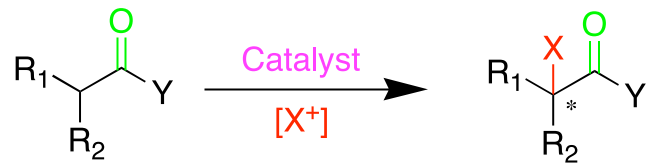
Strategies for Catalytic Asymmetric Electrophilic a Halogenation of Carbonyl Compounds



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

Hamashima, Y.; Sodeoka, M. et al *J. Am. Chem. Soc.* **2002**, *124*, 14530 –14531

France, S.; Lectka, T. et al *J. Am. Chem. Soc.* **2004**, *126*, 4245 – 4255

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

Halland, N. ; Jørgensen, K. A. et al *J. Am.Chem. Soc*. **2004**, *126*, 4790 – 4791

Marigo, M. ; Jørgensen, K. A. et al *Angew. Chem. Int. Ed.* **2004**, *43*, 5507 – 5510

Zhang, Y. ; Shibatomi, K.; Yamamoto, H. *J. Am. Chem. Soc.* **2004**, *126*, 15038 –15039

Marigo, M. ; Jørgensen, K. A. et al *Angew. Chem. Int. Ed.* **2005**, *44*, 2 – 5 (*early view*)

Ali Z. Ding

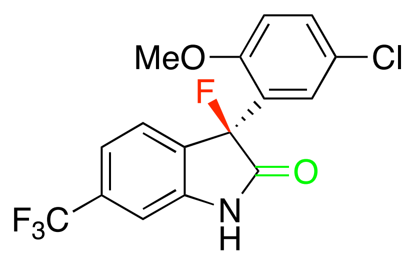
Advisor: Prof. W. D. Wulff

MICHIGAN STATE
UNIVERSITY

May 12 2005

a–Halogenated Carbonyl Compounds

- Linchpins for further stereospecific manipulations
- Halogen substituents can sometimes dramatically alter its physical, chemical and biological properties
- Increasingly important structural motifs in medicinal chemistry and material sciences.



BMS-204352
MaxiPost

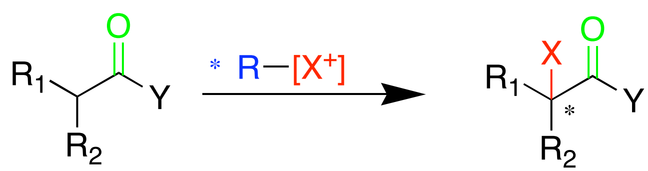
Currently being assessed worldwide in phase III clinical trials for treatment of acute ischemic stoke

Oestreich, M. *Angew. Chem. Int. Ed.*, **2005,** *44*, 2324-2327
Ibrahim, H.; Togni, A. *Chem. Commun.* **2004**, 1147 – 1155

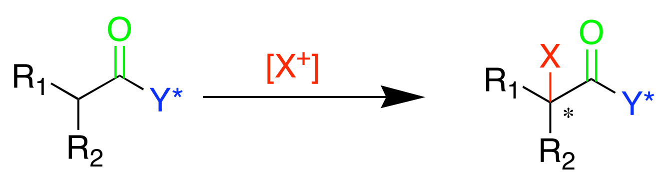
Introduction

Approaches to the Chiral a-Halogenated Carbonyl Compounds

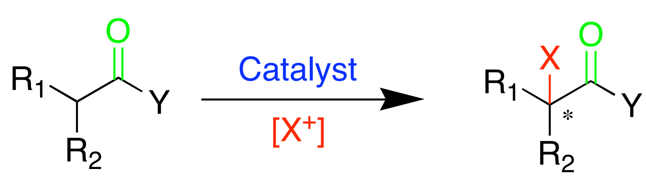
(1) Reagent-controlled halogenation: asymmetric halogenation of enolates using chiral electrophilic halogenating agents



(2) Substrate-controlled halogenation: diastereoselective electrophilic halogenation of chiral enolates or enol ethers



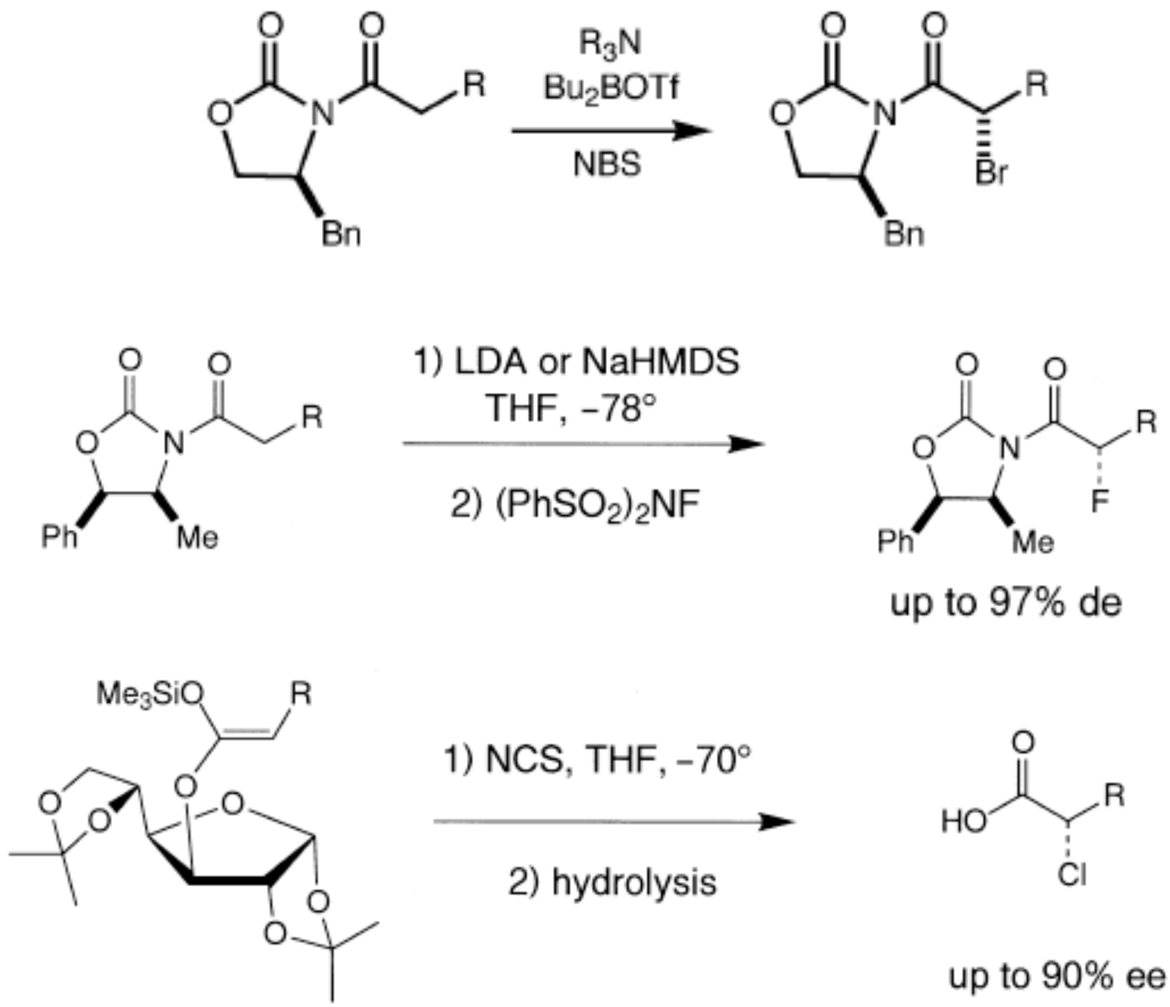
(3) Catalytic asymmetric halogenation of carbonyl compounds



Oestreich, M. *Angew. Chem. Int. Ed.*, **2005,** *44*, 2324-2327

Taylor, S. D.; Kotoris, C. C. and Hum, G. *Tetrahedron*, **1999,** *55,*12431-12477

Substrate-controlled Halogenation: Use of Chiral Auxiliaries

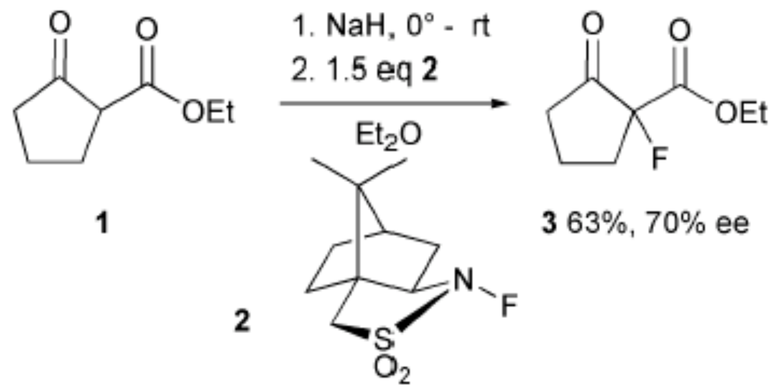


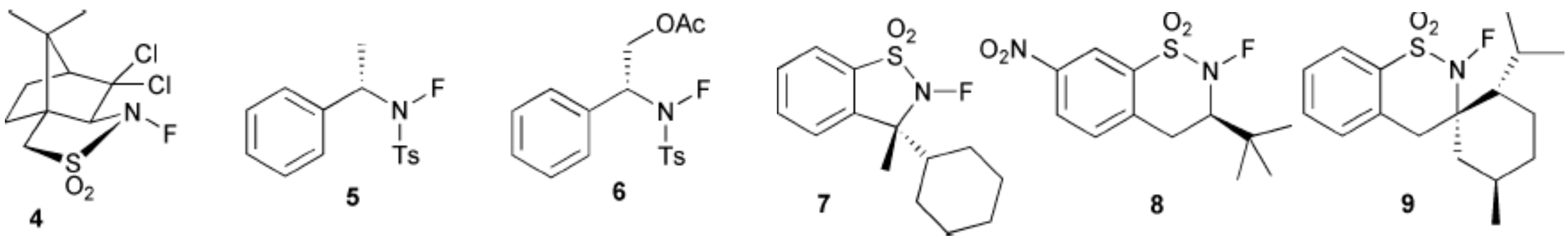
Oestreich, M. *Angew. Chem. Int. Ed.*, **2005,** *44*, 2324-2327

Taylor, S. D.; Kotoris, C. C. and Hum, G. *Tetrahedron*, **1999,** *55*,12431-12477

Reagent-controlled Halogenation: Chiral Fluorinating Reagents

Pioneering work: Differding, E. and Lang, R. W. *Tetrahehron Lett*. **1988**, *29*, 6087-6090



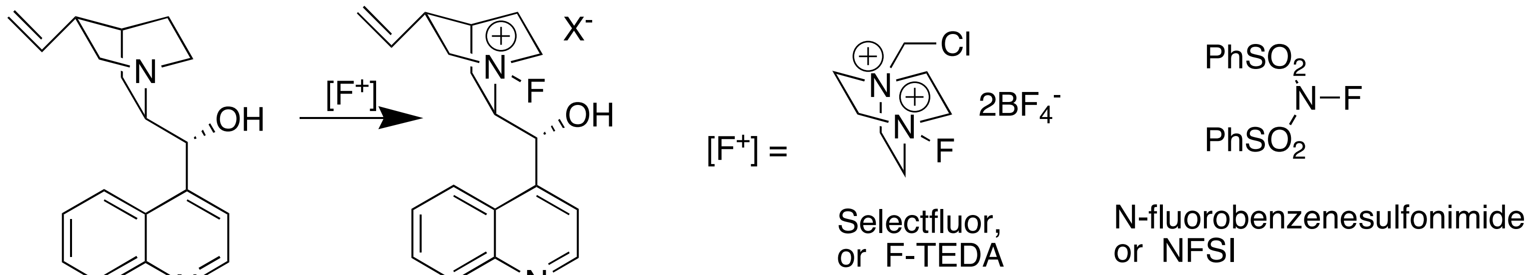


- Moderate yields and low to moderate enantioselectivities
- Syntheses of these reagents require several steps

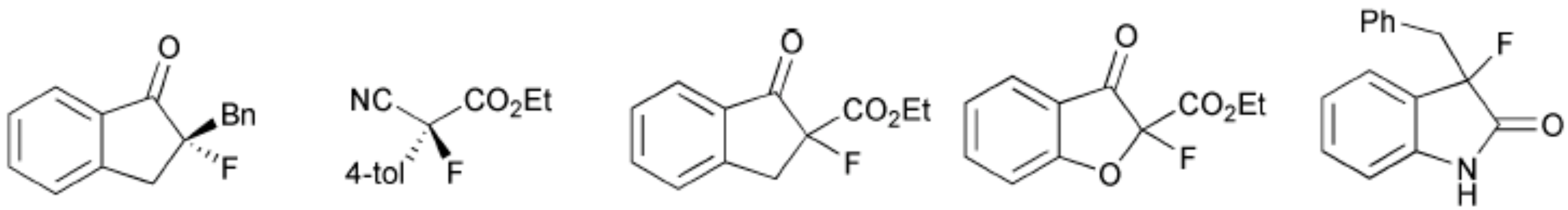
Wong, C.-H., *Angew*. *Chem*. *Int*. *Ed*., **2005,** *44*, 192

Taylor, S. D.; Kotoris, C. C. and Hum, G. *Tetrahedron*, **1999,** *55*,12431-12477

Reagent-controlled Halogenation: Cinchona Alkaloids Fluorinating Reagents



10 11 12 13



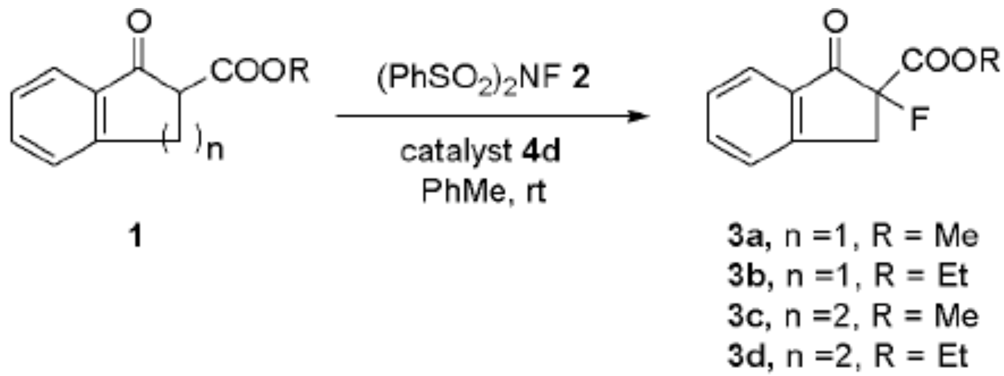
86%, 91% ee | 80%, 87% ee | 89%, 78% ee | 92%, 80% ee | 100%, 78% ee

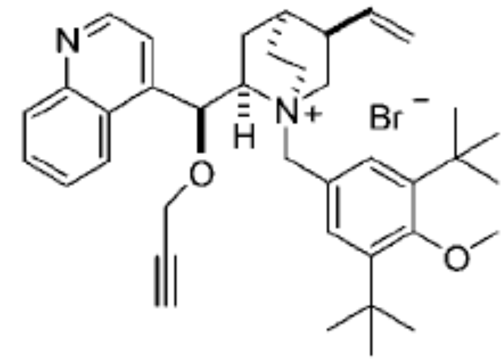
- Cinchona alkaloids (CA) are readily available in both pseudo-enantiomeric forms
- Easily prepare, more reactive
- Can be generated and used *in situ*
- Can be "reloaded" by F-TEDA or NFSI and reused without loss in selectivity

Can such CA be used catalytically in these reactions?

Ibrahim, H.; Togni, A. *Chem. Commun.* **2004**, 1147 – 1155

Organo-Catalytic Enantioselective Fluorination by Phase-Transfer Catalysts





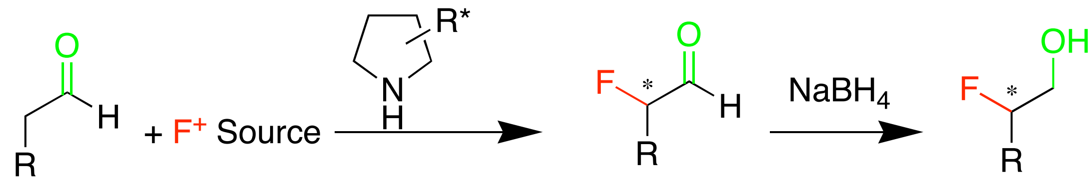
4d

entry	*n*	R	base	yields (%)	ee[a](%)
1	1, **1a**	Me	K_2CO_3	**3a**, 92	69
2	1, **1a**	Me	Cs_2CO_3	**3a**, 94	60
3	1, **1b**	Et	K_2CO_3	**3b**, 92	50
4	1, **1b**	Et	Cs_2CO_3	**3b**, 91	63
5	2, **1c**	Me	RbOH	**3c**, 87	40
6	2, **1c**	Me	Cs_2CO_3	**3c**, 88	48
7	2, **1d**	Et	K_2CO_3	**3d**, 74	41
8	2, **1d**	Et	CsOH	**3d**, 78	52

[a] Enantiopurity of **3** were determined by HPLC analysis with a Chiralcel OD-H column, 2-propanol−hexane (1:9), 1.0 mL/min, λ_{max} = 254 nm. It was established by analysis of racemic **3** that the enantiomers were fully resolved. The excessive enantiomer was (+)-**3**.

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

Organo-Catalytic Enantioselective Fluorination by L-Proline Derevatives



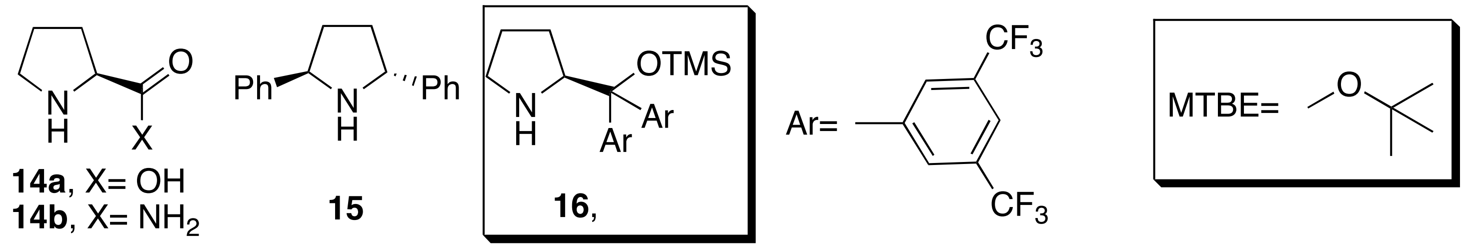
Challenges:

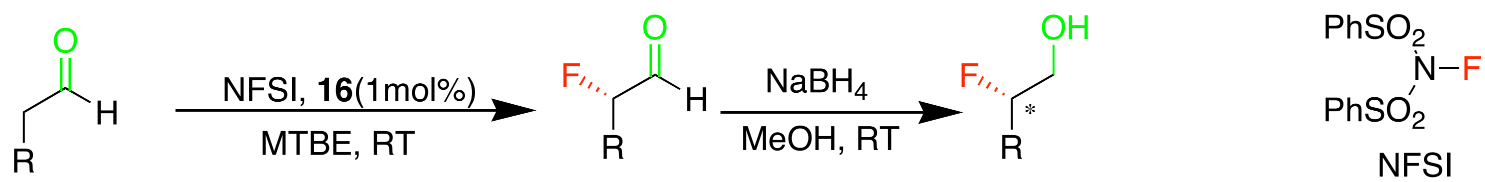
- N-fluorination of catatlyst
    - Fluorination of substrate should be faster
- Racemization and difluorination
    - Both SM and product can form enamine species
    - a-proton of product is more acidic
    - F atom is not big enough to contribute to an added steric shielding
- Products are not stable to survive silica gel

- Screen catalysts and solvents
- Lower the catalyst loading
- Screen fluorinating reagents

Marigo, M. ; Jørgensen, K. A. *et al Angew. Chem. Int. Ed.* **2005**, *44*, 2 – 5

Organo-Catalytic Enantioselective Fluorination by L-Proline Derevatives





R= Pr (96%ee), Bu(91%ee), Hex (96%ee), BnO(CH_2)$_3$(91%ee), Yield: 55-95%

Bn (93%ee), Cy (96%ee), tBu(97%ee), 1-Ad (96%ee)

- In the solvents other than MTBE, catalyst **16** decomposes
- Products were reduced to alcohol in situ

Dr. MacMillan's Work:

Enantioselective Organocatalytic Direct a-Fluorination:

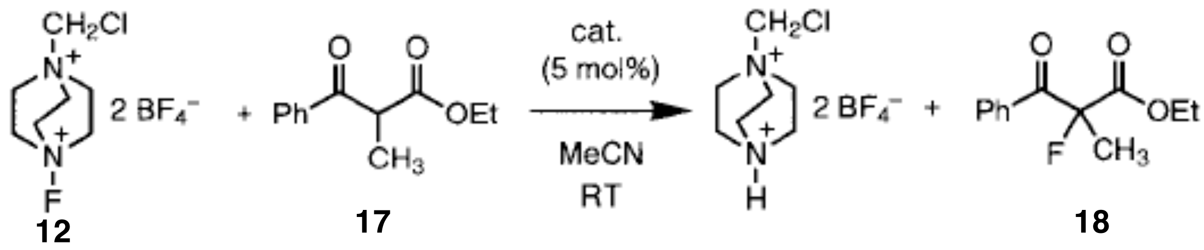
Beeson, T. D. and MacMillan, D. W. C. *J. Am. Chem. Soc.* **2005,** *127*, *in press*

True nucleophiles toward electrophilic fluorine: enols, enolates or enamines

Marigo, M. ; Jørgensen, K. A. *et al Angew. Chem. Int. Ed.* **2005**, *44*, 2 – 5

Chiral Lewis Acid Catalyzed Asymmetric Fluorination

- Addition of sub-stoichiometric amount of Lewis acid significantly accelerates formation of fluorination product



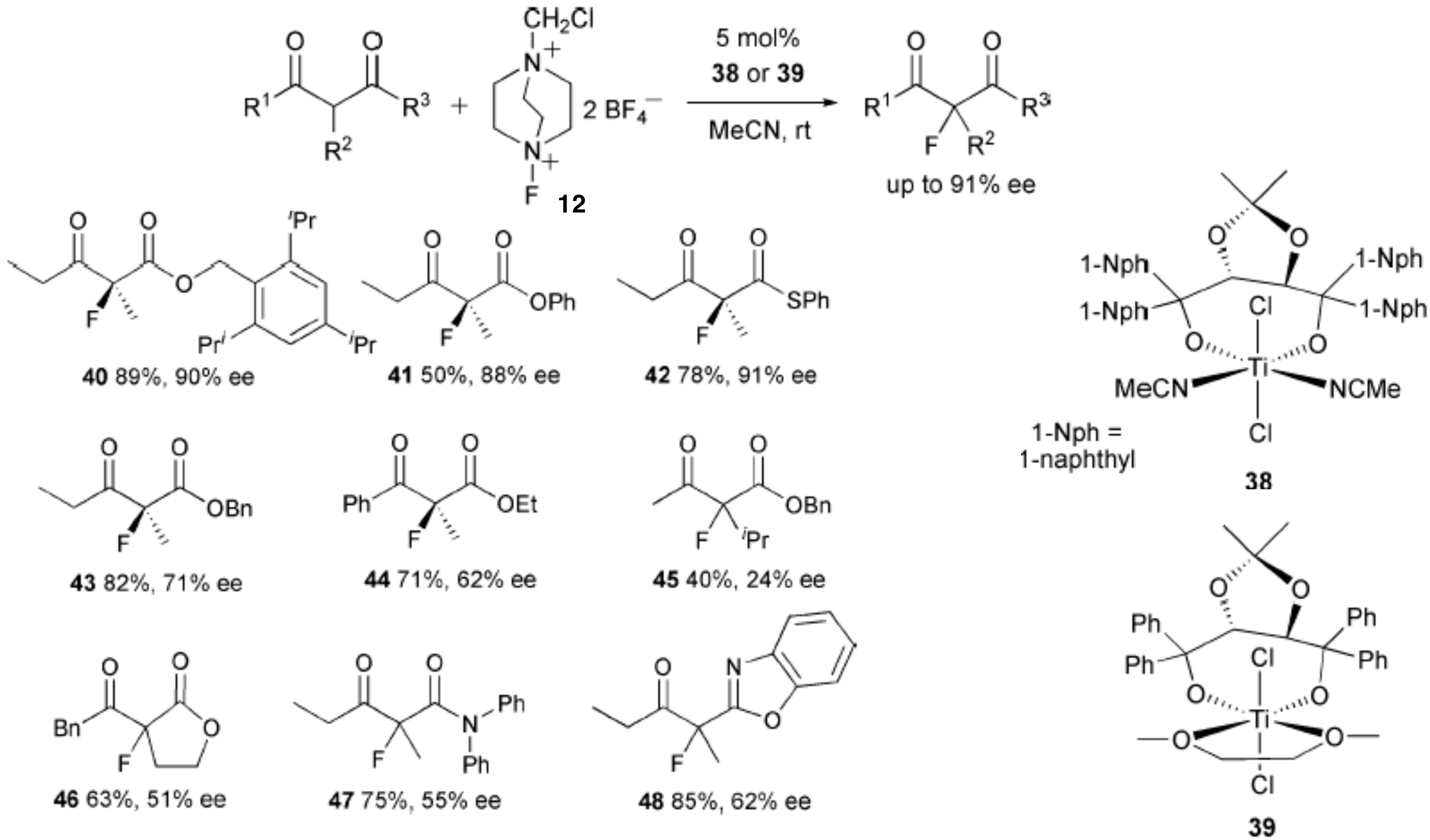
Very fast (<1 h)	Fast (<1 d)	Slow (≤2 w)	Very slow or no reaction (>2 w)
$TiCl_4$	$[CpTiCl_3]$	$[Cp_2Ti(OTf)_2]$	$[Cp_2TiCl_2]$
$AlCl_3$	$[TiCl_2(diolato)]$	HBF_4	HCl
		BF_3	$ZnCl_2$
		Me_3SiOTf	$Cu(ClO_4)_2$
			$[Cp_2Zr(OTf)_2]$
			TiF_4
			$TaCl_5$
			$Yb(OTf)_3$

Ti-based Lewis acids are the most potent catalysts

Umemoto, T et al *J. Am. Chem. Soc.*, **1990**, *112*, 8563–8575

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

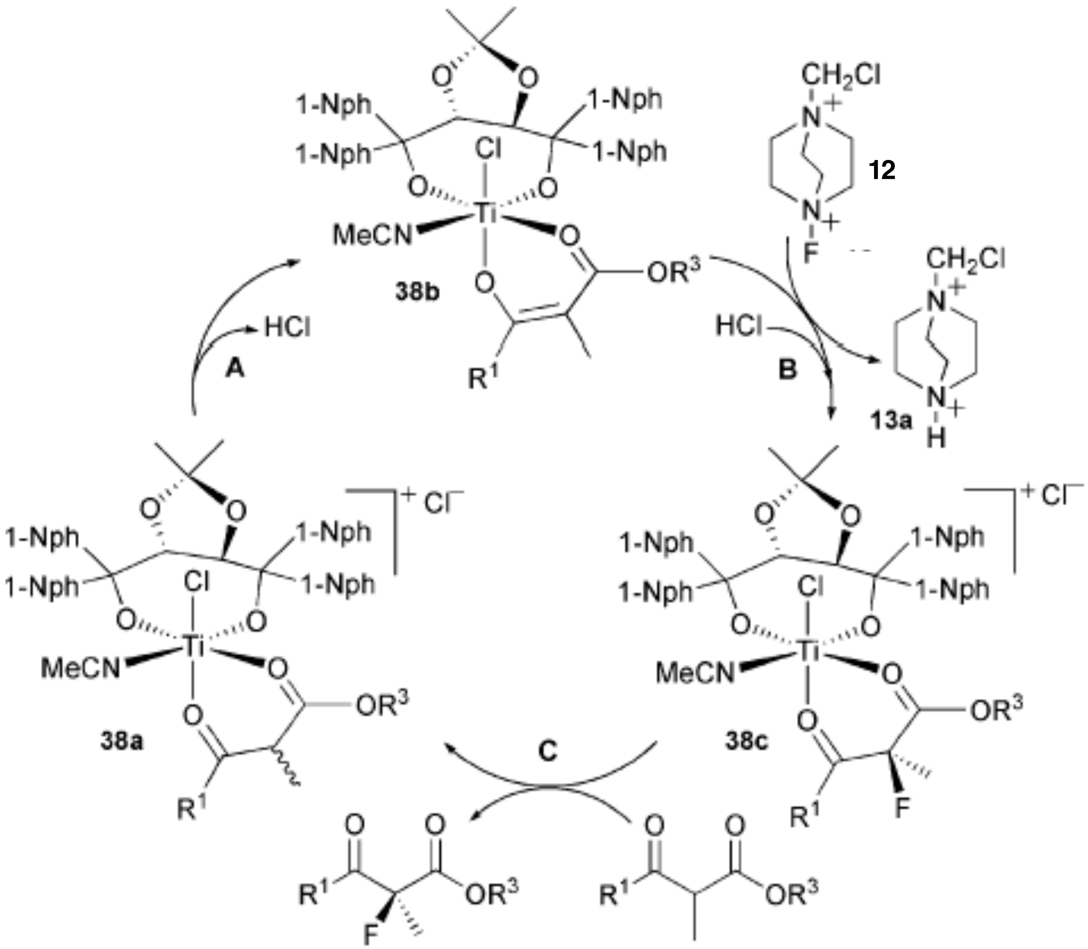
$TiCl_2$ [R,R-(TADDOLLato)] Catalyzed Asymmetric Fluorination

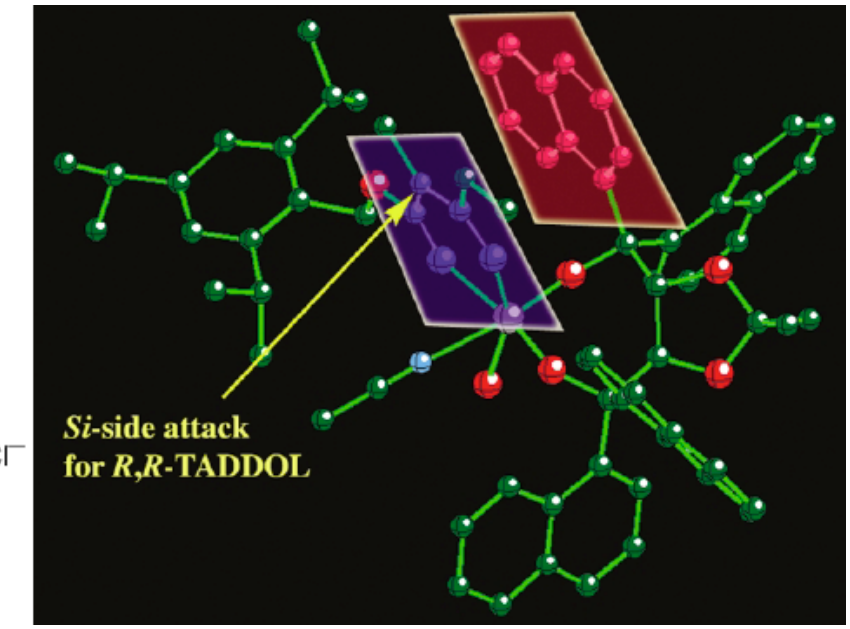


Hintermann, L. ; Togni, A. *Angew. Chem. Int. Ed.* **2000**, *39*, 4359 – 4362

Ibrahim, H.; Togni, A. *Chem. Commun.* **2004**, 1147 – 1155

Mechanism of Ti Catalyzed Asymmetric Fluorination



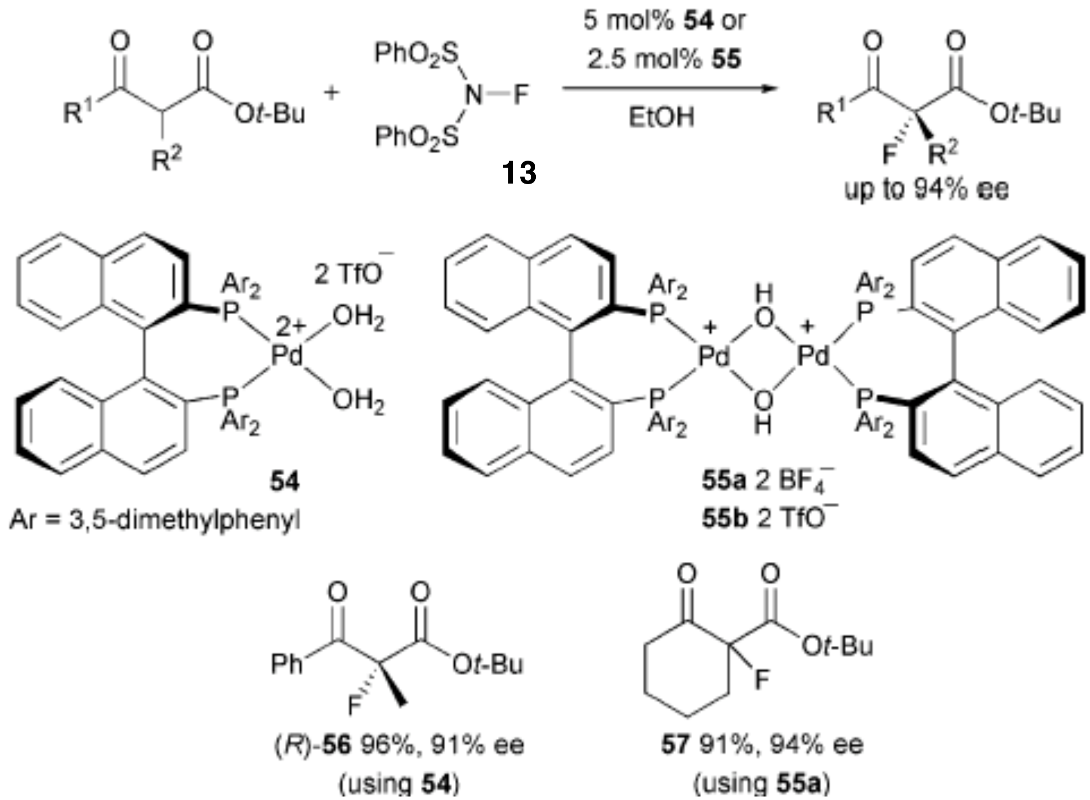


The bidentate nature of substrates is beneficial for high facial selectivity

Piana, S.; Togni, A. et al *Angew. Chem., Int. Ed.*, **2002**, *41*, 979–982

Ibrahim, H.; Togni, A. *Chem. Commun.* **2004**, 1147 – 1155

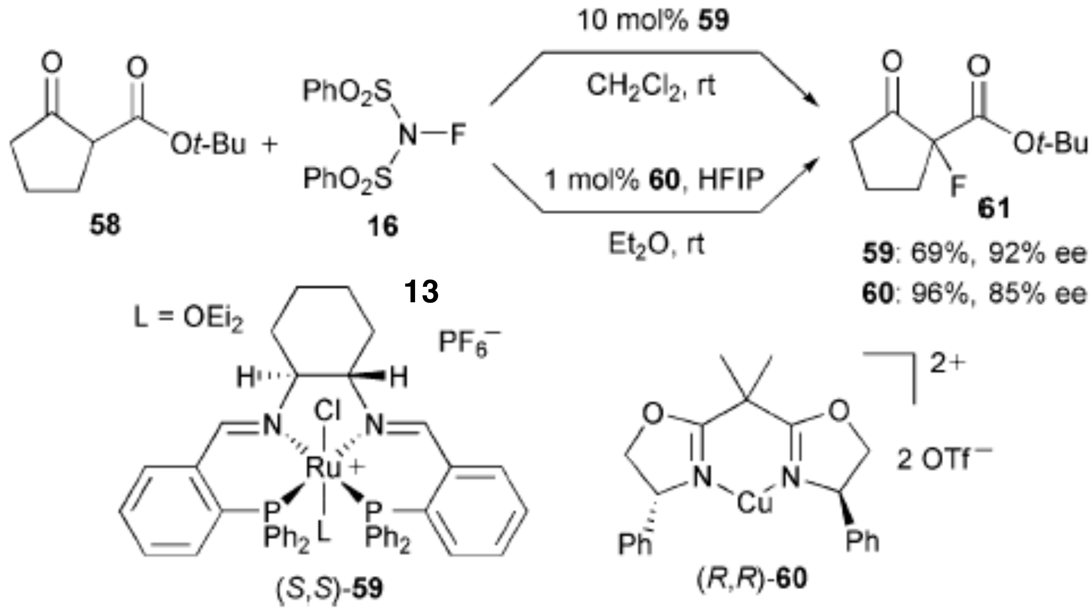
Asymmetric Fluorination Catalyzed by Other Lewis Acids

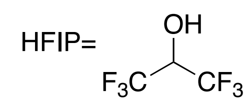


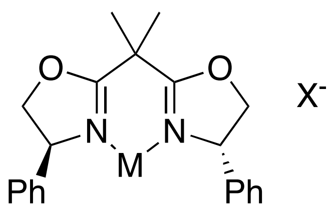
- Alcoholic solvents can work well
- Not sensitive to water
- Catalyst can be recycled and re-used without loss of any slectivity

Hamashima, Y.; Sodeoka, M. et al *J. Am. Chem. Soc.*, **2002**, *124*, 14530–14531.

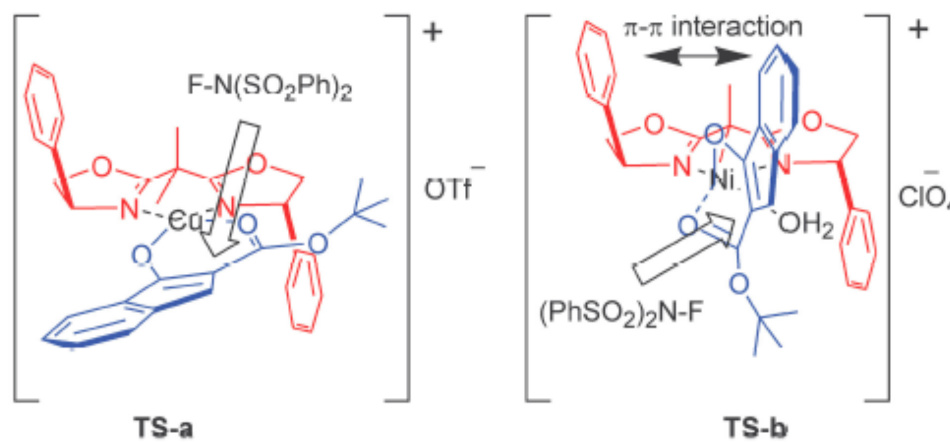
Asymmetric Fluorination Catalyzed by Other Lewis Acids







62 M= Cu, X⁻= OTf
63 M= Ni, X⁻= ClO_4

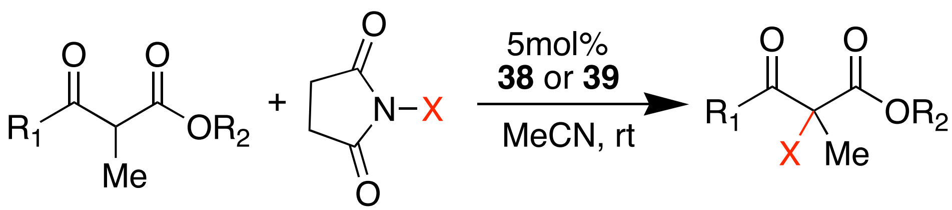


Ibrahim, H.; Togni, A. *Chem. Commun.* **2004**, 1147 – 1155

Ma, J.-A. and Cahard, D. *Tetrahedron: Asymmetry*, **2004**, *15,* 1007

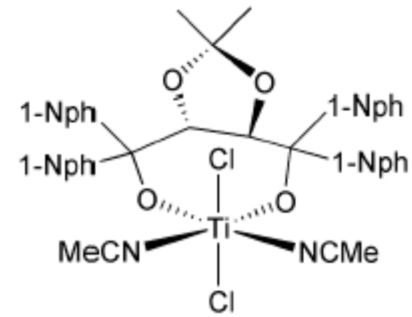
Shibata, N.; Ishimaru, T.; Nagai, T., Kohno, J. and T. Toru *Synlett* **2004**, 1703 –1706

Chiral Lewis Acid Catalyzed Asymmetric Chlorination & Bromination



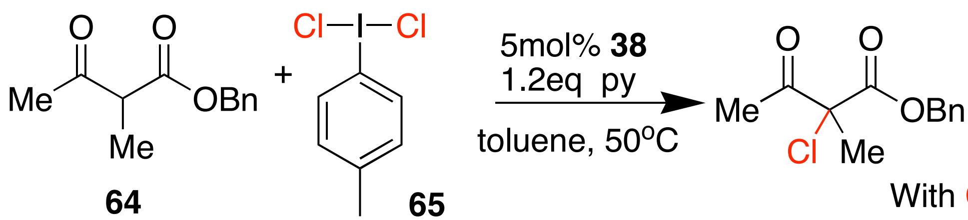
X= Cl, up to 88%ee

X= Br, up to 23%ee



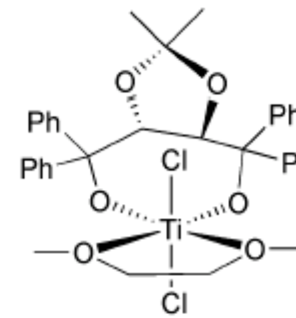
38

Hintermann, L. and Togni, A. *Helv, Chim. Acta*, **2000**, *83*, 2425–2435



(S)-**66**, 67%, 71%ee

With Cl_2, (S)-**66**, 62%, 30%ee



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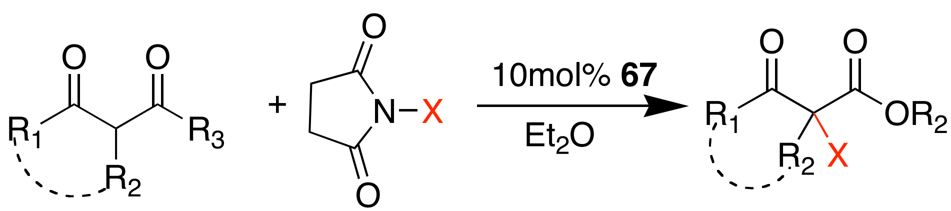
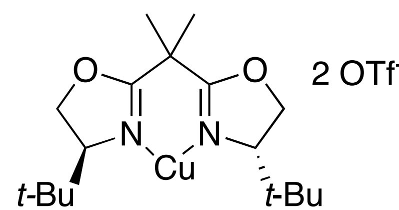
Hintermann, L. and Togni, A. *Helv, Chim. Acta*, **2004**, *87*, 605–610



X= Cl, up to 77%ee

X= Br, up to 82%ee



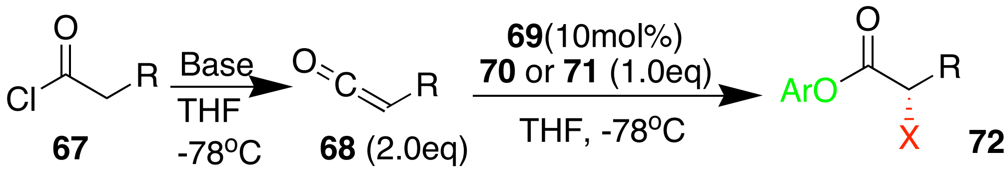
(*S*, *S*)-**67**

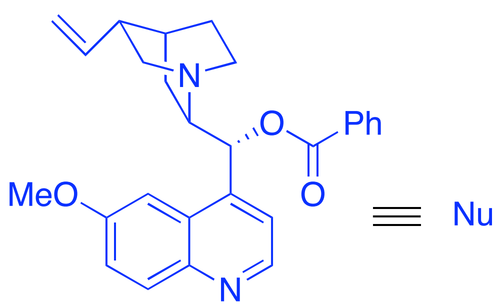
Marigo, M.; Kumaragurubaran, N.; Jørgensen, K. A. *Chem. Eur. J.* **2004**,*10*, 2133 – 2137

Oestreich, M. *Angew. Chem. Int. Ed.*, **2005,** *44*, 2324-2327

Organo-Catalyzed Asymmetric Chlorination & Bromination Acyl Halides

Tadem halogenation/esterification process of acyl halides





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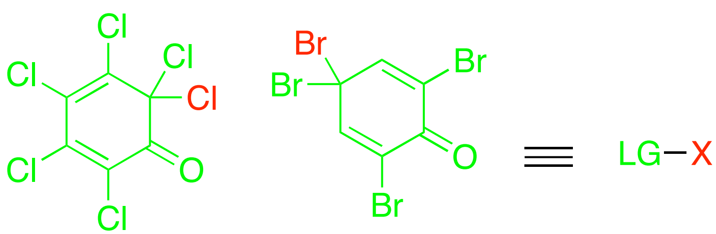

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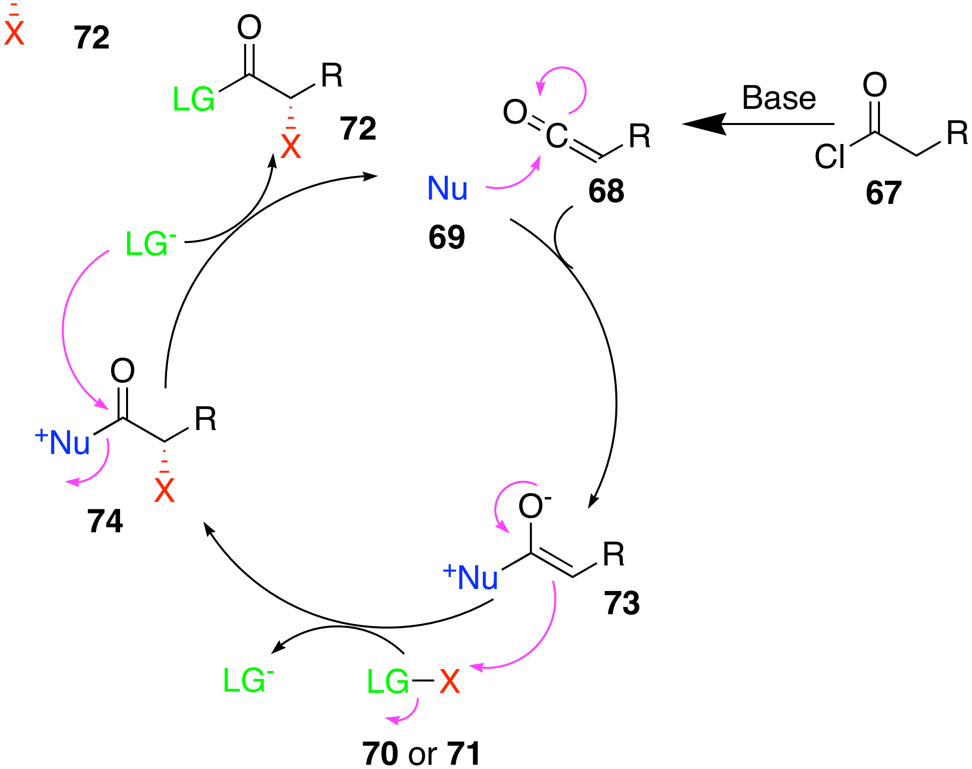
71

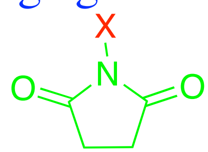


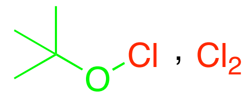
The choice of chlorinating agents is pivotal for the reaction to turn over

France, S.; Lectka, T. *et al J. Am. Chem. Soc.* **2004**, *126*, 4245 – 4255

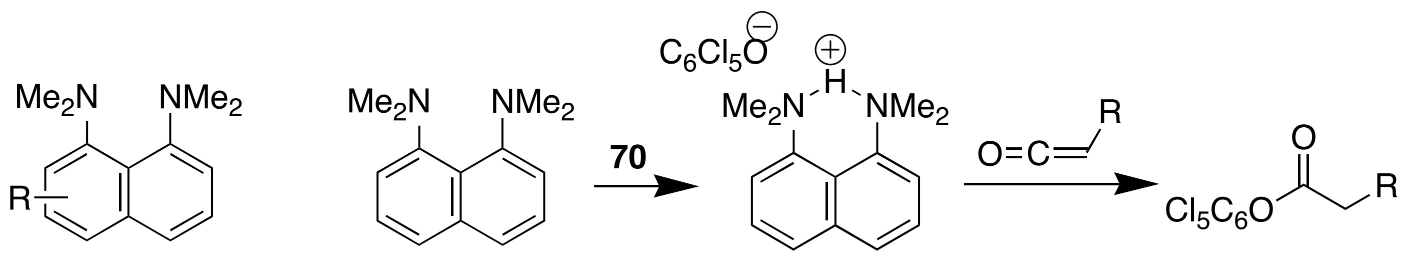
Optimization of Reaction Conditions

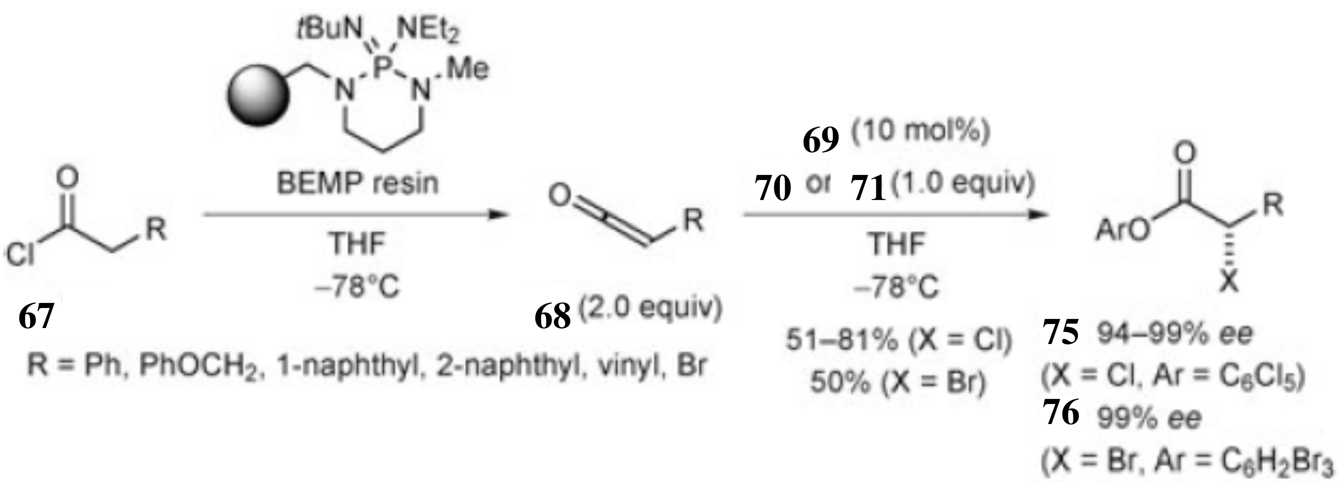
The choice of chlorinating agents: the window is very narrow

Unreactive: 

Too reactive: 

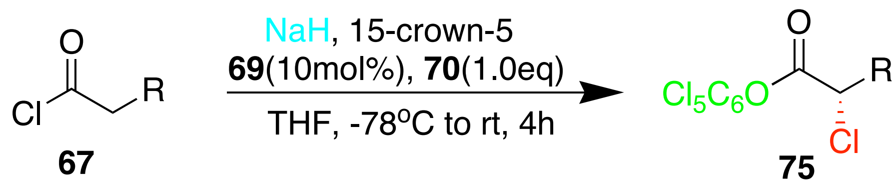
The choice of base: reactive, cheap, easy to handle





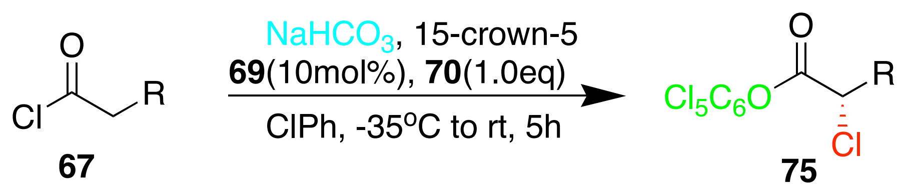
France, S.; Lectka, T. *et al J. Am. Chem. Soc.* **2004**, *126*, 4245 – 4255

Choice of Base and Summary



R= Ph, $PhOCH_2$, 1-Np, *p*-NO_2Ph, Et, *o*-ClPh

Yield: 43-79%, ee: 90-99%



R= Ph, $PhOCH_2$, 1-Np, *p*-MeOPh

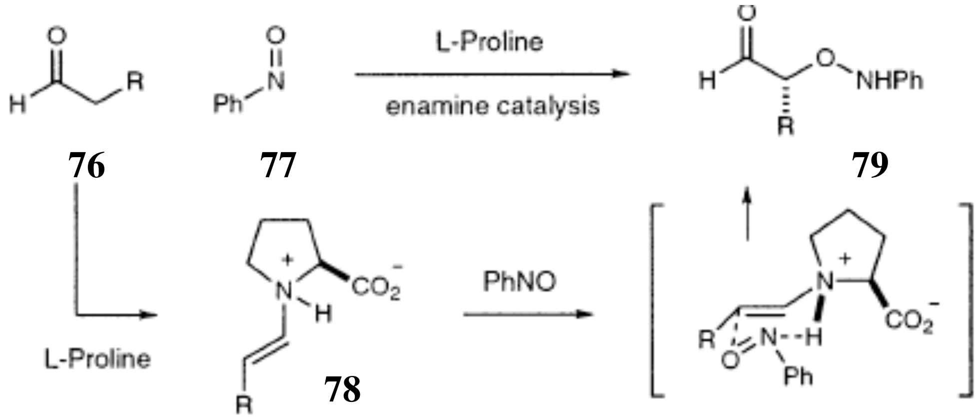
Yield: 56-68%, ee: 88-91%

- Moderate yields, high enantioselectivity
- Inexpensive reagents
- Can be scaled up
- Ketenes from other sources (Wolff rearrangement) can be used as well

France, S.; Lectka, T. *et al J. Am. Chem. Soc.* **2004**, *126*, 4245 – 4255

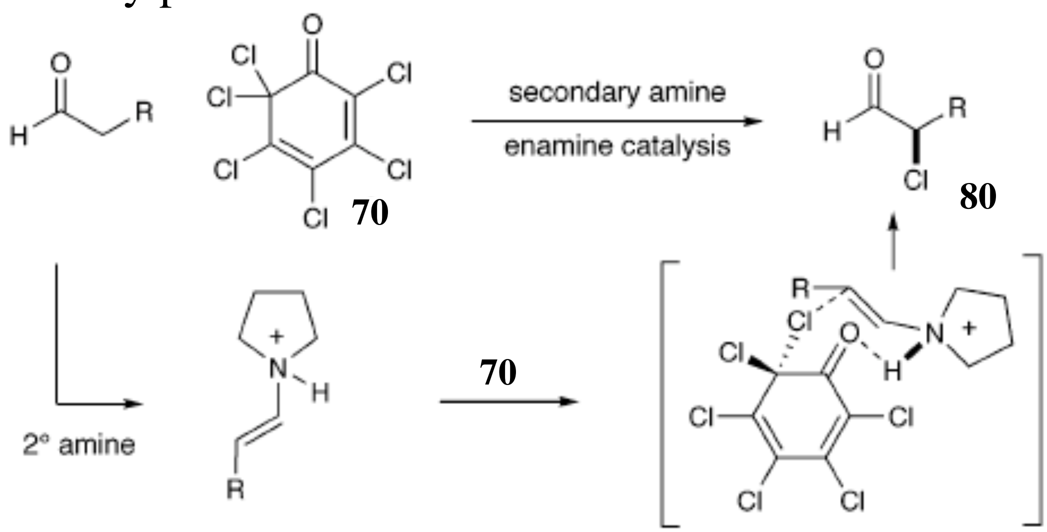
Organo-Catalytic Asymmetric Chlorination

Asymmetric Chlorination of Aldehydes Catalyzed by Chiral Amines



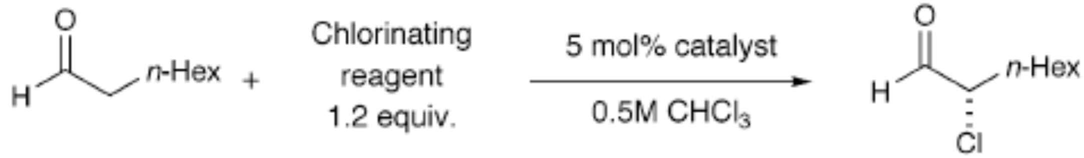
8 examples
Yield: 60-88%
ee: 97-99%

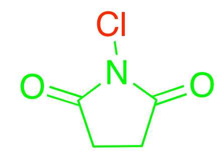
Such cyclic transition state might enforce activation of **70** in the asymmetric environment of an e-rich enamine mediated by proton



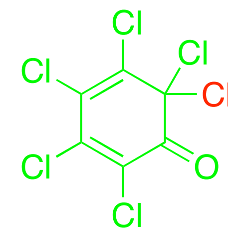
Brochu, M. P.; Brown, S. P. ; MacMillan, D. W. C. *J. Am. Chem. Soc*. **2004**, *126*, 4108 – 4109

Asymmetric Chlorination of Aldehydes: Catalysts and Chlorinating Reagents





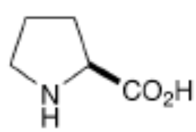
NCS



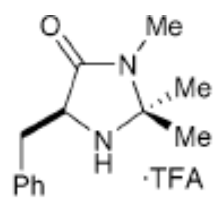
70

entry	catalyst	reagent	temp (°C)	time (h)	% conversion[a]	% ee[b]
1	L-proline	NCS	4	6	99	2
2	**82**	NCS	4	6	20	19
3	**83**	NCS	4	6	60	10
4	L-proline	**70**	4	12	44	2
5	L-proline	**70**	−30	30	NR	NA
6	**82**	**70**	−30	8	91	92
7	**83**	**70**	−30	6	78	42

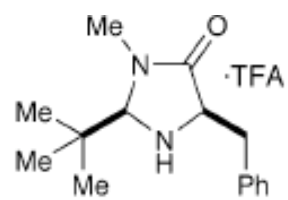
[a] Conversion determined by GLC analysis of product relative to an internal standard (benzyl methyl ether). [b] Enantiomeric excess determined by chiral GLC analysis (Bodman Γ-TA).



81



82

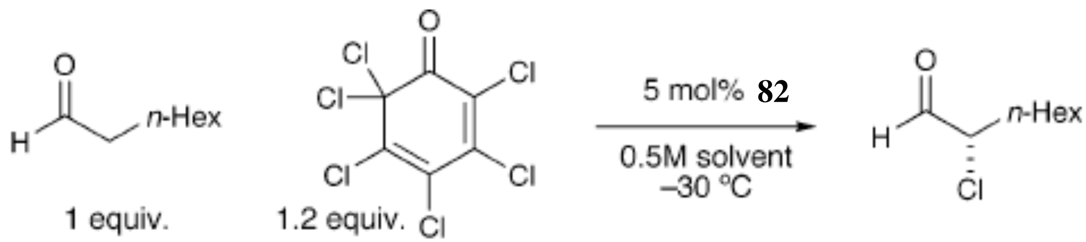


83

- L-Proline doesn't work well
- NCS doesn't work well

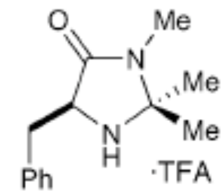
Brochu, M. P.; Brown, S. P. ; MacMillan, D. W. C. *J. Am. Chem. Soc*. **2004**, *126*, 4108 – 4109

Asymmetric Chlorination of Aldehydes: the Solvent Effects



entry	solvent	time (h)	% conversion[a]	% ee[b]
1	EtOAc	12	93	87
2	THF	18	56	89
3	toluene	18	83	89
4	CH_3CN	8	65	92
5	$CHCl_3$	8	91	92
6	acetone	7	93	92

[a] Conversion determined by GLC analysis of product relative to an internal standard (benzyl methyl ether). [b] Enantiomeric excess determined by chiral GLC analysis (Bodman Γ-TA).

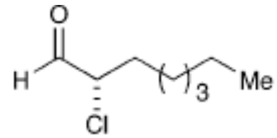
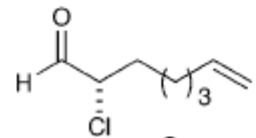
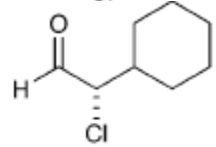
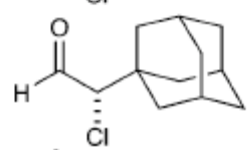
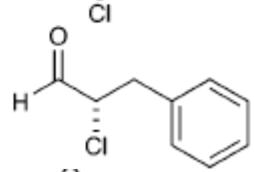
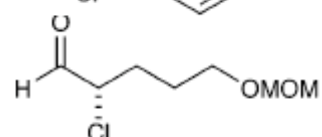
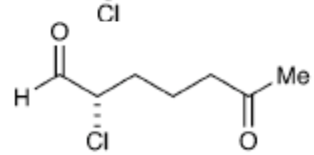


82

- Inert to halogenation reagent
- Optimal selectivity, reaction rate, and chemical yield
- Product epimerization, formation of R,R-dichlorooctanal, or octanal aldol dimerization were comprehensively suppressed using these conditions

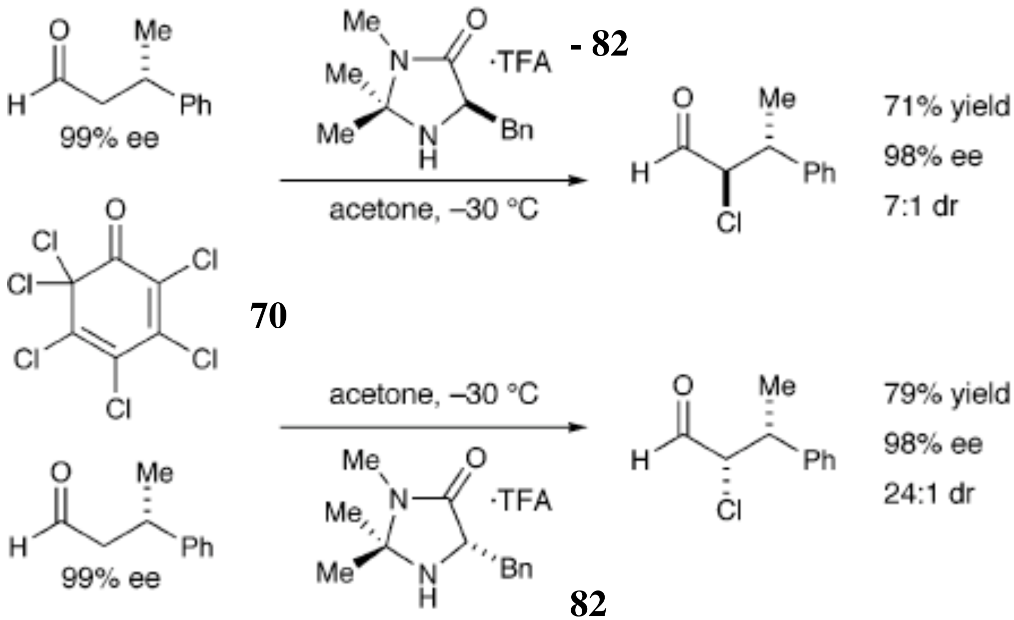
Brochu, M. P.; Brown, S. P. ; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2004**, *126*, 4108 – 4109

Asymmetric Chlorination of Aldehydes: The Scope

entry	product	time (h)	% ee[a,b] crude	% yield	% ee[a] isolated
1		6	95	71	92
2		8	93	76	92
3		8	94	87	94
4		24	NA	85[c]	95[d]
5		6	92	92[e]	80
6		12	93	94[e]	93
7		12	91	78	87

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

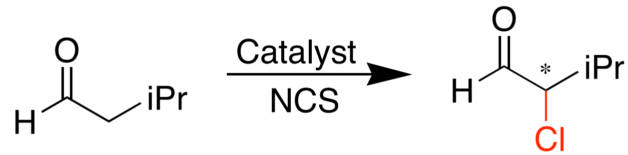
Asymmetric Chlorination of Aldehydes: b-Chiral Aldehydes

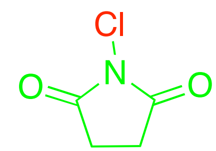


- Internal asymmetric induction is almost completely over-compensated
- Selectivity is sterically and chemically good
- Substrate scope is broad
- All the reagents (**70, 82** and **- 82**) are bench stable and commercially available
- Products are stable

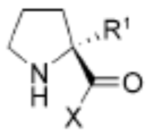
Brochu, M. P.; Brown, S. P. ; MacMillan, D. W. C. *J. Am. Chem. Soc*. **2004**, *126*, 4108 – 4109

Asymmetric Chlorination of Aldehydes: Jørgensen's Work

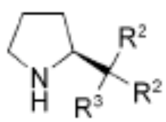




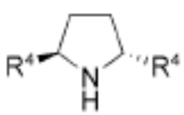
NCS



3a: X = OH, R¹ = H
3b: X = OH, R¹ = Me
3c: X = NH_2, R¹ = H
3d: X = NH*i*Pr, R¹ = H
3e: X = NHGly, R¹ = H



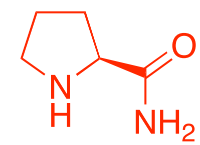
3f: R² = H, R³ = OH
3g: R² = Ph, R³ = OH
3h: R² = 3,5-MePh, R³ = H



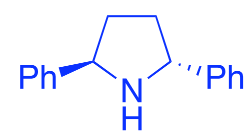
3i: R⁴ = Ph
3j: R⁴ = Bn

entry	catalyst (mol %)	solvent	time (h)	conv.[b] (%)	ee[c] (%)
1	**3a** (20)	$CHCl_3$	1.0	>95	23
2	**3a** (20)	CH_2Cl_2	1.0	>95	25
3	**3b** (20)	DCE	5.0	76	60
4	**3c** (20)	DCE	3.0	>95	78
5	**3c** (20)	DMSO	1.0	<5	<5
6	**3c** (20)	EtOH	1.0	<5	28
7	**3c** (20)	THF	1.0	23	30
8	**3c** (10)	CH_2Cl_2	1.0	>95	82
9	**3d** (20)	DCE	0.5	>95	54
10	**3e** (20)	DCE	1.0	33	81
11	**3f** (20)	DCE	1.0	34	77
12	**3g** (20)	DCE	1.0	15	85
13	**3h** (20)	DCE	0.5	92	64
14	**3i** (20)	DCE	0.5	>95	94
15	**3i** (10)	DCE	1.0	>95	94
16	**3i** (5)	DCE	1.0	77	94
17	**3j** (20)	DCE	1.0	<10	78

[a] Reaction conditions: NCS (2.0 equiv) was added to a mixture of aldehyde at ambient temperature. [b] Measured by ^{1}H NMR of the crude reaction mixture and confirmed by GC, due to the high volatility of the products. [c] ee determined by CSP-GC.



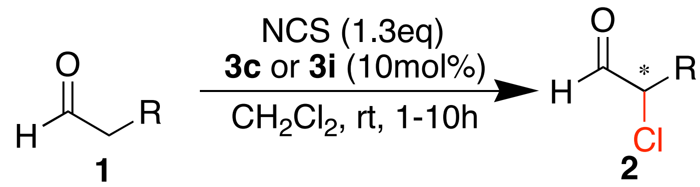
3c

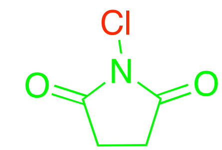


3i

Halland, N. ; Jørgensen, K. A. *et al J. Am.Chem. Soc.* **2004**, *126*, 4790 – 4791

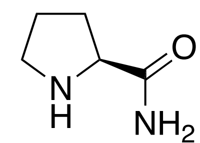
Asymmetric Chlorination of Aldehydes: The Scope



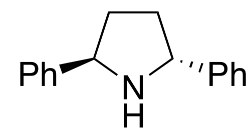


NCS

entry	aldehyde	catalyst 3c yield[b] (%)	catalyst 3c ee (%)	catalyst 3i yield[b] (%)	catalyst 3i ee (%)
1	Me – **1b**	**2b** – 99	75[c] (*R*)[h]	–	–
2	Et – **1c**	**2c** – 99	80[d] (*R*)[j]	**2c** – 90	97[d] (*S*)[j]
3	*i*-Pr – **1a**	**2a** – 95	87[d] (*R*)[h]	**2a** – 90	94[d] (*S*)
4	*t*-Bu – **1d**	**2d** – 93[g]	95[d] (*R*)[i]	**2d** – 30[f]	94[d] (*S*)
5	*n*-Hexyl – **1e**	**2e** – 95	70[c] (*R*)[k]	**2e** – 99	95[c]
6	Allyl – **1f**	**2f** – 90	74[d]	**2f** – 90	95[d]
7	CH_2Ph – **1g**	**2g** – 99	78[e]	**2g** – 82	95[e]
8	$(CH_2)_2OTBS$ – **1h**	**2h** – 92	86	**2h** – 95[g]	81

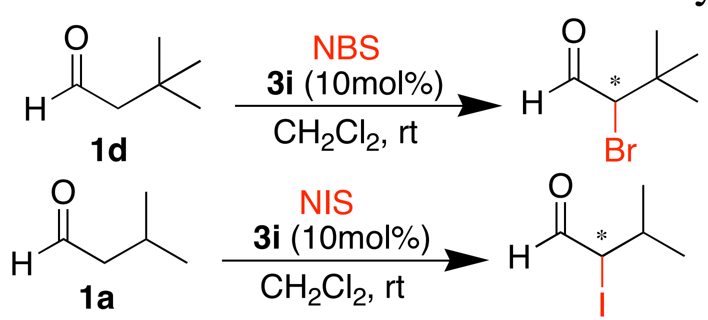


3c



3i

Asymmetric Bromination & Iodination of Aldehydes

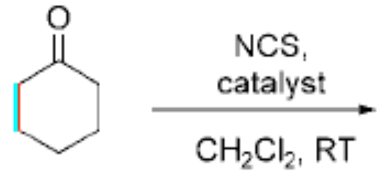


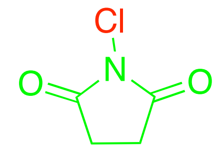
80%ee

24%ee

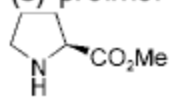
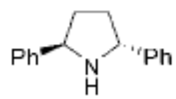
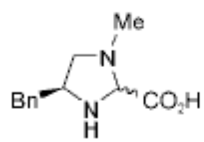
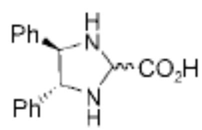
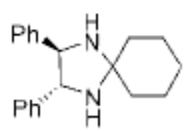
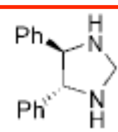
Halland, N. ; Jørgensen, K. A. *et al J. Am.Chem. Soc.* **2004**, *126*, 4790 – 4791

Organo-Catalyzed Asymmetric Chlorination of Ketones



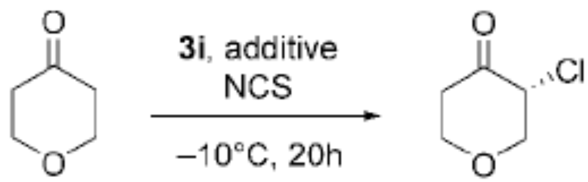


NCS

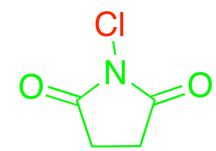
Entry	Catalyst	*t* [h]	Yield [%][b]	*ee* [%]
1	(*S*)-proline (**3a**)	24	65[f]	0
2[d]	(*S*)-prolinamide (**3b**)	24	40[e]	81
3	(*S*)-prolinol (**3c**)	24	5[f]	45
4	 **3d**	24	20[f]	20
5	 **3e**	24	< 5[f]	–
6	 **3f**	0.75	12[f]	23
7		72	58	0
8	 **3g**	0.75	10[f]	62
9		72	34	39
10	 **3h**	22	17[f]	88
11[d]	 **3i**	20	65[e]	97

Marigo, M. ; Jørgensen, K. A. *et al Angew. Chem. Int. Ed.* **2004**, *43*, 5507 – 5510

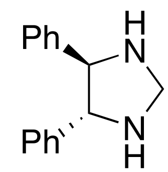
Asymmetric Chlorination of Ketones: Effects of Additives & Solvent



1b **2b**



NCS



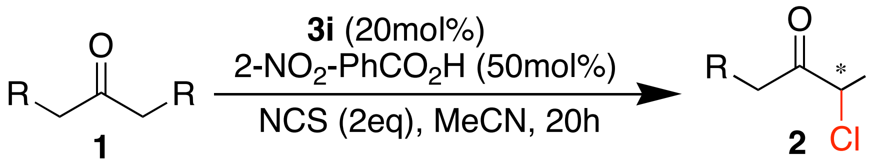
3i

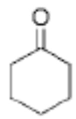
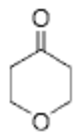
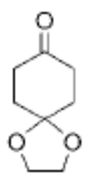
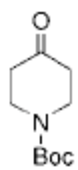
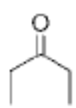
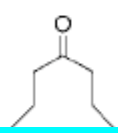
Entry	Add.	Equiv	Solv.	**1 b** (equiv)	NCS (equiv)	Yield [%][b]	*ee* [%]
1	–	–	CH_2Cl_2	5	1	30	90
2	$PhCO_2H$	0.20	CH_2Cl_2	5	1	53	84
3	$PhCO_2H$	0.20	MeCN	2.5	1	15	97
4	AcOH	0.10	MeCN	2.5	1	19	87
5[d]	CF_3CO_2H	0.10	CH_2Cl_2	5	1	62	68
6	$ClCH_2CO_2H$	0.10	MeCN	2.5	1	50	91
7	2-NO_2-$PhCO_2H$	0.25	MeCN	1	1.5	63	97
8[e]	2-NO_2-$PhCO_2H$	0.25	MeCN	1	2.0	72	98

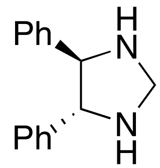
- CH_3CN is the best solvent
- Significant improvement by adding acids:
  - Promotion of enamine formation
  - Suppression of catalyst chlorination

Marigo, M. ; Jørgensen, K. A. *et al Angew. Chem. Int. Ed.* **2004**, *43*, 5507 – 5510

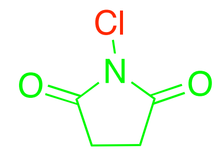
Asymmetric Chlorination of Ketones: The Scope



Entry	Ketone		T [°C]	Prod.	Yield [%][b]	*ee* [%]
1		**1a**	−24	**2a**	82(54)[f]	97
2[d]		**1b**	−24	**2b**	72(50)[g]	98
3		**1c**	−24	**2c**	83(65)	93
4		**1d**	−24	**2d**	76(63)	93
5[e]		**1e**	−10	**2e**	62(51)[h]	86
6[e]		**1f**	−10	**2f**	40(35)[h]	89



3i



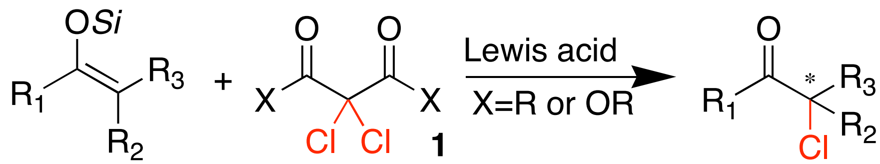
NCS

- High *e.e.*
- Moderate yields: poly-chlorination occurs
- Broad substrate scope

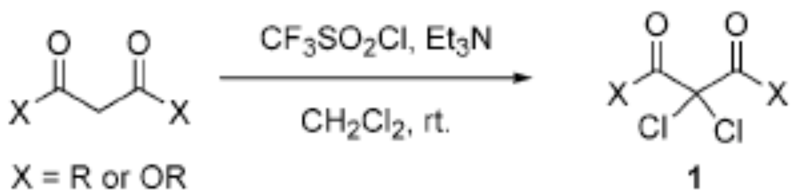
Marigo, M. ; Jørgensen, K. A. *et al Angew. Chem. Int. Ed.* **2004**, *43*, 5507 – 5510

Back to Reagent Controlled Asymmetric Chlorination of Ketones

- Reagent-controlled process can sometimes be competitive alternative!

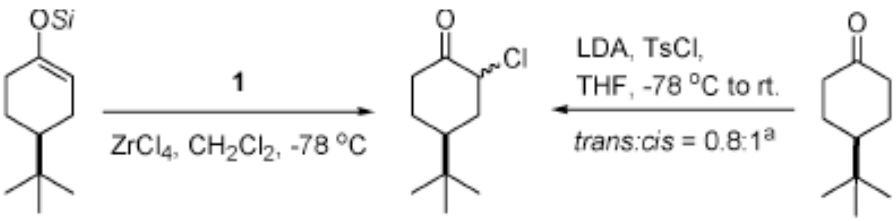


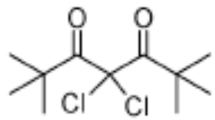
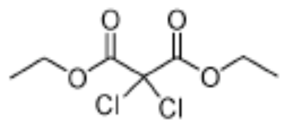
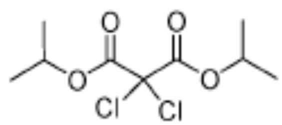
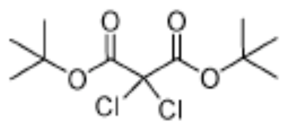
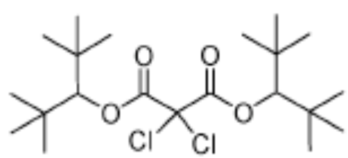
- Chirality of auxiliary (X) could be transferred to silicon enolates
- Lewis acids are necessary to activate **1**
- Chlorinating reagents **1** can be prepared easily



Zhang, Y. ; Shibatomi, K.; Yamamoto, H. *J. Am. Chem. Soc.* **2004**, *126*, 15038 –15039

Asymmetric Chlorination of Ketones: Effects of X group & Si Group



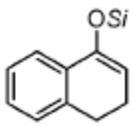
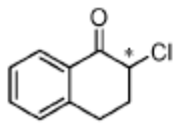
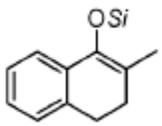
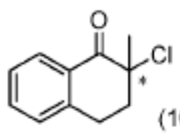
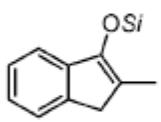
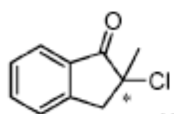
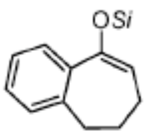
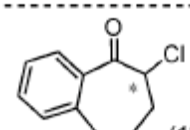
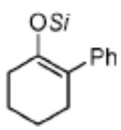
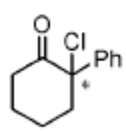
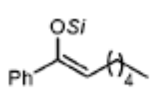
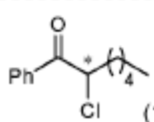
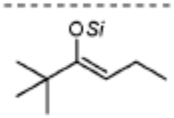
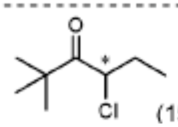
entry	1	*Si*	*trans:cis* [a]
1		TMS	3.5:1
		TBDMS	8.7:1
2		TMS	2.6:1
		TBDMS	4.8:1
3		TMS	3.3:1
		TBDMS	7.9:1
4		TMS	5.7:1
		TBDMS	14:1
5		TMS	14:1
		TBDMS	19:1

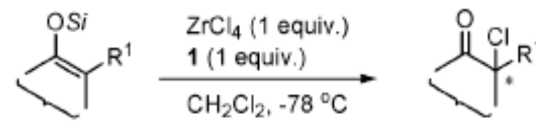
[a] Determined by GC analysis. Yields of the reaction are >90%.

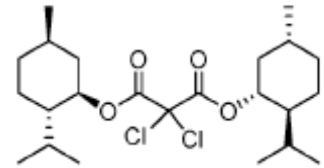
- $ZrCl_4$ is uniquely reactive
- The size of X group
- The size of *si* group
- Yields are high (>90%)

Zhang, Y. ; Shibatomi, K.; Yamamoto, H. *J. Am. Chem. Soc.* **2004**, *126*, 15038 –15039

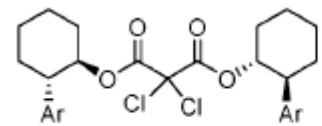
Asymmetric Chlorination of Ketones: Scope

entry	substrate	*Si*	1	product	time(h)	% ee[b]
1	 (2a)	TMS	**1a**	 (9)	2	42
2	(2a)	TMS	**1b**		1.5	67
3	(2a)	TMS	**1c**		2	80
4	(2b)	TBDMS	**1c**		2	88
5	(2b)	TBDMS	**1d**		1.5	77
6	(2c)	DMTS[c]	**1c**		1.5	86
7	 (3)	TMS	**1c**	 (10)	2	48
8	 (4a)	TBDMS	**1c**	 (11)	1.5	86
9	(4a)	TBDMS	**1d**		5	92
10	(4b)	DMTS	**1d**		1.5	98
11	 (5)	TBDMS	**1c**	 (12)	2	68
12	(5)	TBDMS	**1d**		4	55
13	 (6a)	TMS	**1c**	 (13)	4.5	31
14	(6b)	TBDMS	**1c**		5	87
15	(6c)	TIPS	**1c**		5	83
16	(6d)	DMTS	**1c**		1.5	84
17	 (7)	TBDMS	**1d**	 (14)	3	80
18	 (8)	TBDMS	**1d**	 (15)	1	90[d]

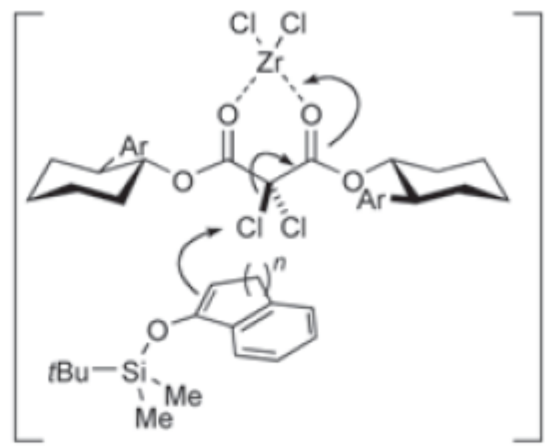




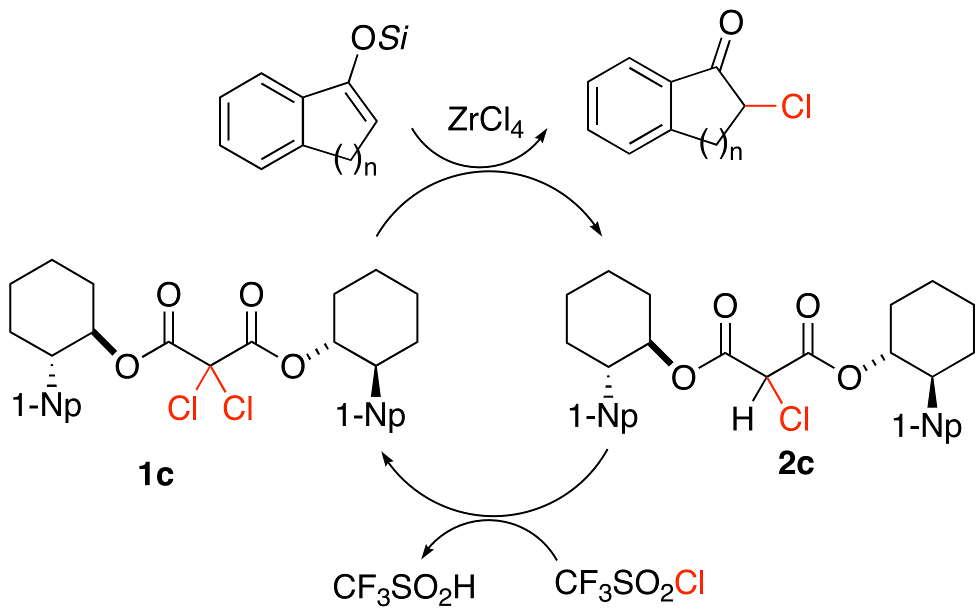
1a



1b: Ar = Ph
1c: Ar = 1-naphthalyl
1d: Ar = 9-phenanthryl



Asymmetric Chlorination of Ketones: Potential to be Catalytic



- **2c** can be easily recovered and chlorinated back to **1c**
- Recovered **1c** can be re-used for the reaction
- This novel process might be extended to catalytic asymmetric variants!

Zhang, Y. ; Shibatomi, K.; Yamamoto, H. *J. Am. Chem. Soc.* **2004**, *126*, 15038 –15039

Conclusions

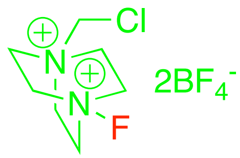
- Enantioselective electrophilic a-halogenation of carbonyl compounds: a topical area of current asymmetric catalysis
- A new tool has presented itself to synthetic organic chemistry
- More applications are expected

This is a good topic. There're problems for this chemistry before...

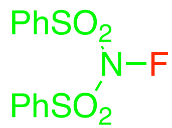
To What They Should Thank?

Dr. Togni
ETH

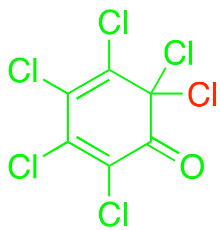
Dr. Lectka
Johns Hopkins U.



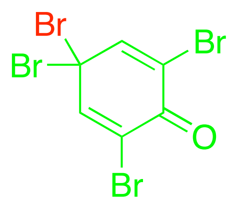
Selectfluor,
or F-TEDA
12



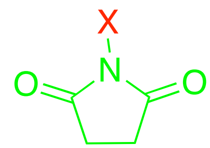
N-fluorobenzenesulfonimide
or NFSI
13



70



71



X= Cl, NCS
X= Br, NBS
X= I , NIS

Wong, C.-H., *Angew. Chem. Int. Ed.*, **2005,** *44*, 192

Taylor, S. D.; Kotoris, C. C. and Hum, G. *Tetrahedron*, **1999,** *55,*12431-12477

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