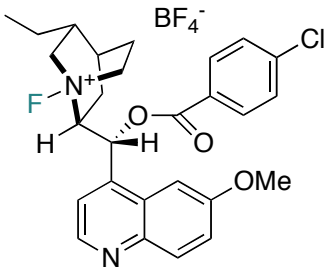
Cinchona Alkaloids Fluorinating Reagents



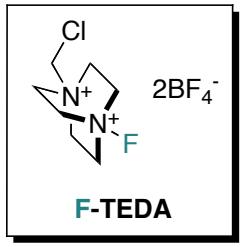
F-TEDA or NFSI



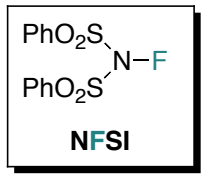
***N*F-Q · BF_4**



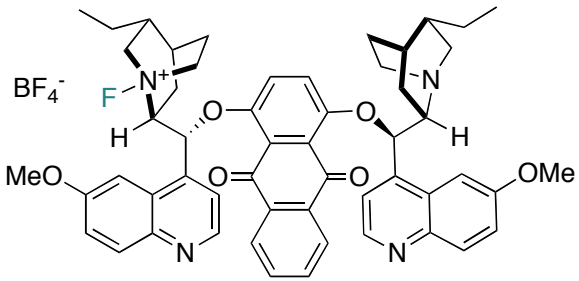
***N*F-DHQB · BF_4**



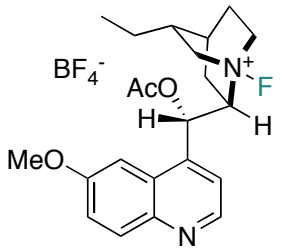
F-TEDA



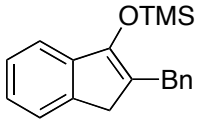
NFSI

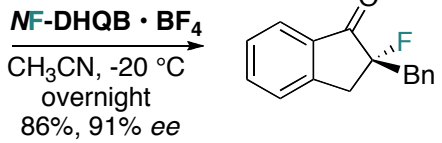


***N*F-$(DHQ)_2$AQN · BF_4**



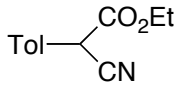
***N*F-DHQDA · BF_4**

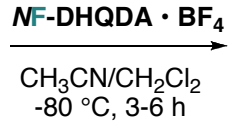




***N*F-DHQB · BF_4**

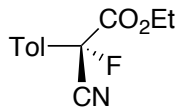
CH_3CN, -20 °C
overnight
86%, 91% *ee*

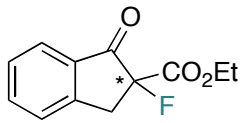




***N*F-DHQDA · BF_4**

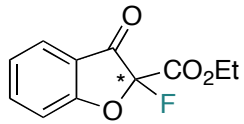
CH_3CN/CH_2Cl_2
-80 °C, 3-6 h
80%, 87% *ee*





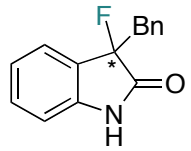
***N*F-DHQDA · BF_4**

89%, 87% *ee*



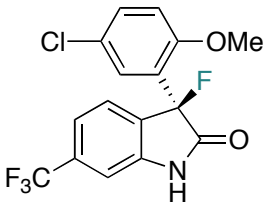
***N*F-DHQDA · BF_4**

92%, 80% *ee*



***N*F-$(DHQ)_2$AQN · BF_4**

100%, 78% *ee*

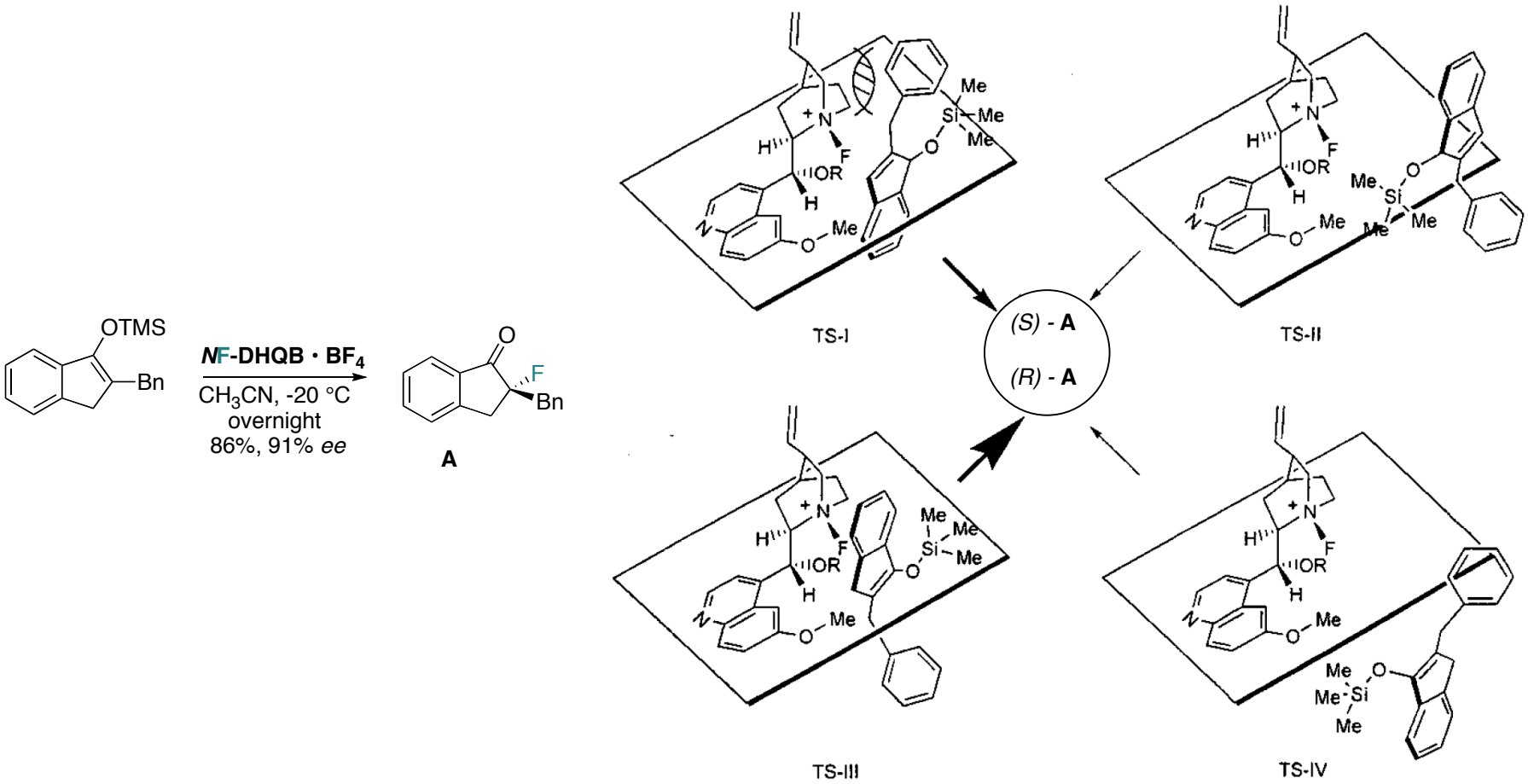


***N*F-$(DHQ)_2$AQN · BF_4**

94%, 84% *ee*

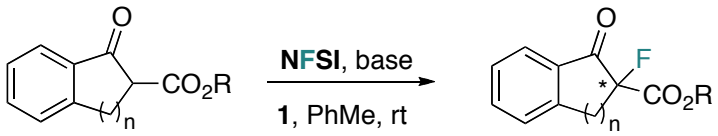
1. Shibata, N.; Suzuki, E.; Asahi, T.; Shiro, M. *J. Am. Chem. Soc.* **2001**, *123*, 7001-7009. 2. Shibata, N.; Suzuki, E.; Takeuchi, Y. *J. Am. Chem. Soc.* **2000**, *122*, 10728-10729. 3. Shibata, N.; Ishimaru. T.; Suzuki, E.; Kirk, K. L.; *J. Org. Chem.* **2003**, *68*, 2494-2497.

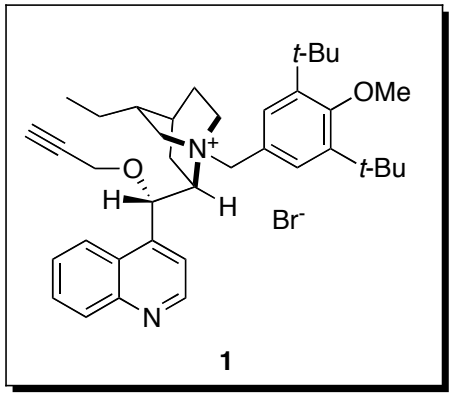
More in Depth: Origin of Stereoselectivity



Shibata, N.; Suzuki, E.; Asahi, T.; Shiro, M. *J. Am. Chem. Soc.* **2001**, *123*, 7001-7009.

Cinchona Alkaloids in PTC Asymmetric Fluorination: A Catalytic Version

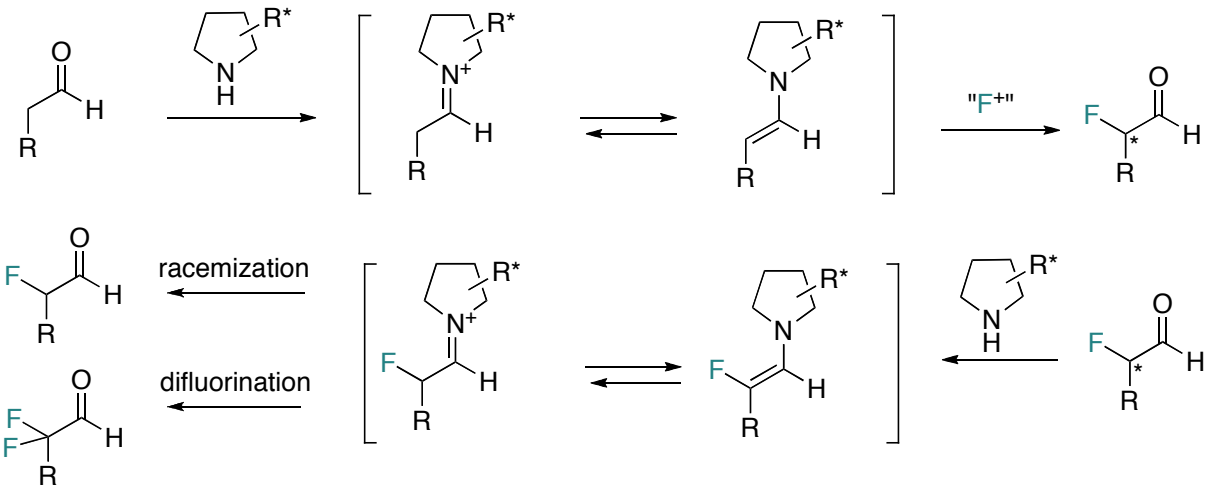


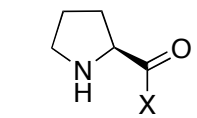


R	Base	n	Yield (%)	*ee* (%)
Me	K_2CO_3	1	92	69
Me	Cs_2CO_3	1	94	60
Et	K_2CO_3	1	92	50
Et	Cs_2CO_3	1	91	63
Me	RbOH	2	87	40
Me	Cs_2CO_3	2	88	48

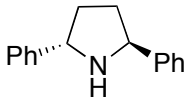
Kim, D. Y.; Park, E. J. *Org. Lett.* **2002**, *4*, 545-547.

L-Proline Derivatives in Enantioselective Fluorination: A Challenging Task





***L*-Pro-OH**, X = OH
***L*-Pro-NH$_2$**, X = NH_2



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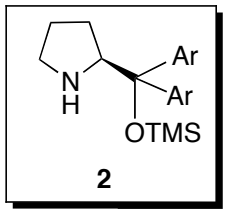

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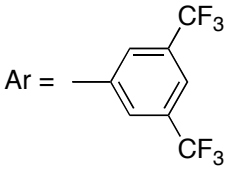
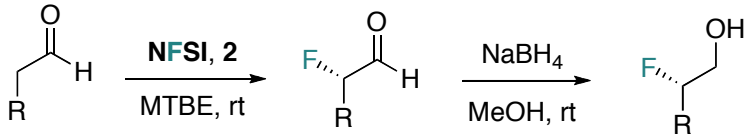
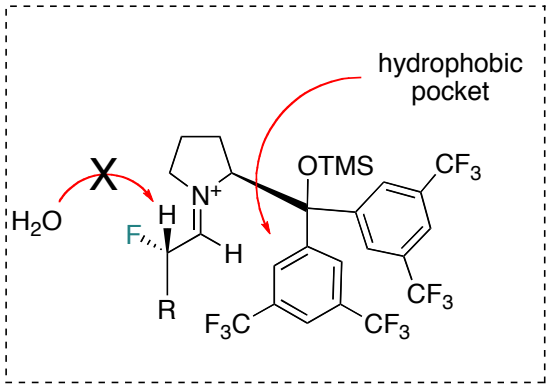


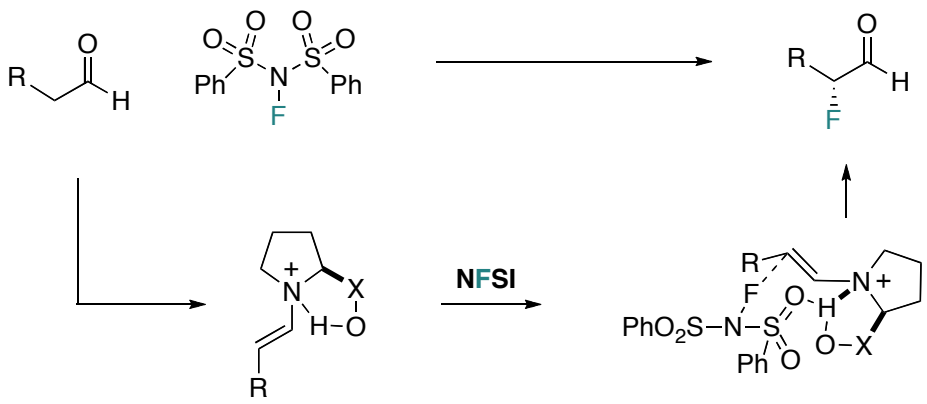


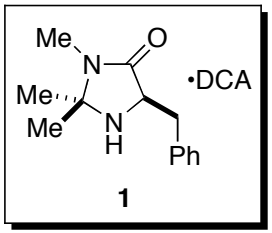
R = Pr (95%, 96% *ee)*; Bu (90%, 91% *ee*); Hex (55%, 96% *ee*); $BnO(CH_2)_3$ (64%, 91% *ee*); Bn (74%, 93% *ee*); Cy (69%, 96% *ee*); *t*-Bu (> 90%, 97% *ee*); 1-Ad (75%, 96% *ee*).

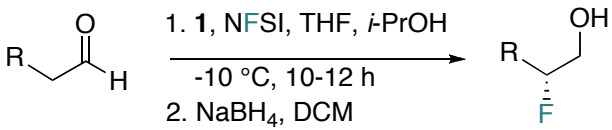


Marigo, M.; Fielenbach, D.; Braunton, A.; Kjaersgaard, A.; Jørgensen, K. A. *Angew. Chem. Int. Ed.* **2005**, *44*, 3703-3706.

MacMillan's Catalyst in Action: Enantioselective Organocatalytic α-Fluorination of Aldehydes





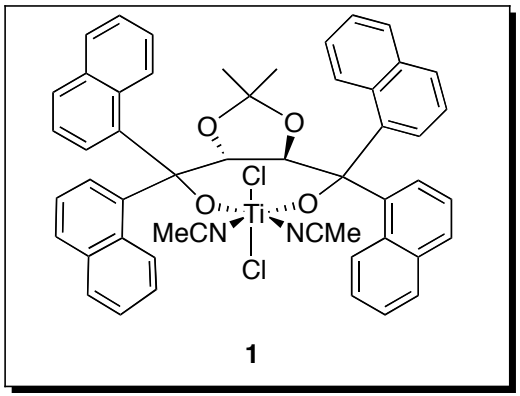


R = Oct (70%, 94% *ee*); 1-Octenyl (79%, 94% *ee*), Cy (96%, 99% *ee*)

Ph (54% 99% *ee*); Bn (71%, 96% *ee*); 1-Ad (82%, 98% *ee*)

Beeson, T. D.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2005**, *127*, 8826-8828.

$TiCl_2$[*R*,*R*-(TADDOLLato)] Catalyzed Asymmetric Fluorination



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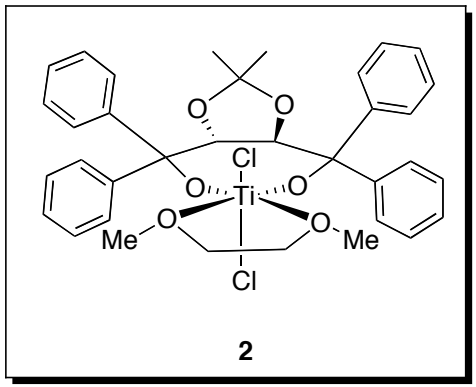

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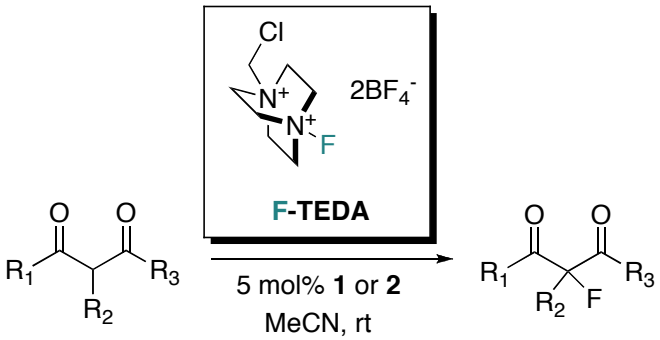
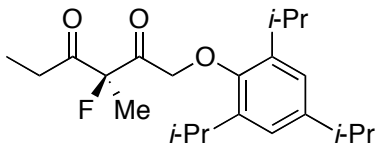
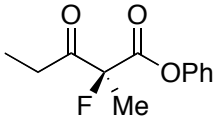
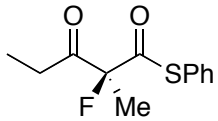




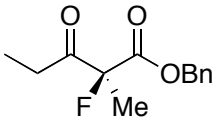
89%, 90% *ee*



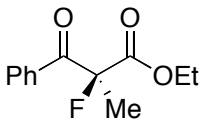
50%, 88% *ee*



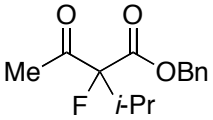
78%, 91% *ee*



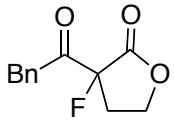
82%, 71% *ee*



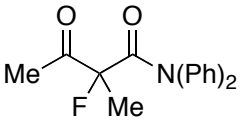
71%, 62% *ee*



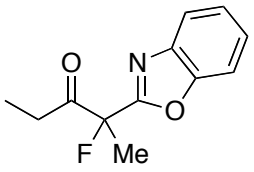
40%, 24% *ee*



63%, 51% *ee*



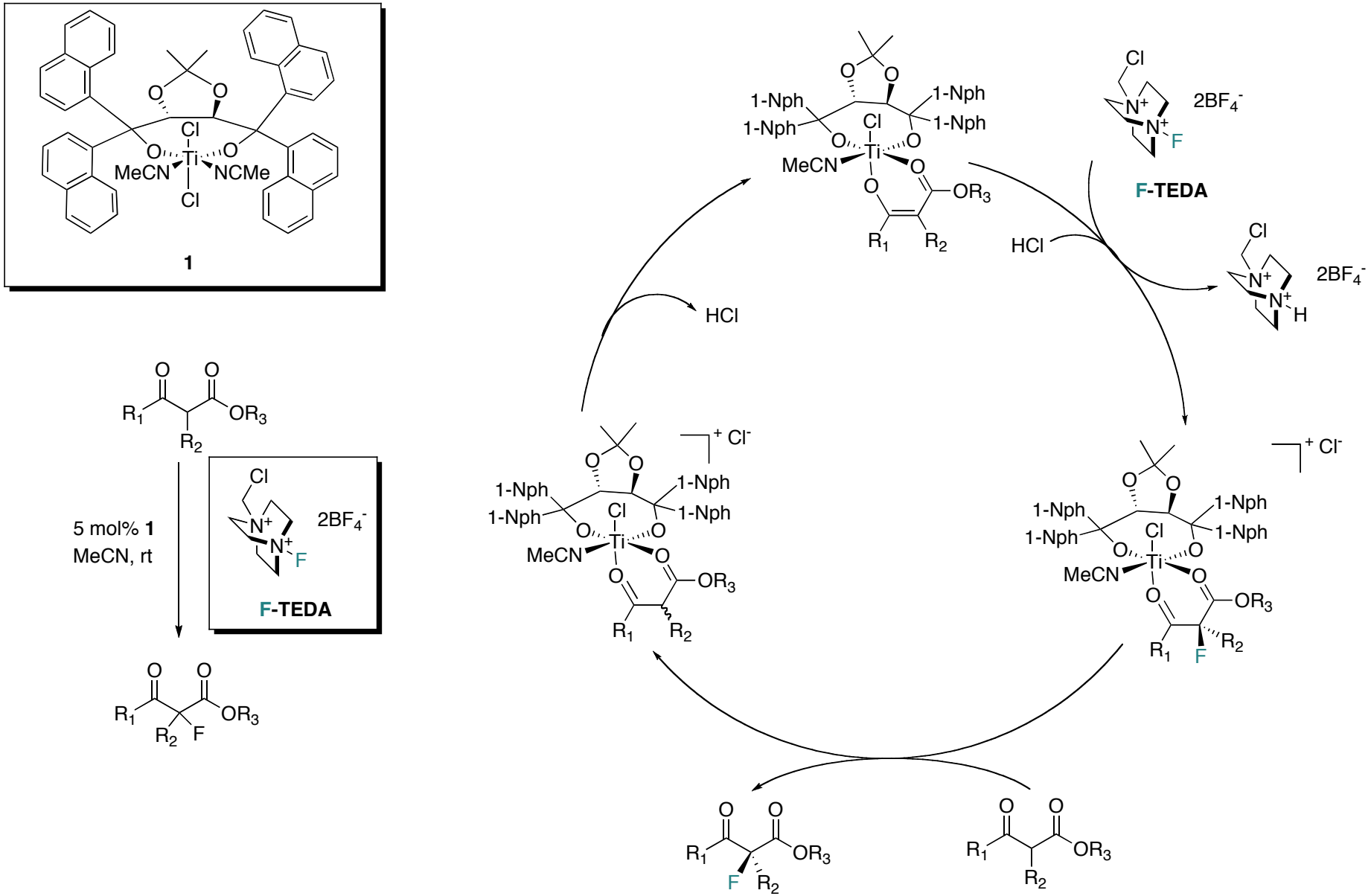
75%, 55% *ee*



85%, 62% *ee*

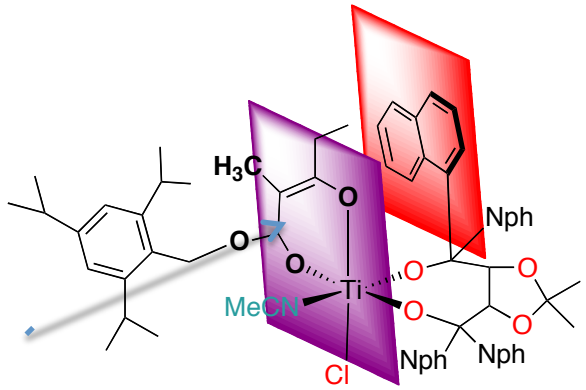
Hintermann, L.; Togni, A. *Angew. Chem. Int. Ed.* **2000**, *39*, 4359-4362.

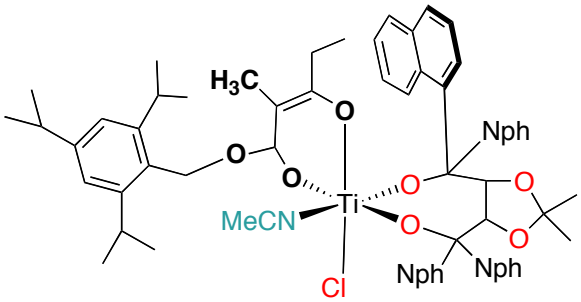
$TiCl_2$[*R*,*R*-(TADDOLLato)] Catalyzed Asymmetric Fluorination: Mechanism

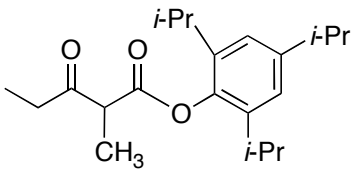


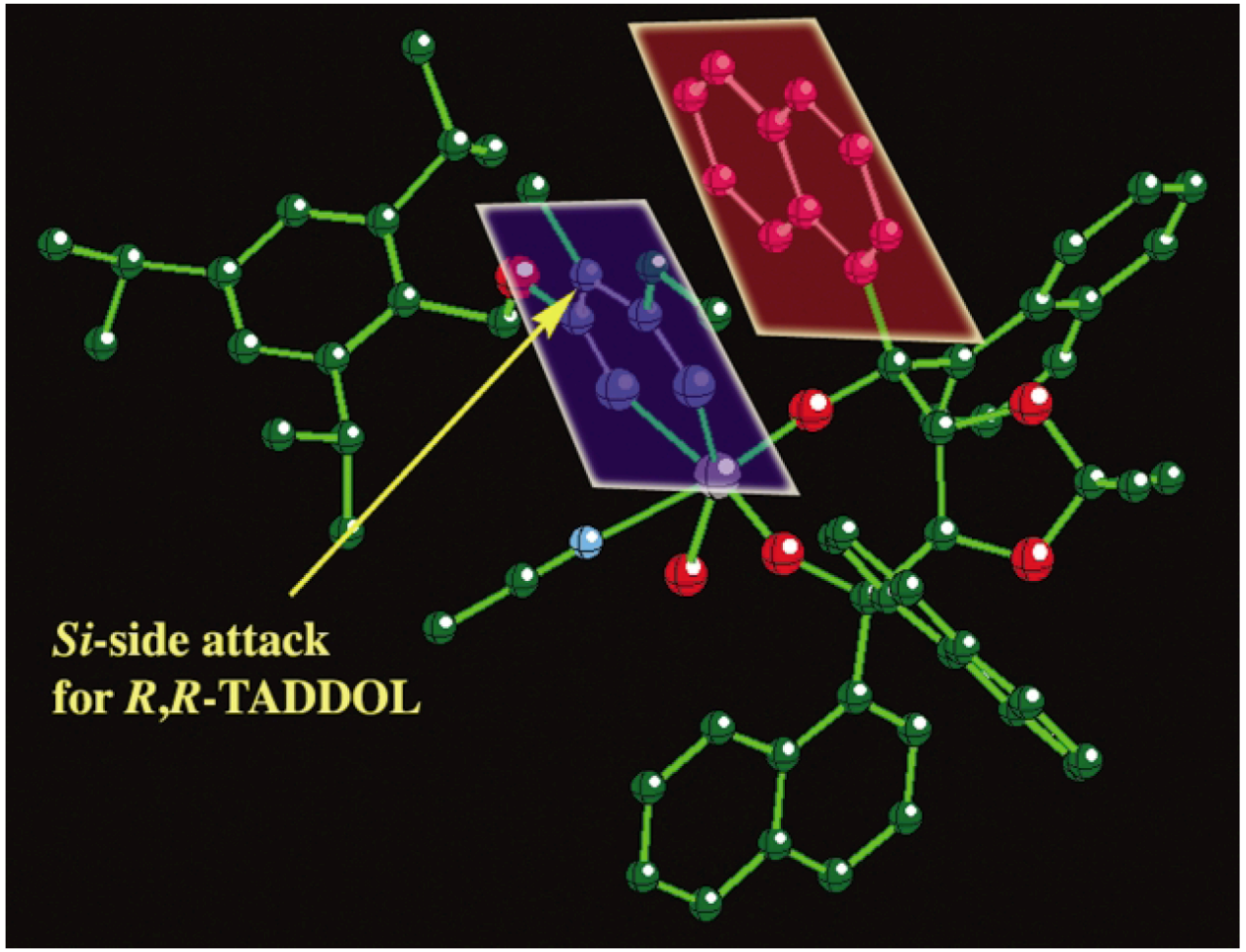
Hintermann, L.; Togni, A. *Angew. Chem. Int. Ed.* **2000**, *39*, 4359-4362.

$TiCl_2$[*R*,*R*-(TADDOLLato)]: Almost Perfectly Parallel Arrangement



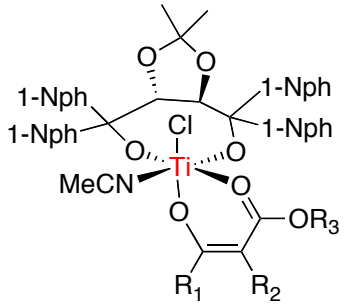




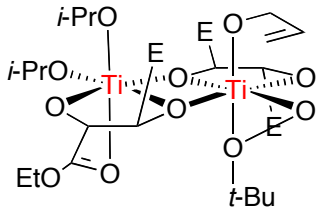


1. Hintermann, L.; Togni, A. *Angew. Chem. Int. Ed.* **2000**, *39*, 4359-4362. 2. Ibrahim, H.; Togni, A. *Chem. Commun.* **2004**, 1147-1155. 3. Pianna, S.; Devillers, I.; Togni, A.; Rothlisberger, U. *Angew. Chem. Int. Ed.* **2002**, *41*, 979.

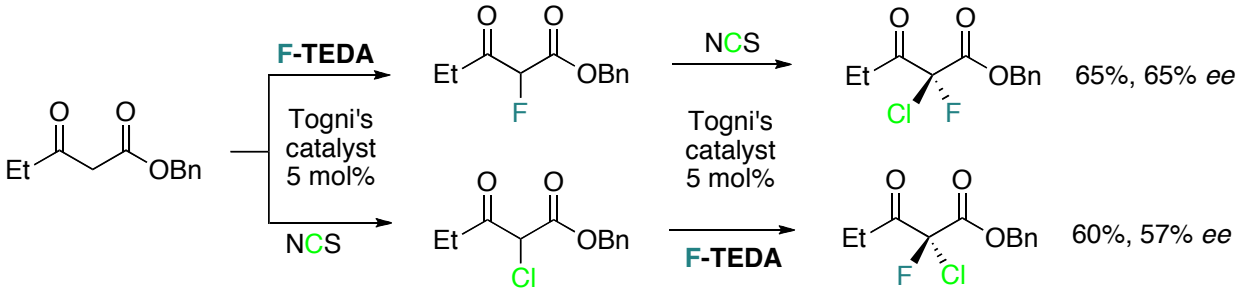
Similar or Not Similar: Titanium Complex Chemistry in Organic Synthesis



Togni's catalyst

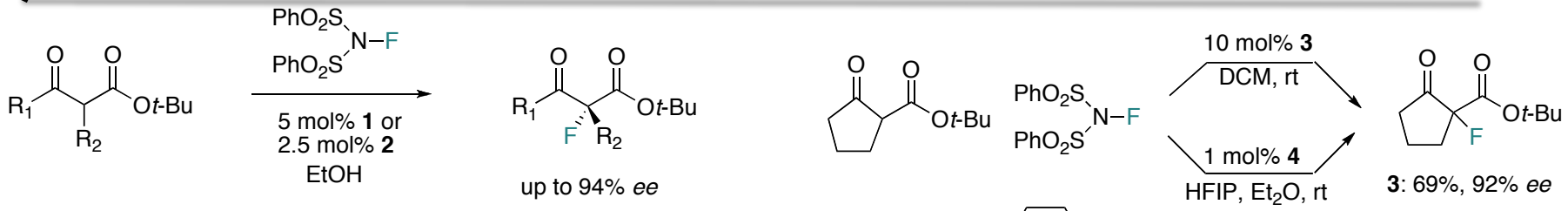


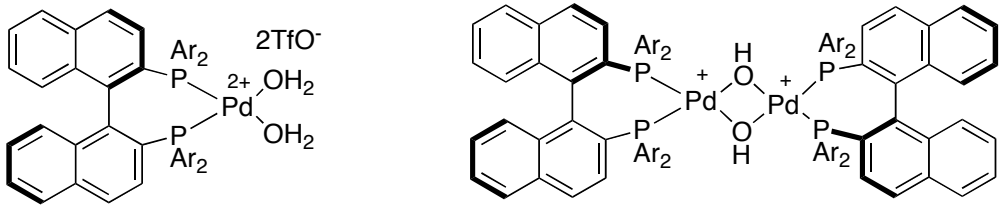
Sharpless' catalyst



Frantz, R.; Hintermann, L.; Perseghini, M.; Broggni, D.; Togni, A. *Org. Lett.* **2003**, *5*, 1709-1712.

Other Lewis Acids as Catalyst: Asymmetric Fluorination

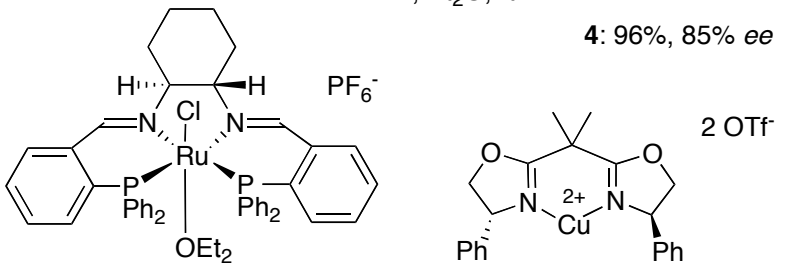




1 Ar = 3,5-dimethylphenyl

2a $2BF_4^-$
2b $2TfO^-$

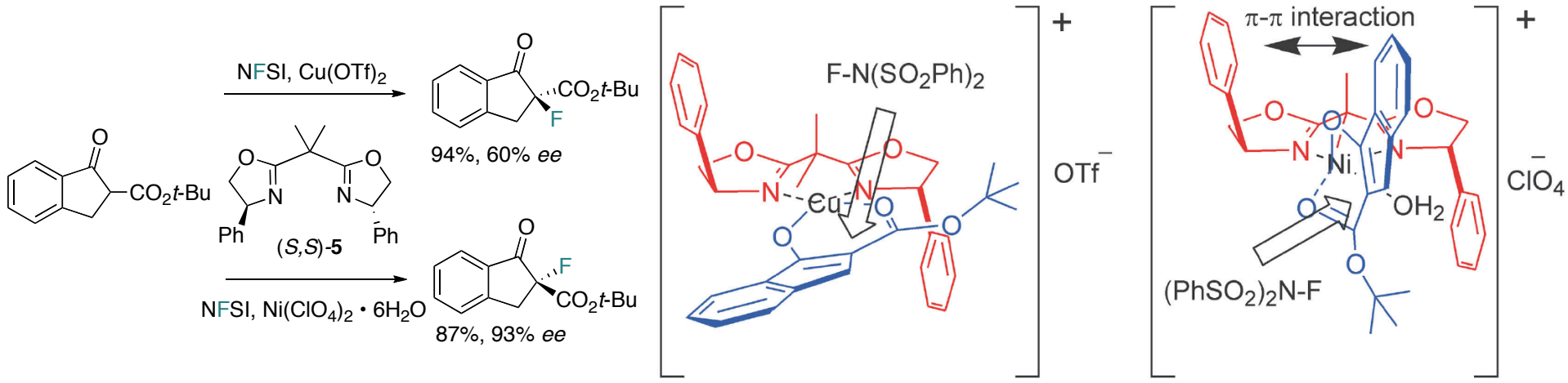
Hamashima, Y.; Yagi, K.; Takano, H.; Tomas, L.; Sodeoka, M. *J. Am. Chem. Soc.* **2002**, 1*24*, 14530-14531.



(*S,S*)-**3**

(*R,R*)-**4**

Ibrahim, H.; Togni, A. *Chem. Commun.* **2004**, 1147-1155;
Ma, J. -A.; Cahard, D. *Tetrahedron: Asymmetry* **2004**, 1*5*, 1007-1011.



Shibata, N.; Ishimaru, T.; Nagai, T.; Kohno, J.; Toru, T. *Synlett* **2004**, *10*, 1703-1706

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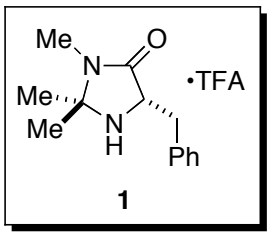
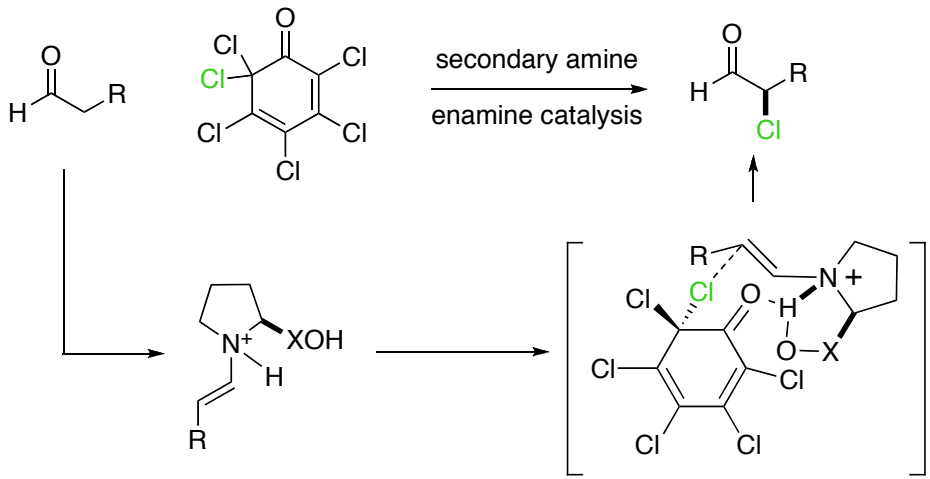
Asymmetric Chlorination of Aldehydes: MacMillan

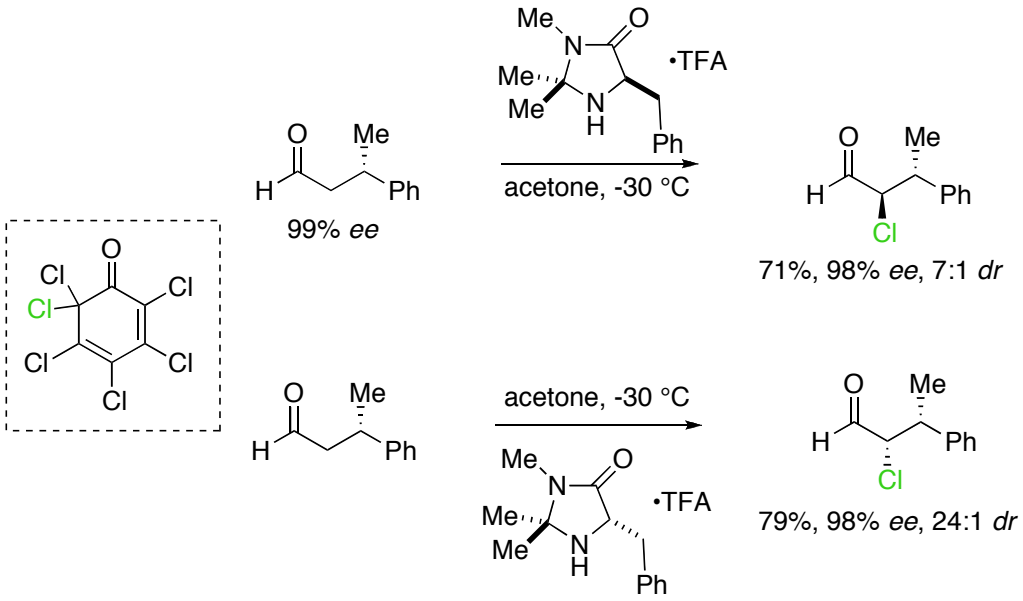


1



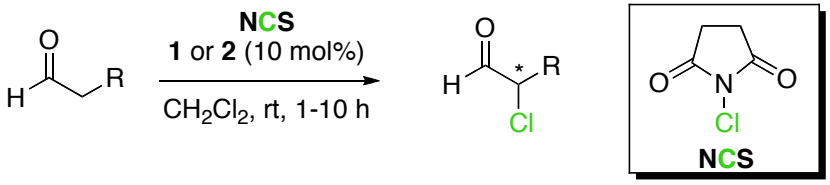
R = *n*-Hex (71%, 92% *ee*); Cy (87%, 94% *ee*); 1-Ad (85%, 95% *ee*);

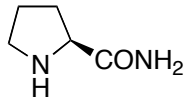
Ph (92%, 80% *ee*); CH_2CH_2OMOM (94%, 93% *ee*); $CH_2CH_2CO_2Me$ (78%, 87% *ee*)



Brochu, M. P.; Brown, S. P.; MacMillan, D. W. C. *J. Am. Chem. Soc* **2004**, *126*, 4108-4109.

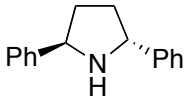
Asymmetric Halogenation of Aldehydes and Ketones: Jørgensen





1

R = Me (99%, 75% *ee R*); Et (99%, 80% *ee R*); *i*-Pr (95%, 87% *ee R*); *t*-Bu (93%, 95% *ee R*); Allyl (90%, 74% *ee*); Bn (99%, 78% *ee).*

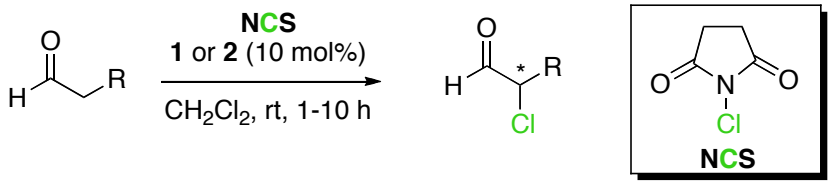


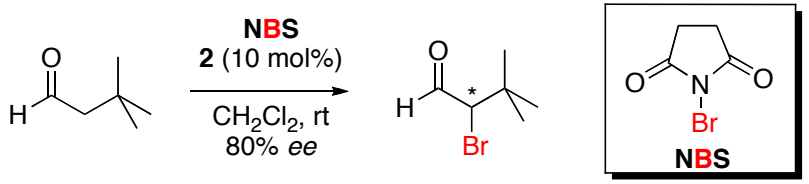
2

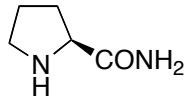
R = Et (90%, 97% *ee S*); *i*-Pr (90%, 94% *ee S*); *t*-Bu (30%, 94% *ee S*); Allyl (90%, 95% *ee*); Bn (82%, 95% *ee).*

Halland, N.; Braunton, A.; Bachmann, S.; Marigo, M.; Jørgensen, K. A. *J. Am. Chem. Soc* **2004**, *126*, 4790-4791.

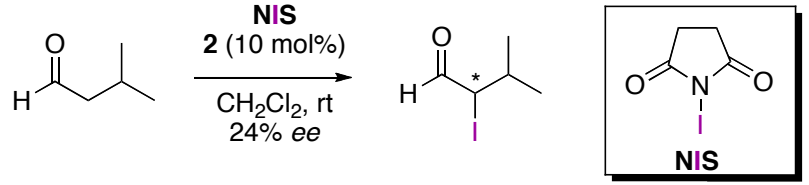
Asymmetric Halogenation of Aldehydes and Ketones: Jørgensen

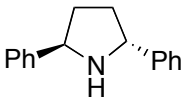






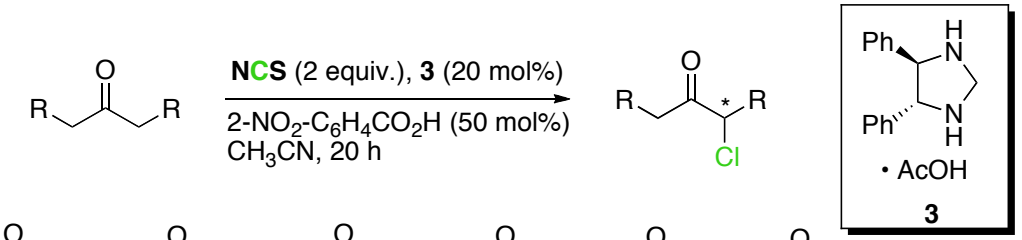
R = Me (99%, 75% *ee R*); Et (99%, 80% *ee R*); *i*-Pr (95%, 87% *ee R*); *t*-Bu (93%, 95% *ee R*); Allyl (90%, 74% *ee*); Bn (99%, 78% *ee).*

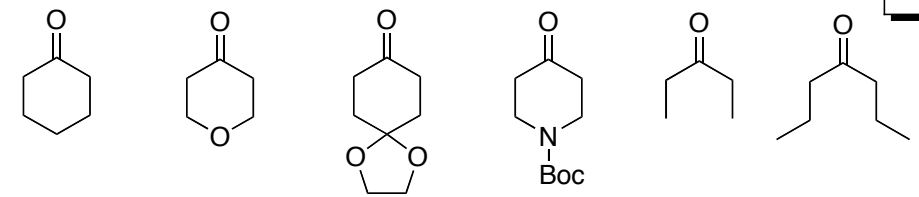




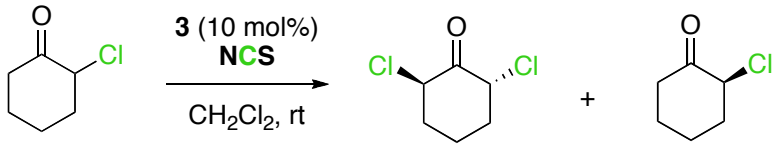
R = Et (90%, 97% *ee S*); *i*-Pr (90%, 94% *ee S*); *t*-Bu (30%, 94% *ee S*); Allyl (90%, 95% *ee*); Bn (82%, 95% *ee).*

Halland, N.; Braunton, A.; Bachmann, S.; Marigo, M.; Jørgensen, K. A. *J. Am. Chem. Soc* **2004**, *126*, 4790-4791.





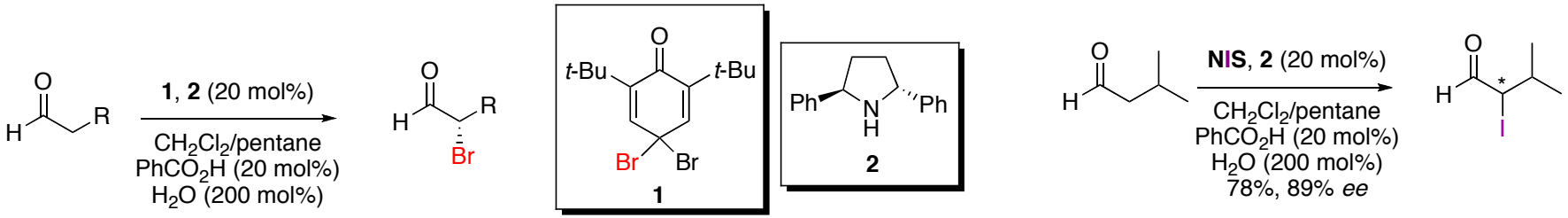
82% 97% *ee* | 72% 98% *ee* | 83% 93% *ee* | 76% 93% *ee* | 62% 86% *ee* | 40% 89% *ee*



Addition of acid:
- promotion of enamine formation
- supression of catalyst chlorination

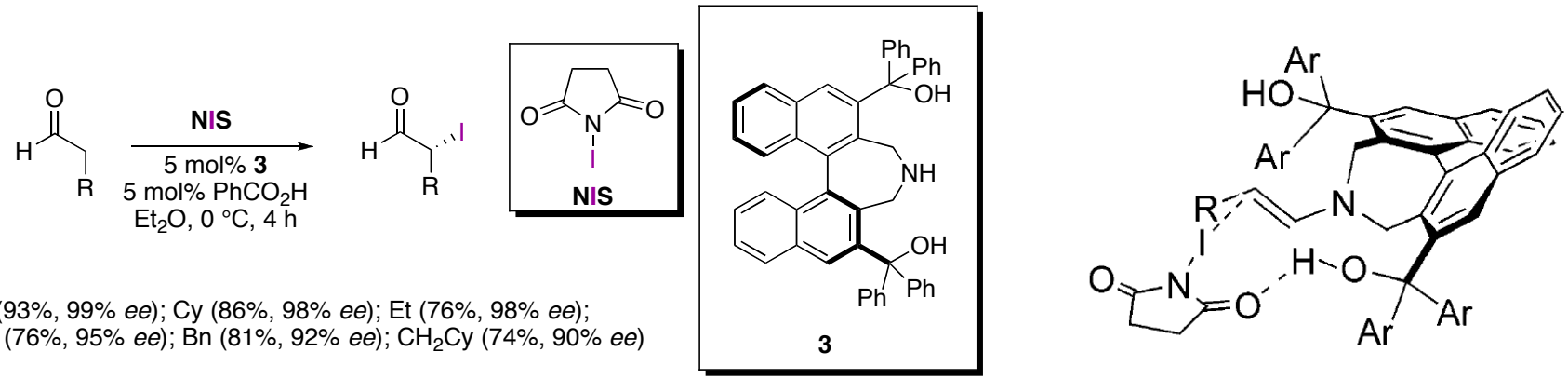
Marigo, M.; Bachman, S.; Halland, N.; Braunton, A.; Jørgensen, K. A. *Angew. Chem. Int. Ed.* **2004**, *43*, 5507-5510.

Asymmetric Bromination and Iodination of Aldehydes



R = *i*-Pr (87%, 96% *ee*); *t*-Bu (94%, 89% *ee*); Et (72%, 77% *ee*);
n-Pr (82%, 85% *ee*); Cy (92%, 73% *ee*); Allyl (74%, 76% *ee*)

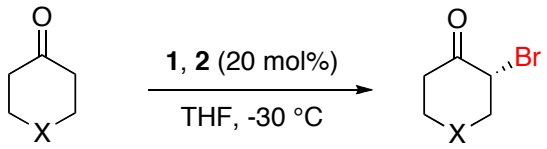
Bertelsen, S.; Halland, N.; Bachmann, S.; Marigo, M.; Braunton, A.; Jørgensen, K. A. *Chem. Commun.* **2005**, 4821-4823.



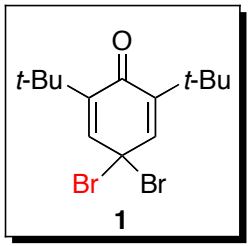
R = *i*-Pr (93%, 99% *ee*); Cy (86%, 98% *ee*); Et (76%, 98% *ee*);
Allyl (76%, 95% *ee*); Bn (81%, 92% *ee*); CH_2Cy (74%, 90% *ee*)

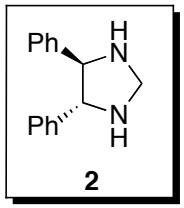
Kano, T.; Ueda, M.; Maruoka, K. *J. Am. Chem. Soc.* **2008**, *130*, 3728-3729.

Asymmetric Bromination of Ketones

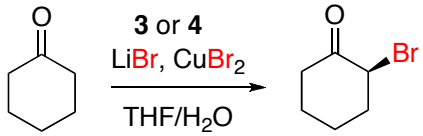


X = CH_2 (76%, 91% *ee*)
O (80%, 89% *ee*)
$C(OCH_2CH_2O)$ (67%, 73% *ee*)

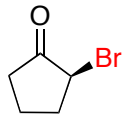




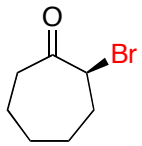
Bertelsen, S.; Halland, N.; Bachmann, S.; Marigo, M.; Braunton, A.; Jørgensen, K. A. *Chem. Commun.* **2005**, 4821-4823.



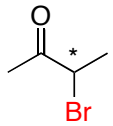
3: 78% (76% *ee*)
4: 86% (85% *ee*)



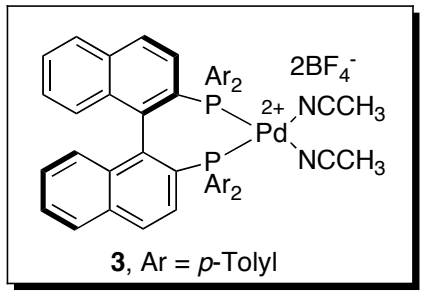
3: 75% (78% *ee*)
4: 84% (82% *ee*)

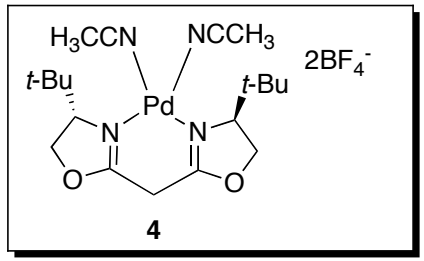


3: 70% (80% *ee*)
4: 80% (89% *ee*)



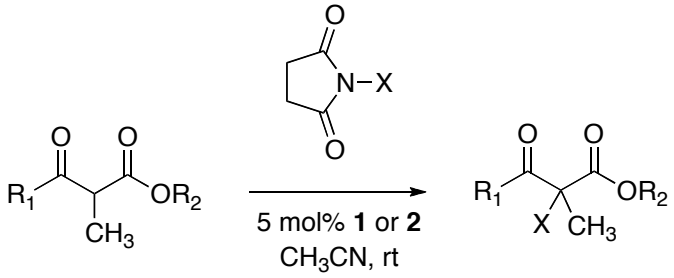
3: 80% (68% *ee*)
4: 88% (72% *ee*)

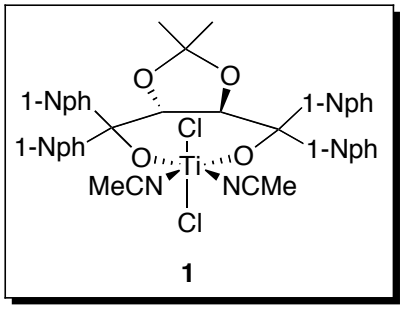




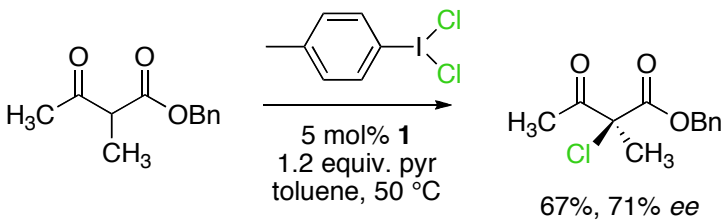
El-Qisairi, A.; Qaseer, H. *Jordan J. Chem.* **2007**, *2*, 69-78.

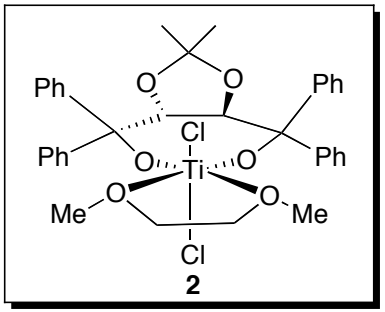
Chiral Lewis Acid Catalyzed Asymmetric Chlorinations and Brominations



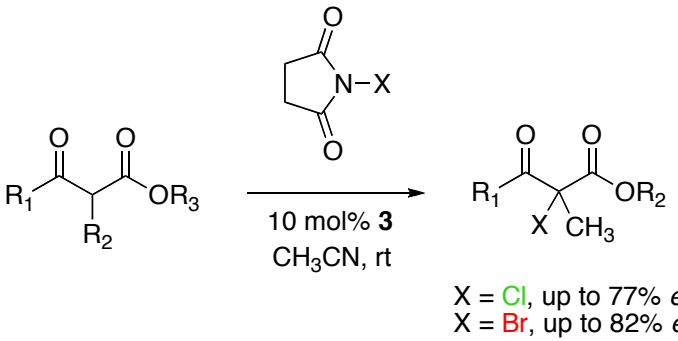


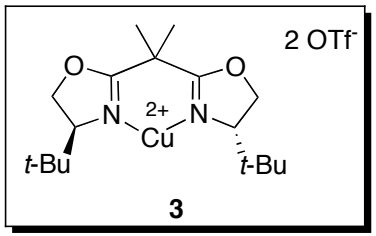
Hintermann, L.; Togni, A. *Helv. Chim. Acta* **2000**, *83*, 2425-2435.





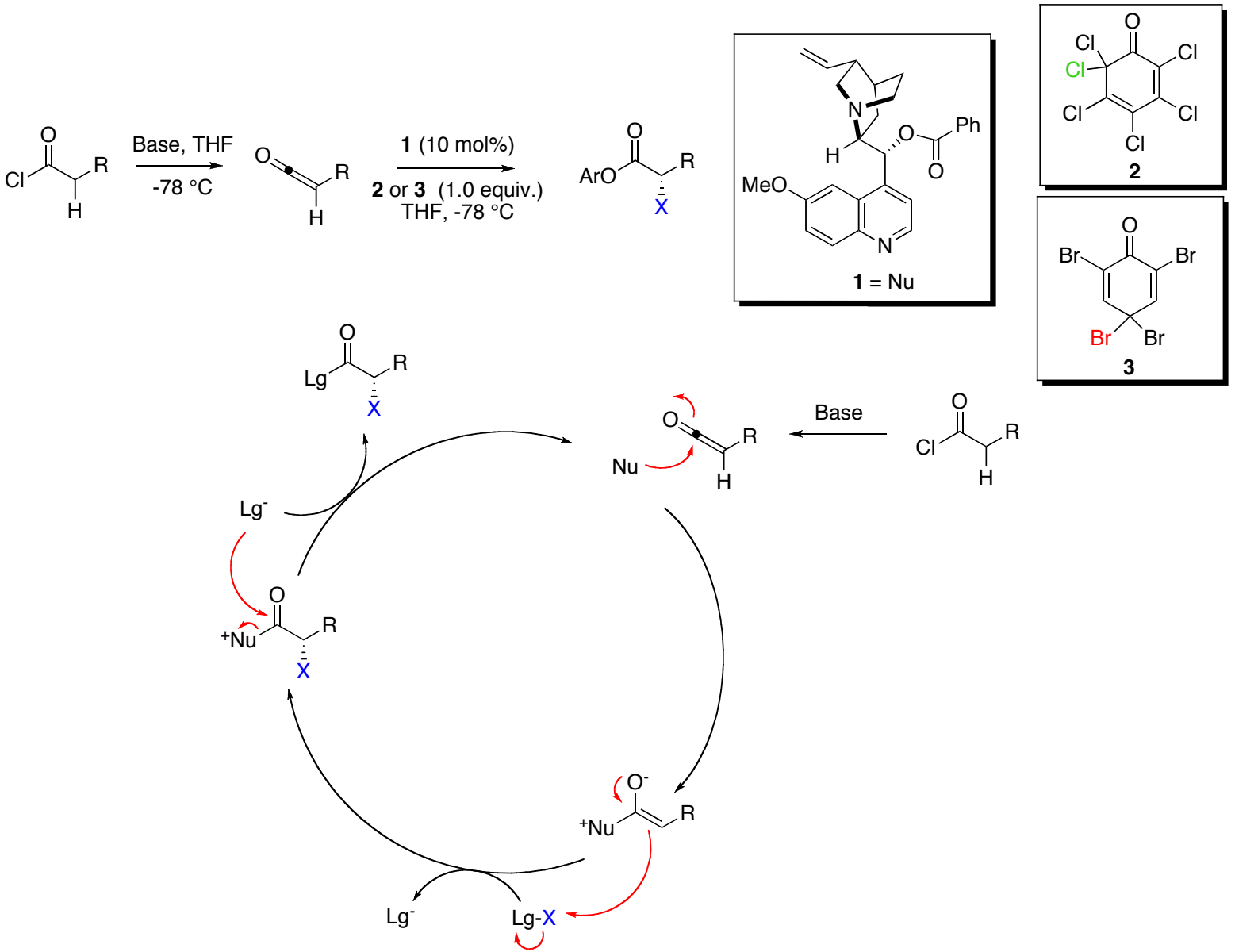
Hintermann, L.; Togni, A. *Helv. Chim. Acta* **2004**, *87*, 605-610.





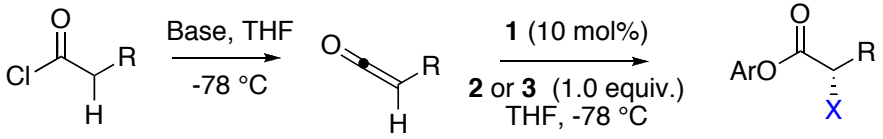
Mariago, M. ; Kumaragurubaran, N.; Jørgensen, K. A. *Chem. Eur. J.* **2004**, *10*, 2133-2137.

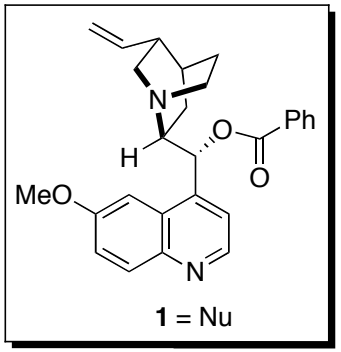
Chlorination and Bromination of Acyl Halides

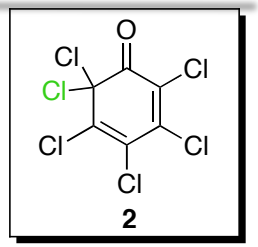


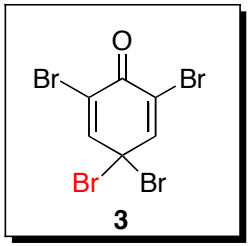
1. Wack, H.; Taggi, A. E.; Hafez, A. M.; Drury, W. J. III; Lectka, T. *J. Am. Chem. Soc.* **2001**, *123*, 1531-1532. 2. France, S.; Wack, H.; Taggi, A. E. Hafez, A. M.; Wagerle, T. R.; Shah, M. H.; Dusich, C. L.; Lectka, T. *J. Am. Chem. Soc.* **2004**, *126*, 4245-4255.

Chlorination and Bromination of Acyl Halides

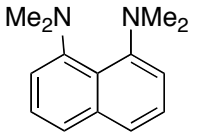




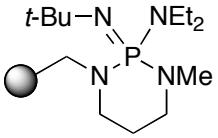




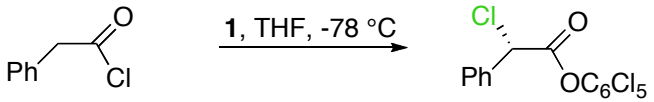
Choice of base: reactive, cheap, easy to handle



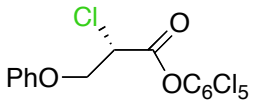
4



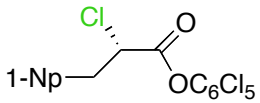
5 (BEMP)



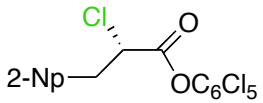
chlorination source	base	yield (%)	*ee* (%)
2	**4**	40	95
2	**5**	80	99
(*ent*-**1**) **2**	**5**	81	(*R*) 99



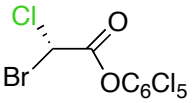
57%, 97% *ee*



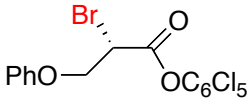
57%, 95% *ee*



63%, 94% *ee*



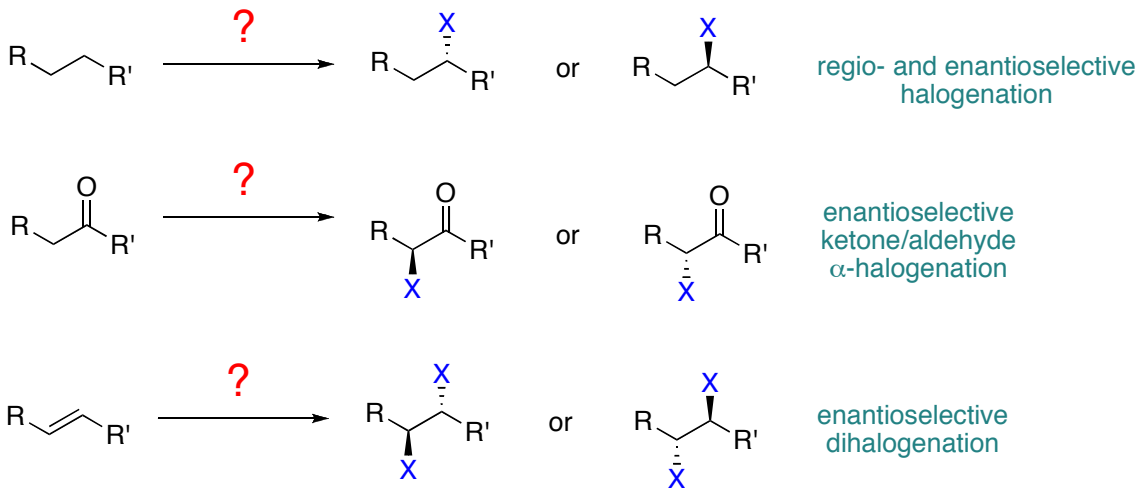
51%, 97% *ee*
(no racemization after weeks)

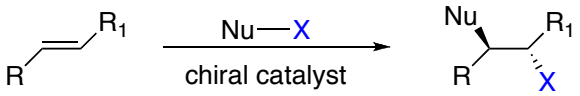


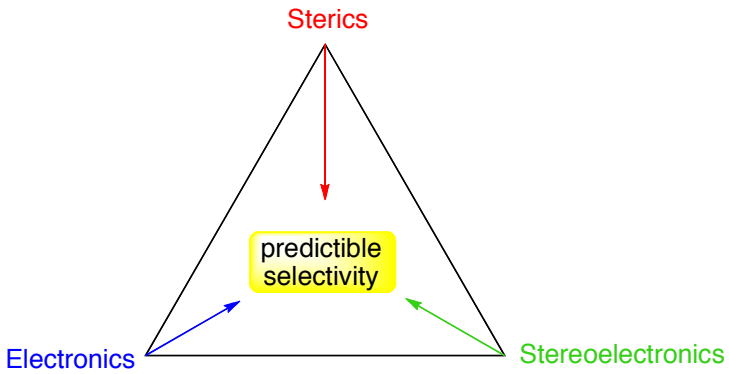
50%, 99% *ee*

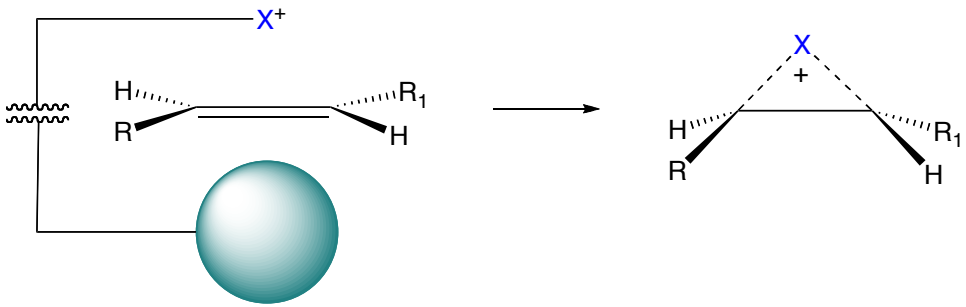
1. Wack, H.; Taggi, A. E.; Hafez, A. M.; Drury, W. J. III; Lectka, T. *J. Am. Chem. Soc.* **2001**, *123*, 1531-1532. 2. France, S.; Wack, H.; Taggi, A. E. Hafez, A. M.; Wagerle, T. R.; Shah, M. H.; Dusich, C. L.; Lectka, T. *J. Am. Chem. Soc.* **2004**, *126*, 4245-4255.

Asymmetric Halogenations

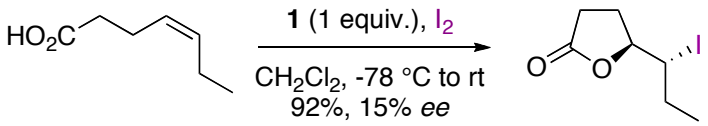


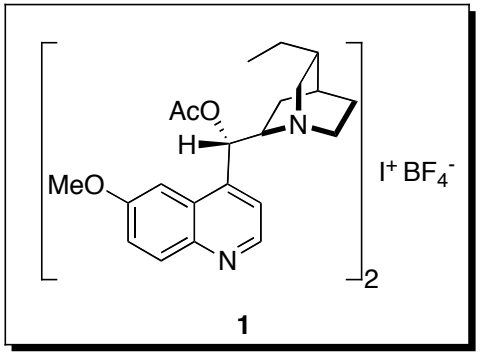




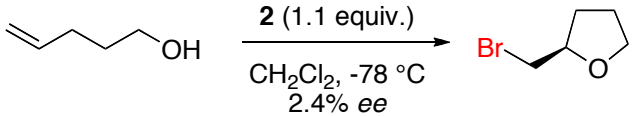


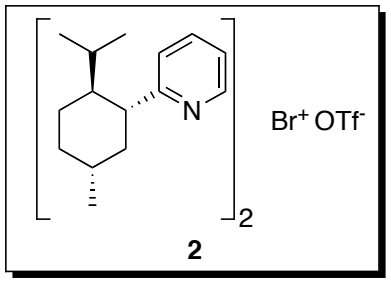
Early Times in Asymmetric Olefin Halogentaions



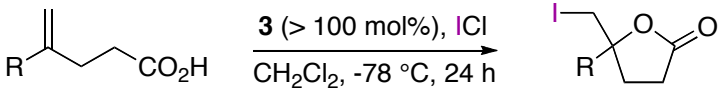


Grossman, R. B.; Trupp, R. J. *Can. J. Chem.* **1998**, *76*, 1233-1237.

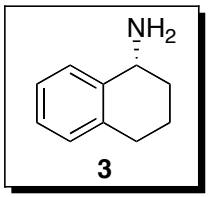




Cui, X. L.; Brown, R. S. *J. Org. Chem.* **2000**, *65*, 5653-5658.

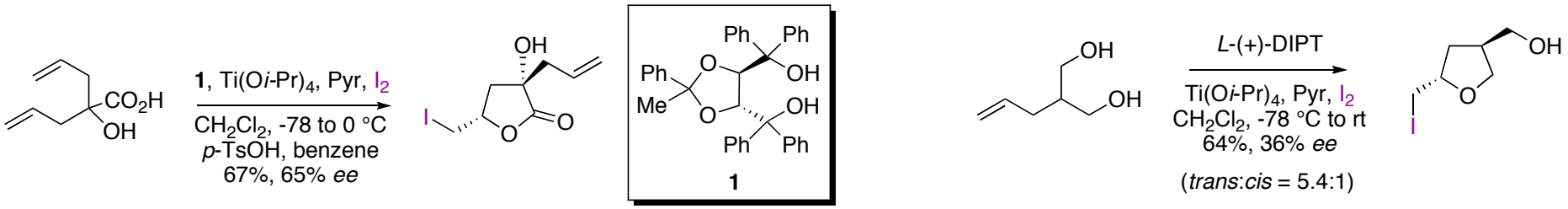


R = Ar (*ca.* 50% *ee*); R = Me (0% *ee*)

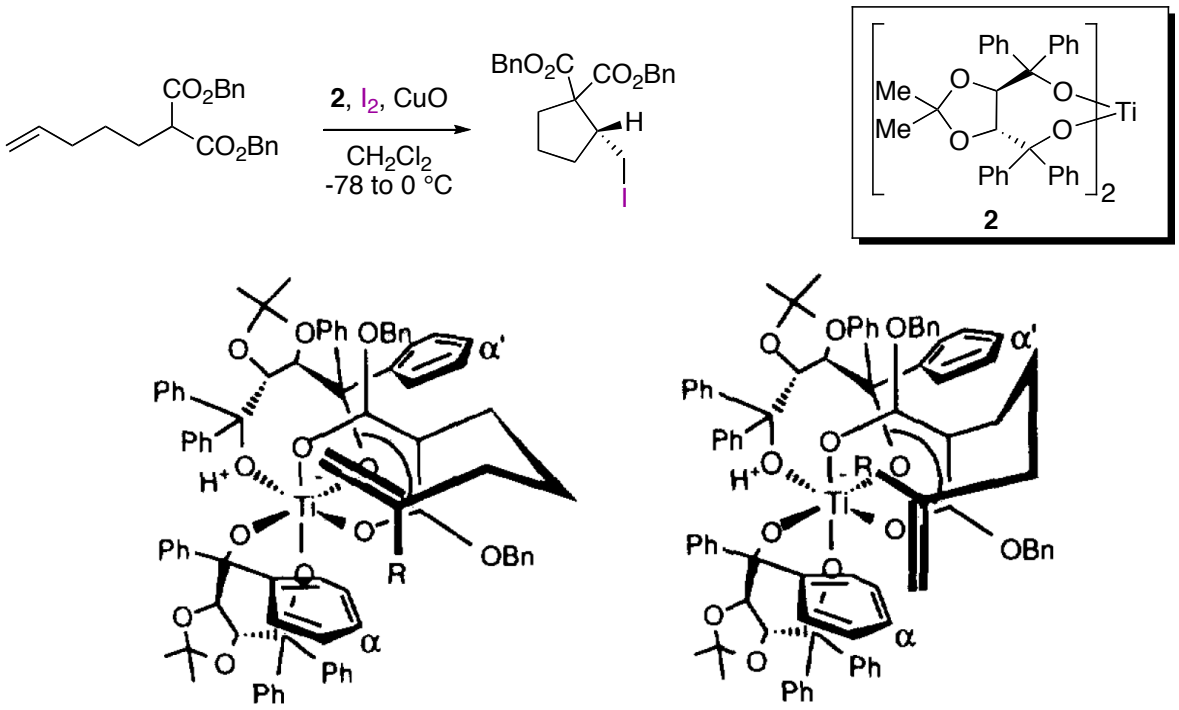


Haas, J.; Bissmire, S.; Wirth, T. *Chem. Eur. J.* **2005**, *11*, 5777-5785.

Desymmetrization by Chiral Titanium Complexes

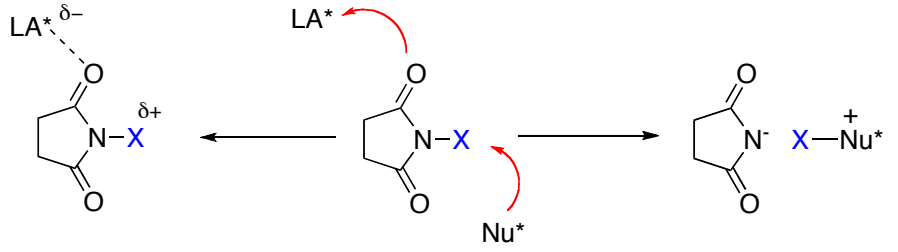


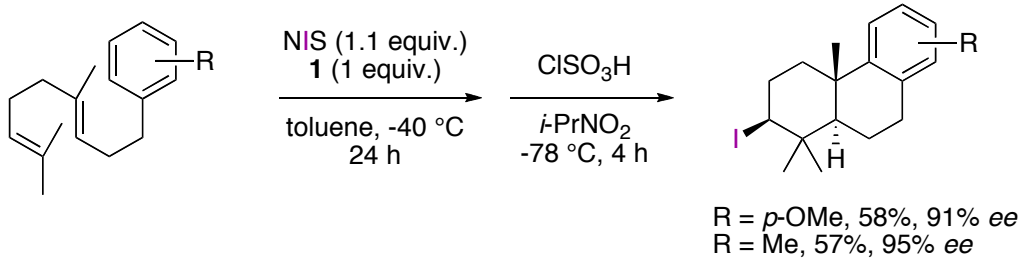
Kitagawa, O.; Hanano, T.; Tanabe, K.; Shiro, M.; Taguchi, T. *J. Chem. Soc Chem. Commun.* **1992**, 1005-1007.



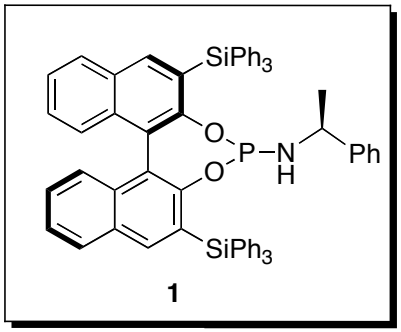
Inoue, T.; Kitagawa, O.; Ochiai, O.; Shiro, M.; Taguchi, T. *Tetrahedron Lett.* **1995**, *36*, 9333-9336.

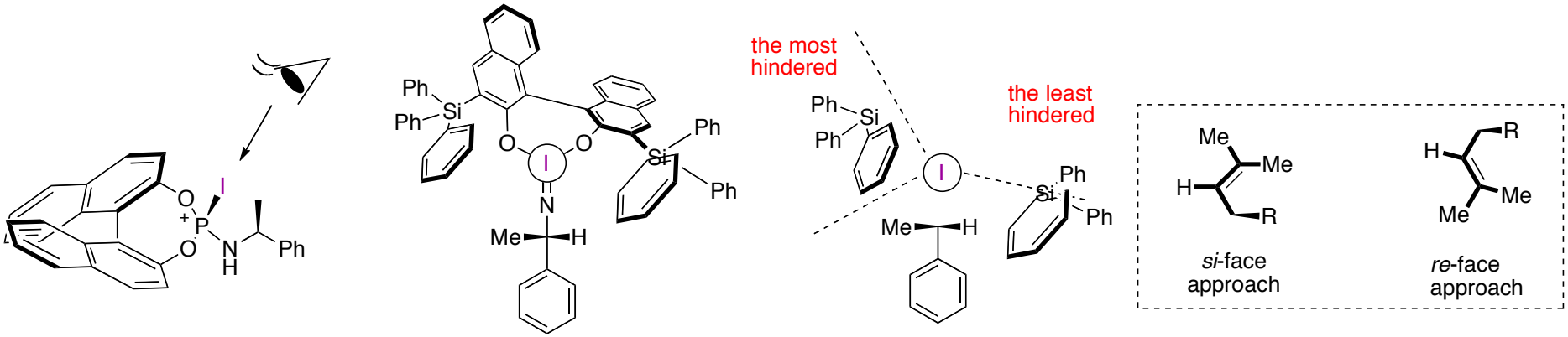
Enantioselective Halocyclization of Popyprenoids





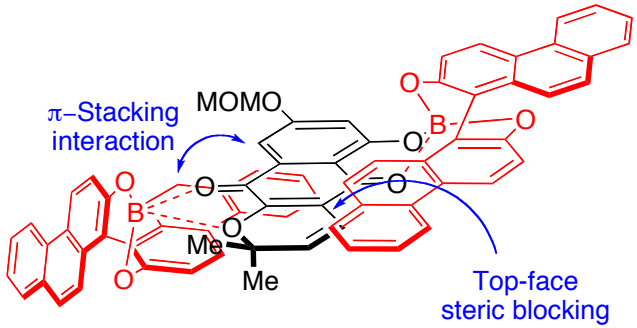
R = *p*-OMe, 58%, 91% *ee*
R = Me, 57%, 95% *ee*

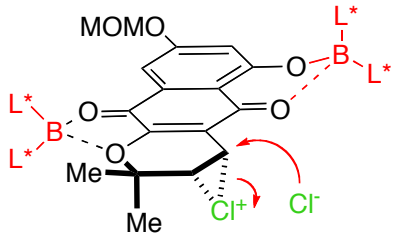


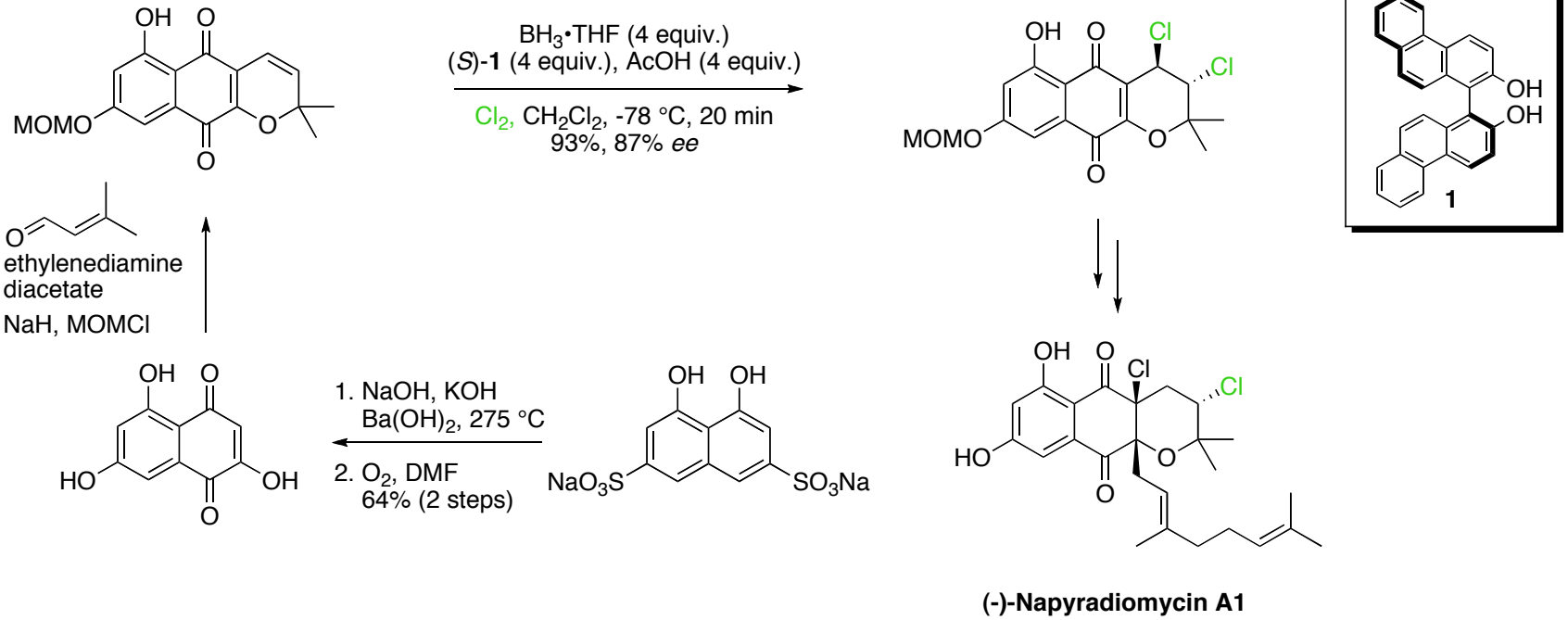


Sakakura, A.; Ukai, A.; Ishihara, K. *Nature* **2007**, *445*, 900-903.

Asymmetric Chlorination of an Isolated Olefin: Synthesis of Napyradiomycin A1

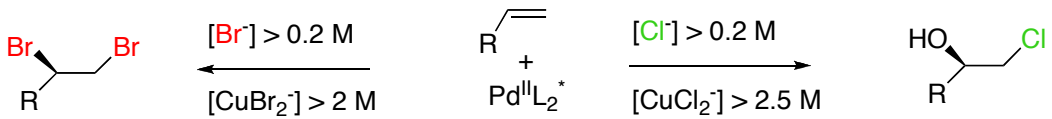


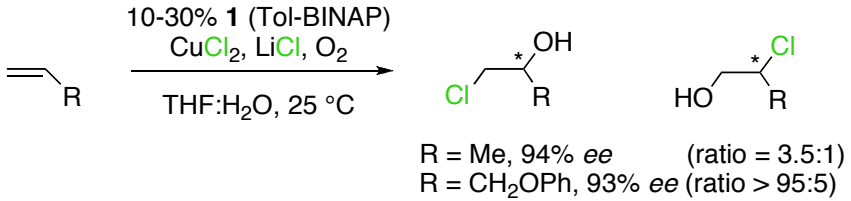


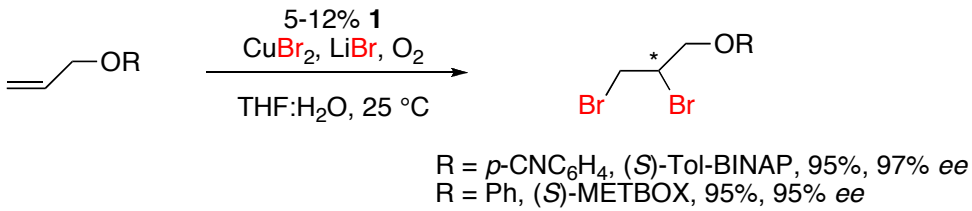


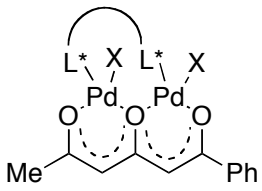
Snyder, S.A.; Tang, Z.-Y.; Gupta, R. *J. Am. Chem. Soc.* **2009**, *131*, 5744-5745.

Asymmetric Halogenations of Olefins: Catalytic Methods

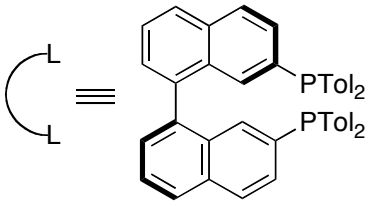




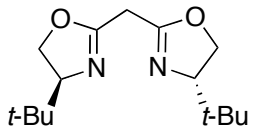




bimetallic complex **1**



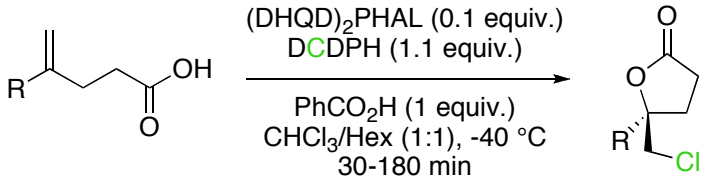
Tol-BINAP

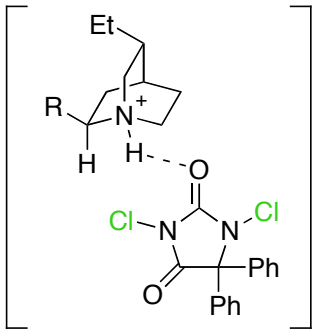


METBOX

1. El-Qisairi, A.; Hamed, O.; Henry, P. M. *J. Org. Chem.* **1998**, *63*, 2790-2791. 2. El-Qisari, A.; Quaseer, H. A.; Katsigras, G.; Lorenzi, P.; Trivedi, U.; Tracz, S.; Hartman, A.; Miller, J. A.; Henry, P. M. *Org. Lett.* **2003**, *5*, 439-441. 3. El-Qisairi, A. K.; Qaseer, H. A.; Henry, P. M. *J. Organomet. Chem.* **2002**, *656*, 168-176.

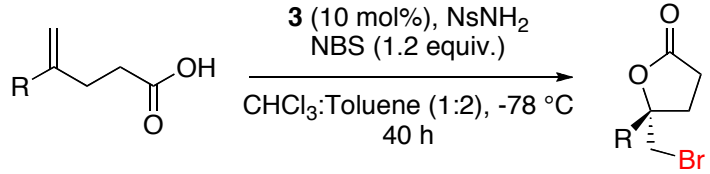
Organocatalytic Enantioselective Halolactonization

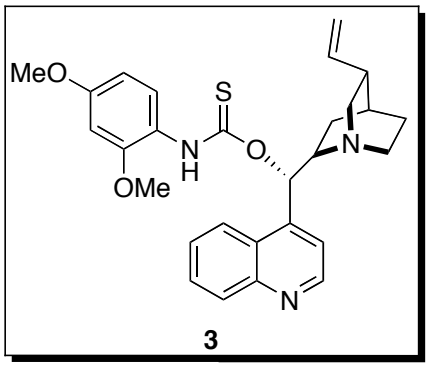




R = Ph, 86%, 89% *ee*
R = *p*-$CF_3C_6H_4$, 61%, 90% *ee*
R = Cy, 55%, 43% *ee*

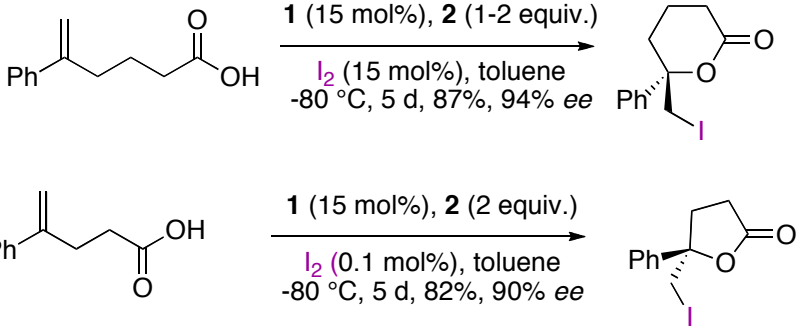
Whitehead, D. C.; Yousefi, R.; Jaganathan, A.; Borhan, B. *J. Am. Chem. Soc.* **2010**, *132*, 3298-3300.

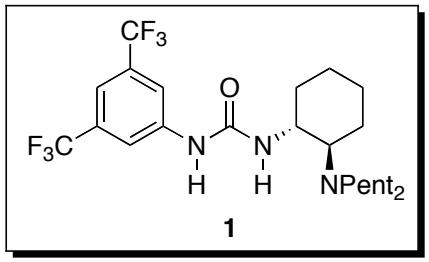




R = Ph, 99%, 90% *ee*
R = *p*-$CF_3C_6H_4$, 71%, 85% *ee*
R = Cy, 99%, 92% *ee*

Zhou. L.; Tan, C. K.; Jiang, X.; Chen, F.; Yeung, Y. -Y. *J. Am. Chem. Soc.* **2010**, *132*, 15474-15476.





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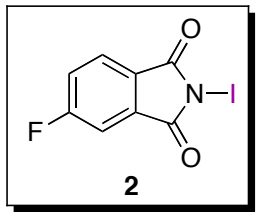

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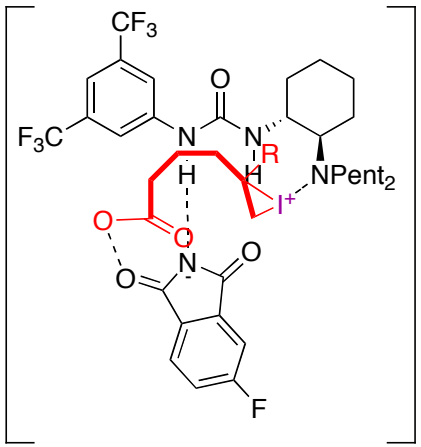
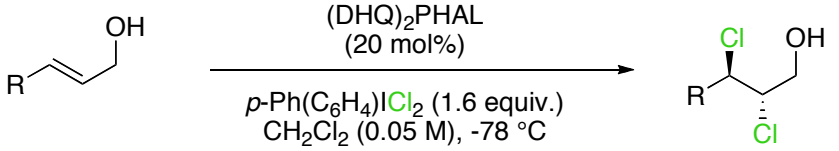
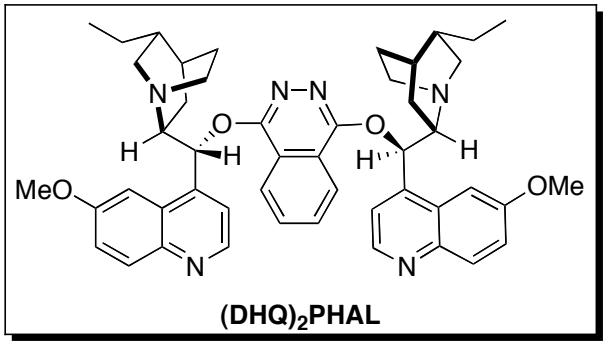
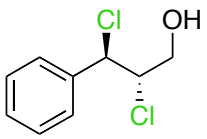


Veitch, G. E.; Jacobsen, E. N. *Angew. Chem. Int. Ed.* **2010**, *49*, 7332-7335.

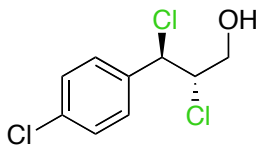
Enantioselective Dichlorination of Allylic Alcohols



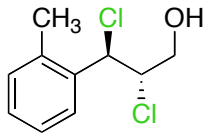




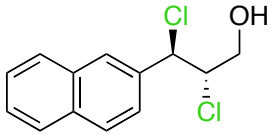
63%, 81% *ee*



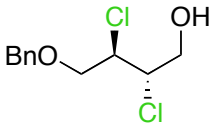
81%, 71% *ee*



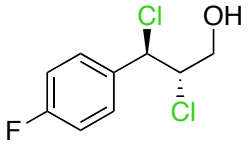
63%, 68% *ee*



84%, 74% *ee*

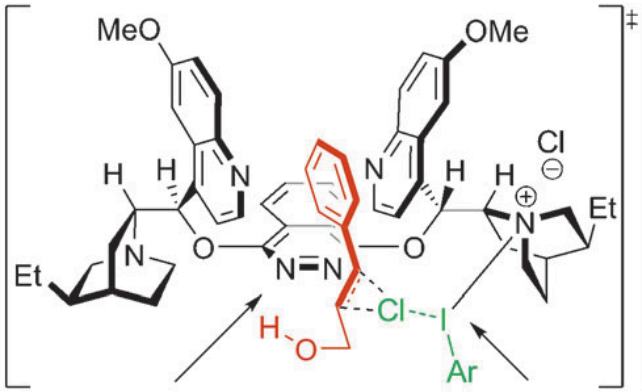


59%, 54% *ee*

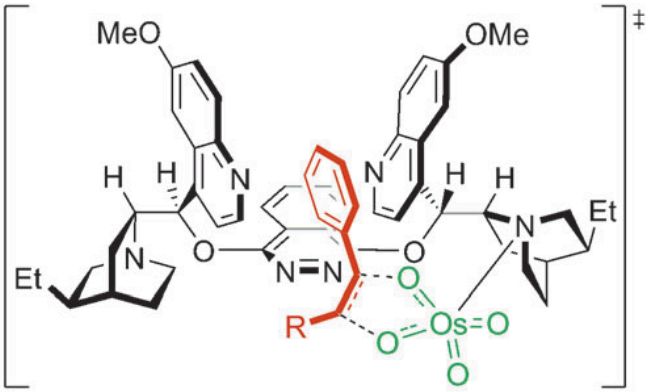


73%, 72% *ee*

"electrophilic chlorination"
proposed transition state

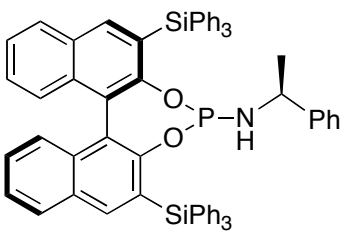


"Sharpless AD"
proposed transition state

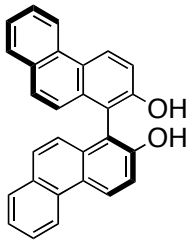


Nicolaou, K.C.; Simmons, N.L.; Ying, Y.; Heretsch, P.M.; Chen, J.S. *J. Am. Chem. Soc.* **2011**, *133*, 8134-8137.
Monaco, M. R.; Bella, M. *Angew. Chem. Int. Ed.* **2011**, *50*, 2-5.

Conclusions



Ishihara



Snyder

C-F, C-Cl, C-Br, C-I

enzymatically

NATURE

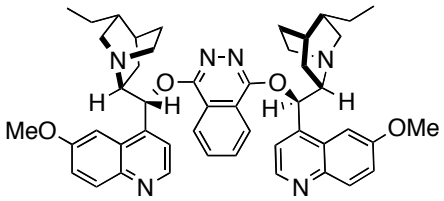
Vaillancourt, F. H.; Yeh, E.; Vosburg, D. A.; Garneau-Tsodikova, S.; Walsh, C. T. *Chem. Rev.* **2006**, *106*, 3364-3378.

asymmetric halogenations of olefines

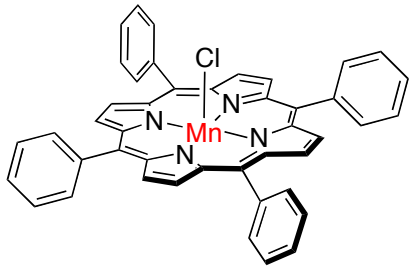
C—X

unactivated C-H chlorination

Groves, J. T. (Mn); Fuijii, H. (Fe); Ricci, M. (Ni)



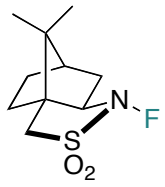
Nicolaou



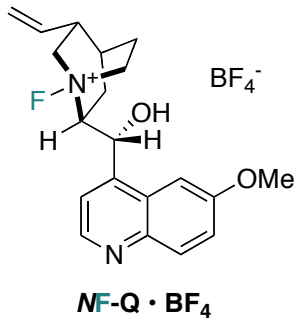
α-halogenations of carbonyl compounds

Sodeoka (Pd); Togni (Ru); Cahard (Cu); Shibata, Toru (Cu, Ni)

Lectka: chlorination and bromination of acyl chlorides

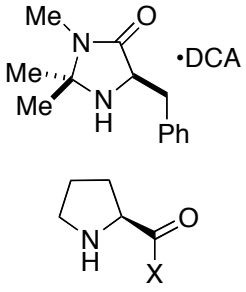


Differding, Lang
Takeuchi, Davis

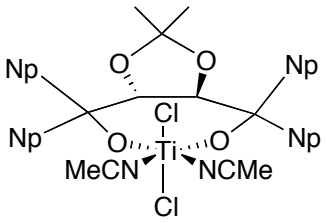


***N*F-Q · BF$_4$**

Takeuchi, Cahard

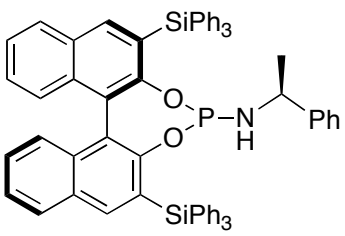


MacMillan, Jorgensen

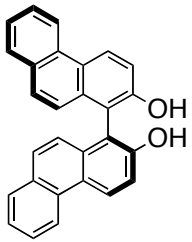


Togni

Conclusions



Ishihara



Snyder

C-F, C-Cl, C-Br, C-I

enzymatically

NATURE

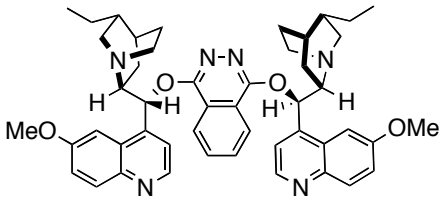
Vaillancourt, F. H.; Yeh, E.; Vosburg, D. A.; Garneau-Tsodikova, S.; Walsh, C. T. *Chem. Rev.* **2006**, *106*, 3364-3378.

asymmetric halogenations of olefines

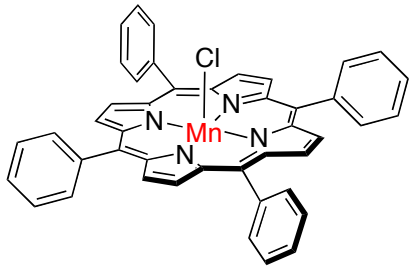
C—X

unactivated C-H chlorination

Groves, J. T. (Mn); Fuijii, H. (Fe); Ricci, M. (Ni)



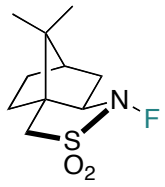
Nicolaou



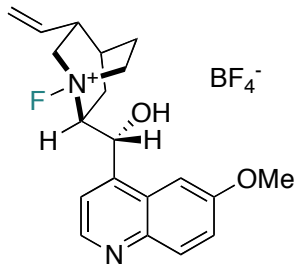
α-halogenations of carbonyl compounds

Sodeoka (Pd); Togni (Ru); Cahard (Cu); Shibata, Toru (Cu, Ni)

Lectka: chlorination and bromination of acyl chlorides

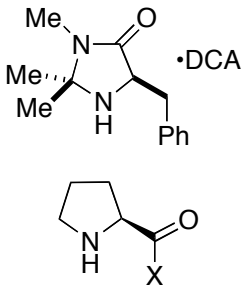


Differding, Lang
Takeuchi, Davis

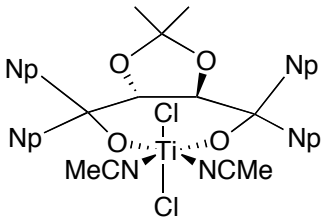


***N*F-Q · BF$_4$**

Takeuchi, Cahard



MacMillan, Jorgensen



Togni