Enantioslective Aminocatalytic α-Chlorination of Aldehydes

2021.5.22.

Kyohei Takaoka

Contents

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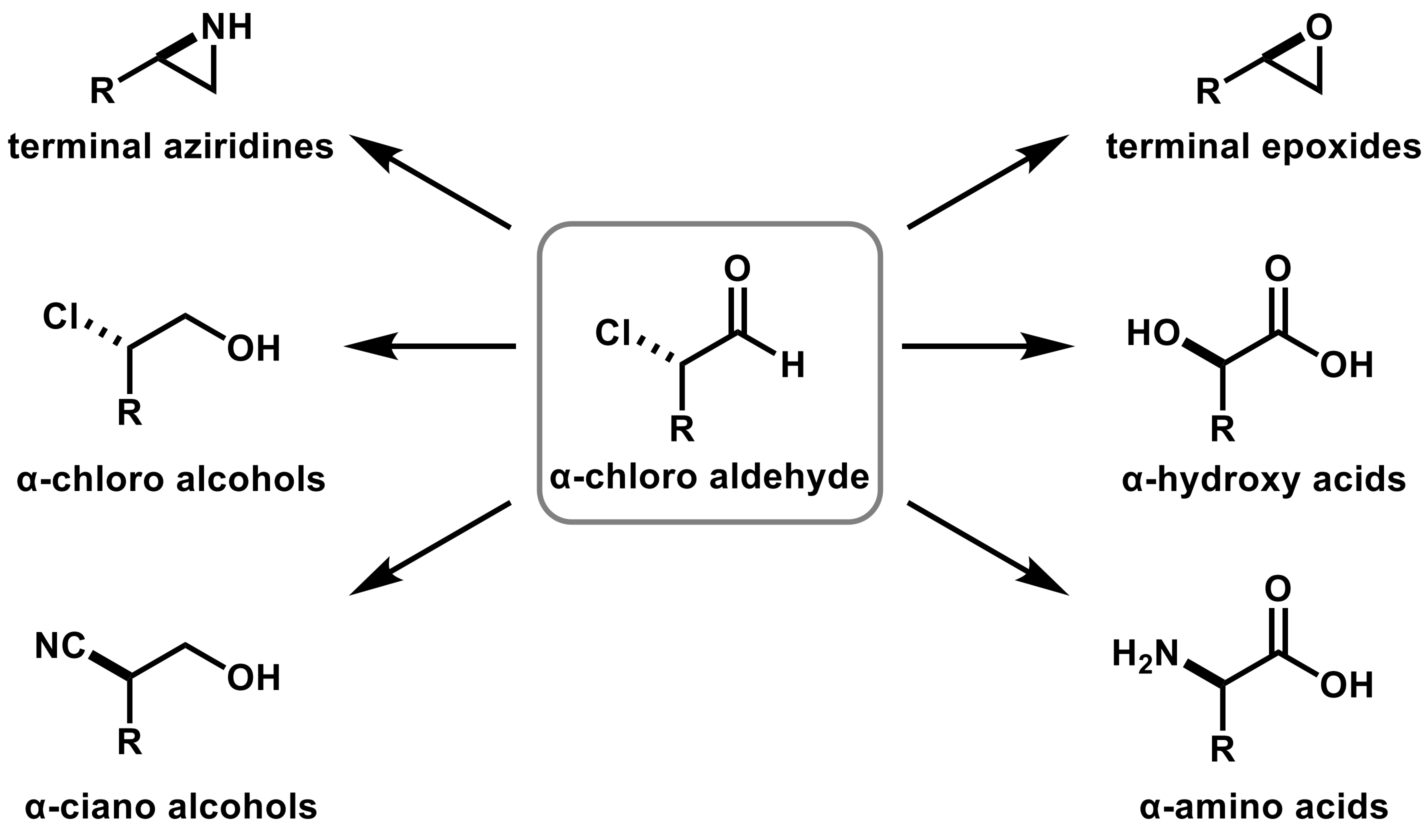
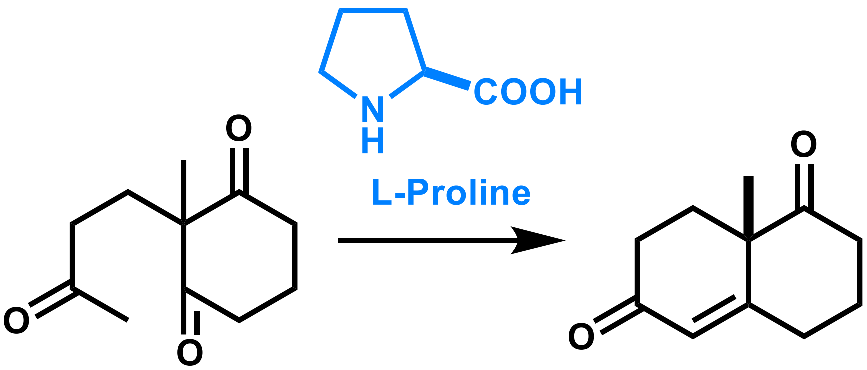
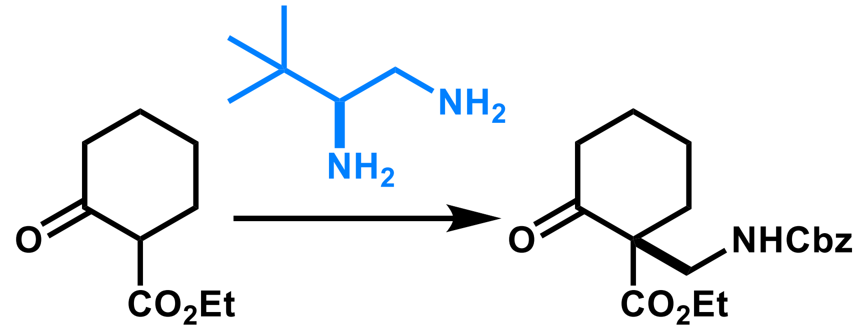
α-Chloro Aldehyde



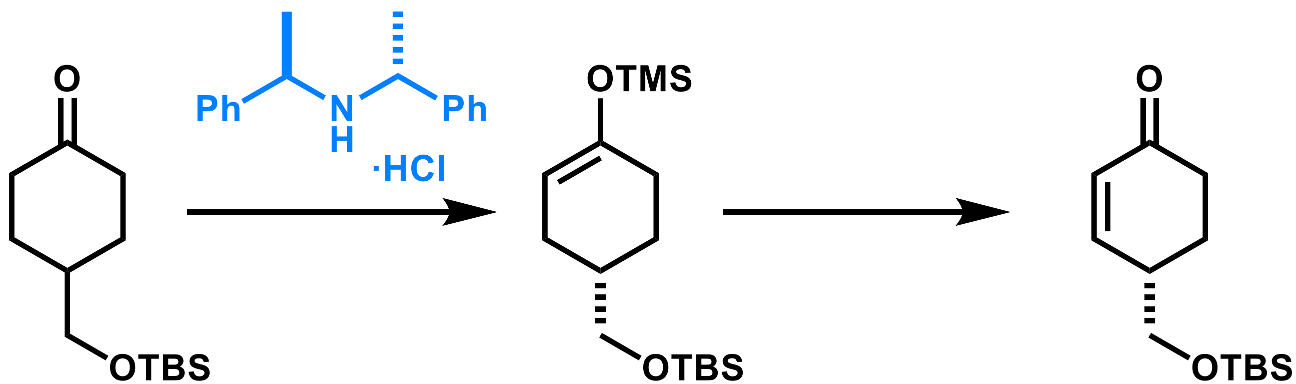
Chiral Amine as Organocatalyst



81%, 79% ee.

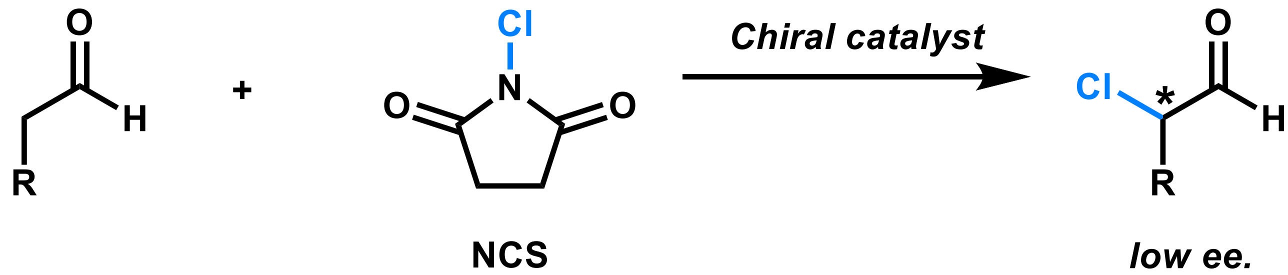


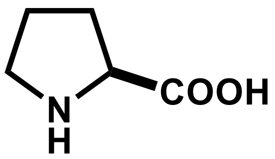
90%, 99% ee.



66% (2 steps)
86% ee.

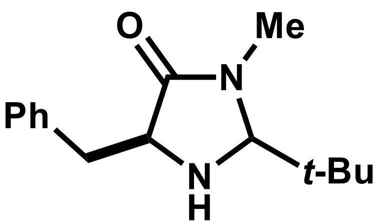
Difficulty of Asymmetric α-Chlorination



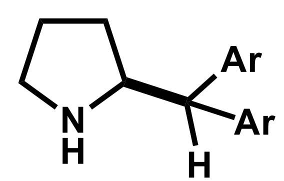


L-proline

Aldehyde	Chiral catalyst	Yield (%)	ee. (%)
R = *n*-hex	L-proline	99	2
R = *n*-hex	A	60	10
R = *i*-Pr	L-proline	> 95	25
R = *i*-Pr	B	92	64



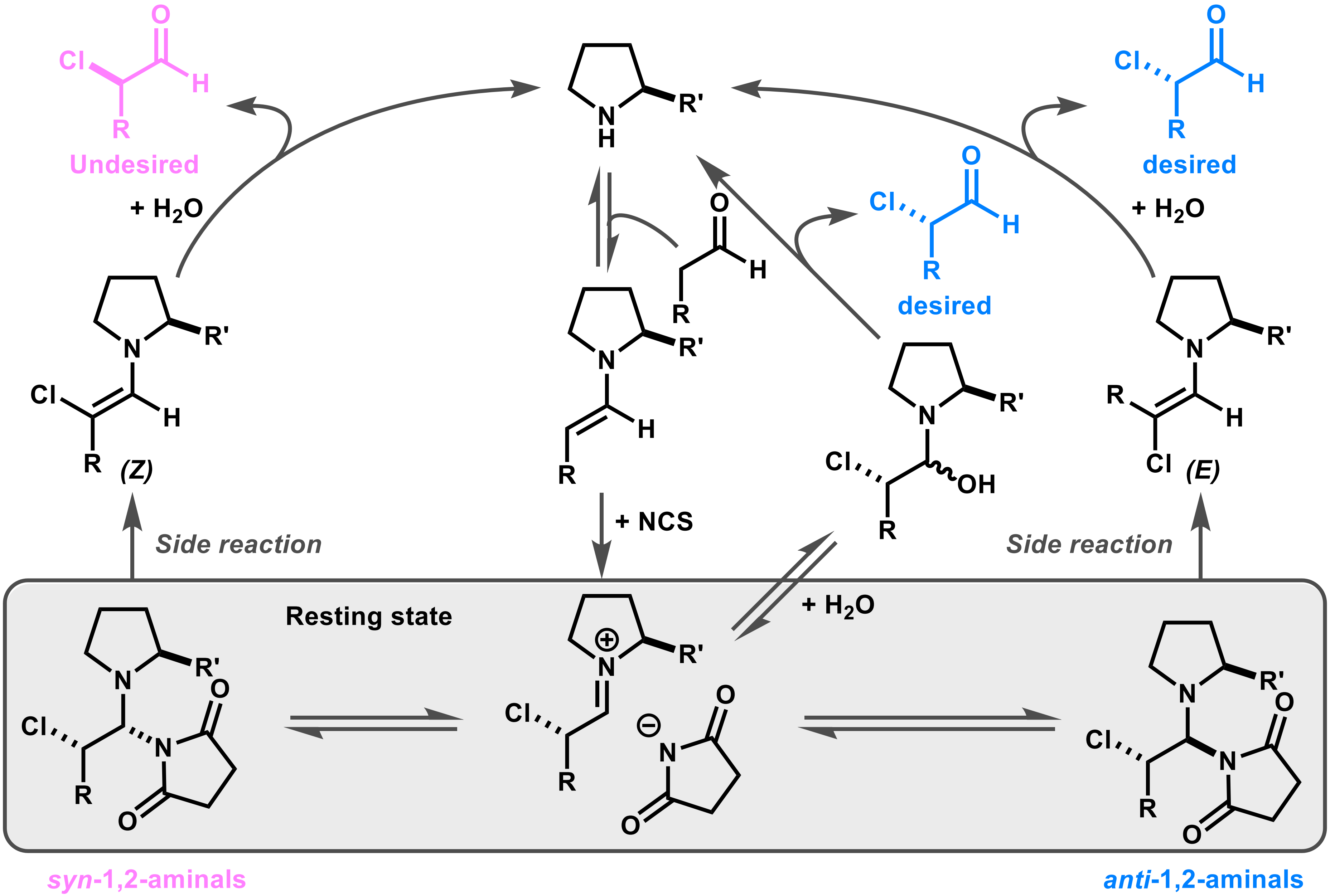
A



B
Ar = 3,5-$Me_2C_6H_3$

1) Brochu, M, P.; Brown, S. P.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2004**, *126*, 4108-4109.
2) Halland, N.; Braunton, A.; Bachmann, S.; Marigo, M.; Jørgensen, K. A. *J. Am. Chem. Soc*. **2004**, *126,* 4790-4791.

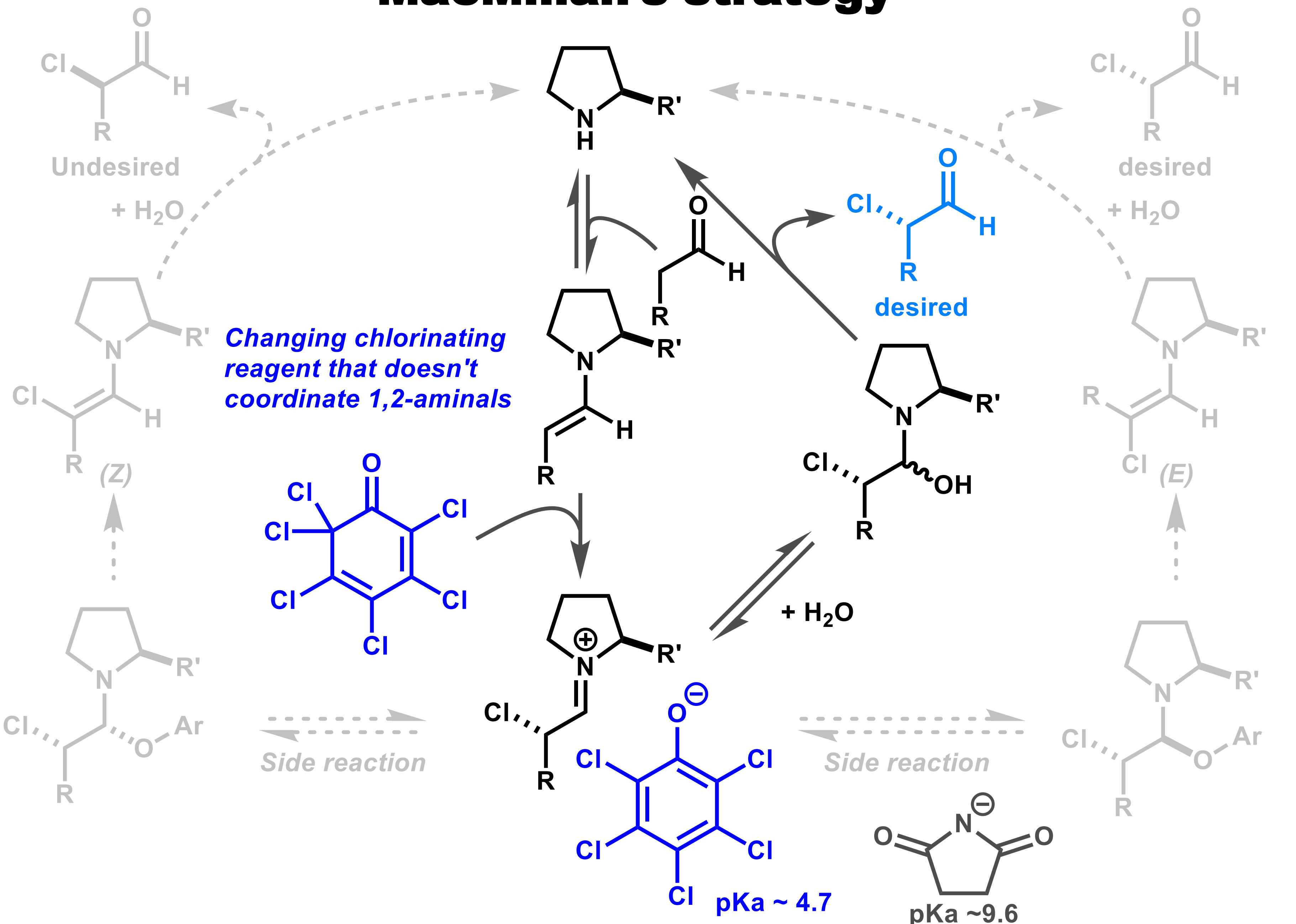
Proposed Mechanism of Racemization



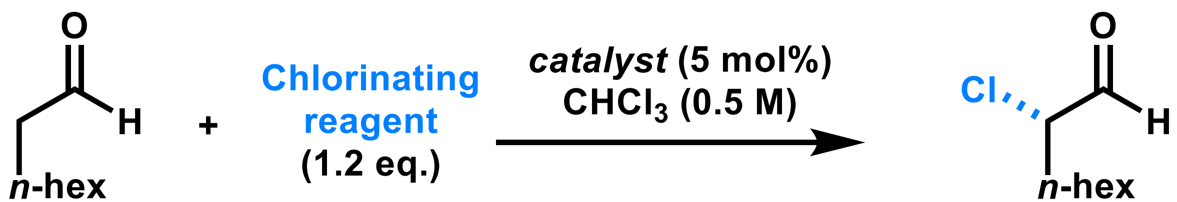
1) Burès, J.; Armstrong, A.; Blackmond, G. C.; *J. Am. Chem. Soc.* **2012**, *134*, 6741-6750.

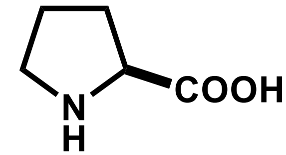
Contents

MacMillan's strategy

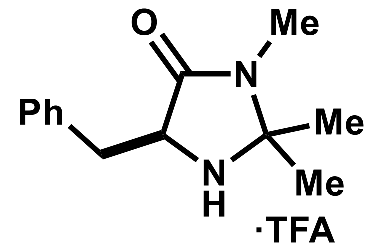


Optimization (1)

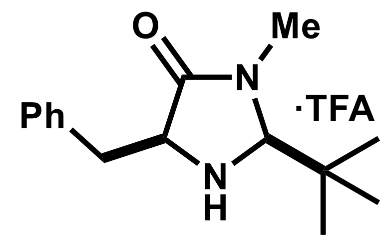




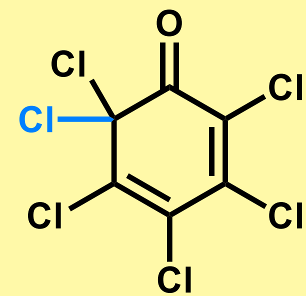
L-proline



A



B



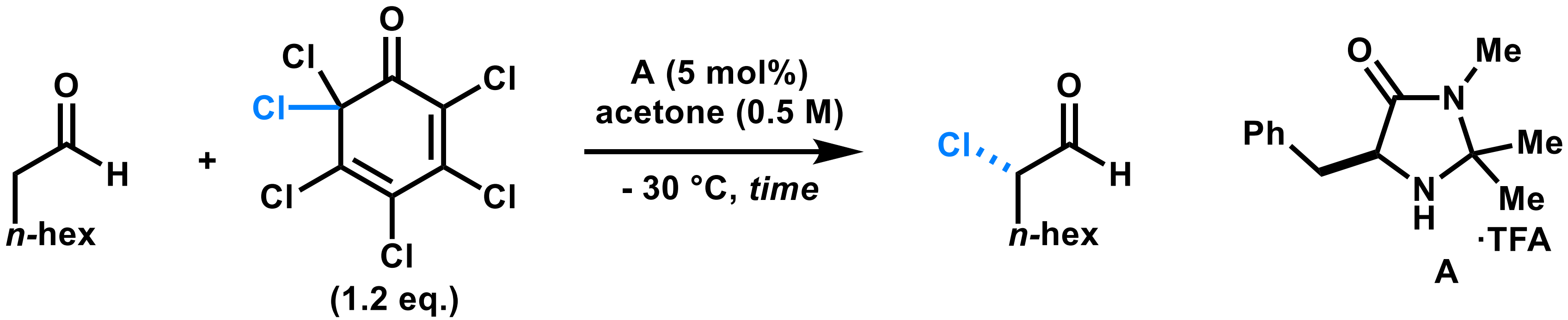
1

Entry	Catalyst	Reagent	Temp. (°C)	Conversion (%)[a]	ee (%)[b]
1	L-proline	NCS	4	99	2[c]
2	A	NCS	4	20	19
3	B	NCS	4	60	10
4	L-proline	1	4	44	2[c]
5	**A**	**1**	**-30**	**91**	**92**
6	B	1	-30	78	42

[a] Conversion determined by GLC analysis of product relative to an internal standard (benzyl methyl ether). [b] Enantiometric excess determined by chiral GLC analysis (Bodman Γ-TA). [c] Different enantiomer would be generated.

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

Optimization (2)

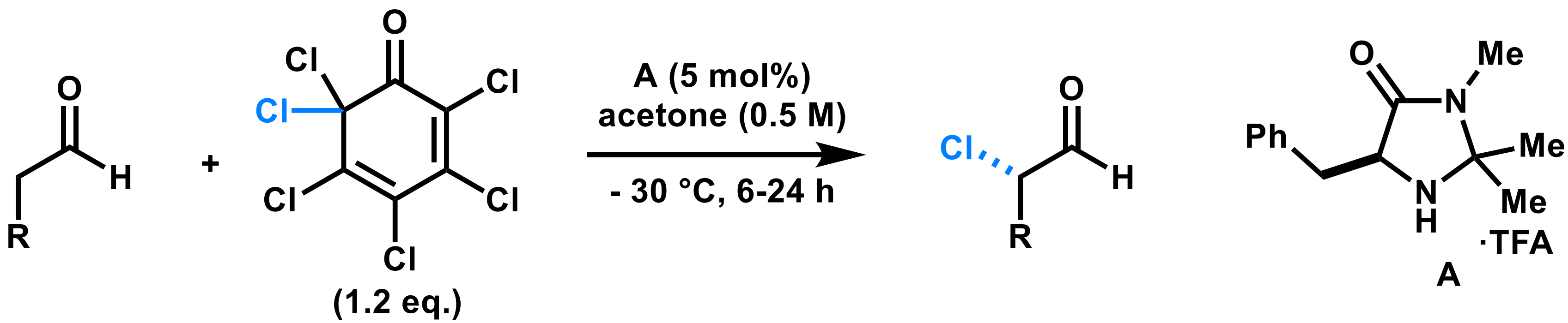


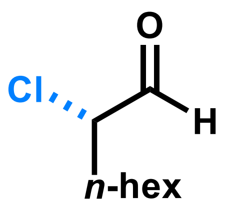
Entry	Solvent	Time (h)	Conversion (%)[a]	ee (%)[b]
1	EtOAc	12	93	87
2	THF	18	56	89
3	toluene	18	83	89
4	CH_3CN	8	65	92
5	$CHCl_3$	8	91	92
6	**acetone**	**7**	**93**	**92**

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

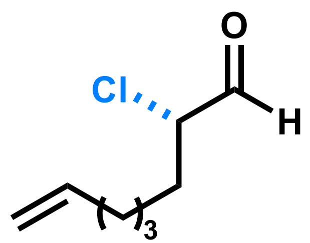
1) Brochu, M, P.; Brown, S. P.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2004**, *126*, 4108-4109.

Substrate Scope

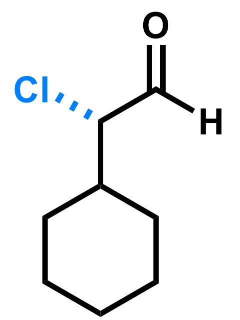




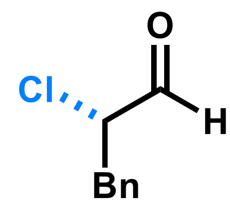
71%, 92% ee.



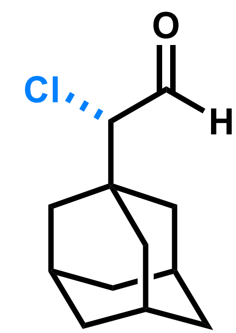
76%, 92% ee.



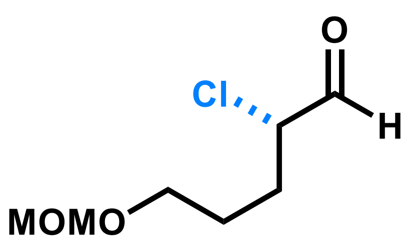
87%, 94% ee.



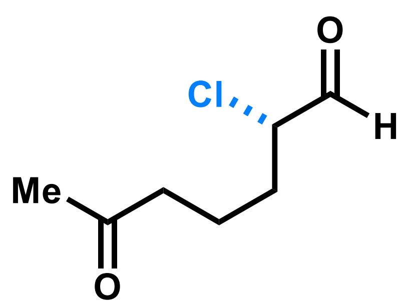
92%, 80% ee.



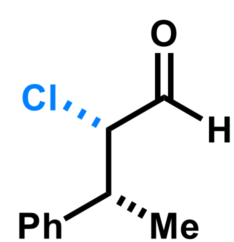
85%, 95% ee.



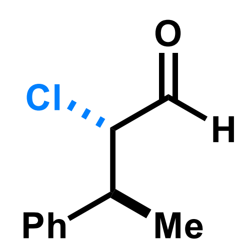
94%, 93% ee.



78%, 87% ee.



79%, 24:1 dr.

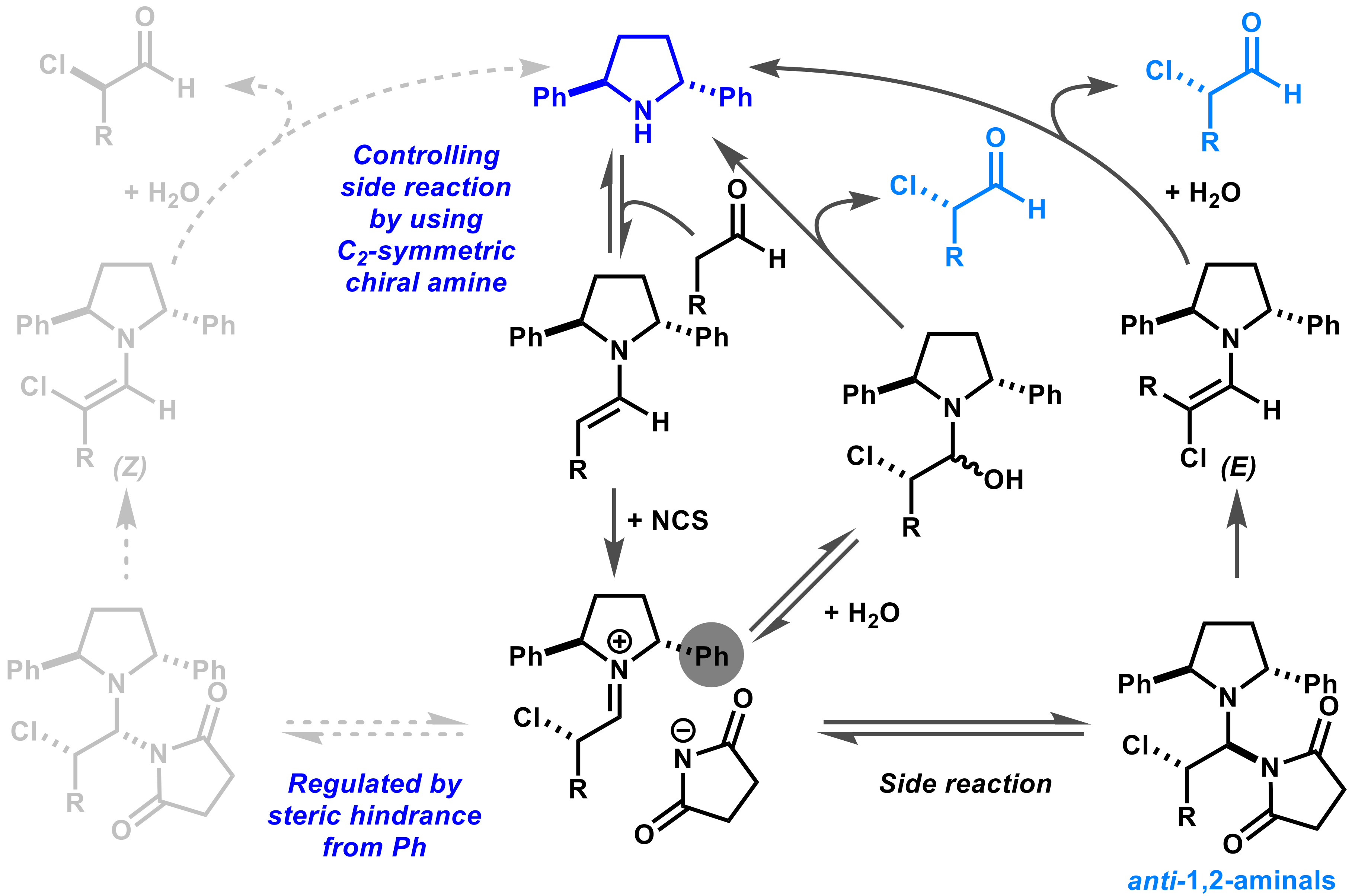


71%, 7:1 dr.

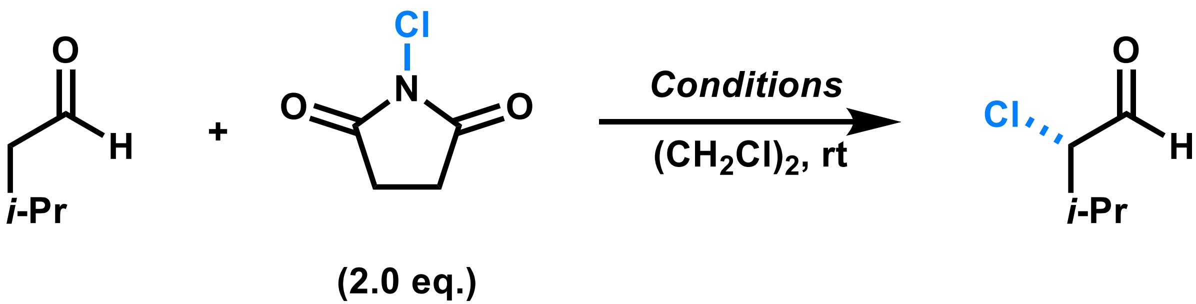
1) Brochu, M, P.; Brown, S. P.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2004**, *126*, 4108-4109.

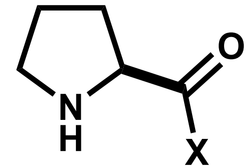
Contents

Jøgensen's Strategy

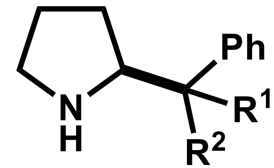


Optimization

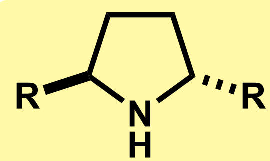




1a: X = OH
1b: X = NH_2



2a: R^1 = Ph, R^2 = OH
2b: R^1 = 3,5-Me_2Ph, R^2 = H



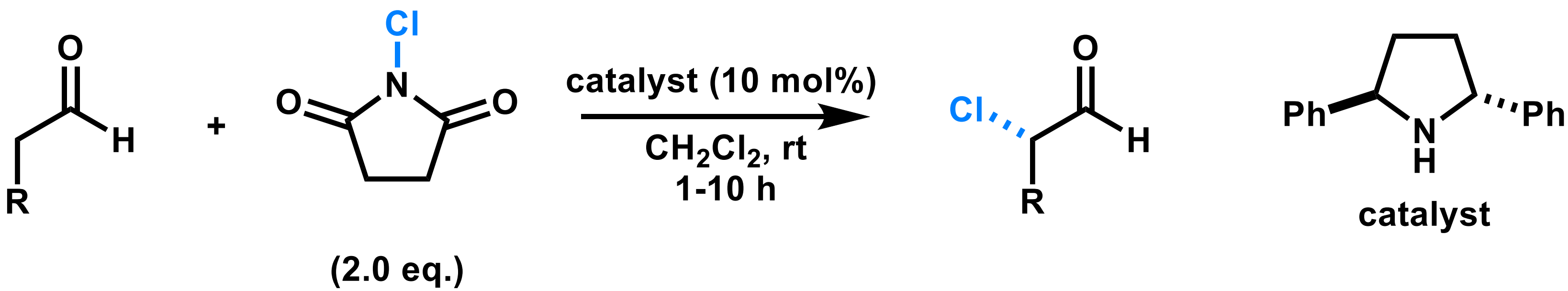
3a: R = Ph
3b: R = Bn

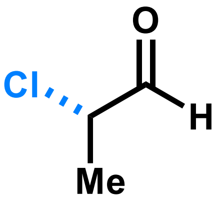
Entry	Catalyst (mol%)	Time (h)	Conversion (%)[a]	ee. (%)[b]
1[c]	1a (20)	1.0	> 95	25[d]
2	1b (20)	3.0	> 95	78[d]
3	2a (20)	1.0	15	85
4	2b (20)	0.5	92	64
5	3a (20)	0.5	> 95	94
6	3a (10)	1.0	> 95	94
7	3a (5)	1.0	78	94
8	3b (20)	1.0	< 10	78

[a] Measured by ^{1}H NMR of the crude reaction mixture and confirmed by GC, due to the high volatility of the products. [b] ee determined by GSP-GC. [c] CH_2Cl_2 was used instead of $(CH_2Cl)_2$. [d] Different enantiomer would be generated.

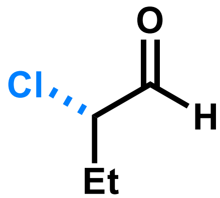
1) Halland, N.; Braunton, A.; Bachmann, S.; Marigo, M.; Jørgensen, K. A. *J. Am. Chem. Soc.* **2004**, *126*, 4790-4791.

Substrate Scope

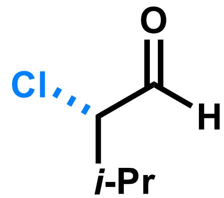




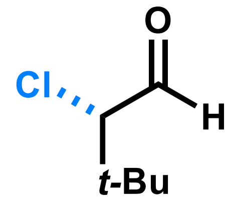
90%, 97% ee.



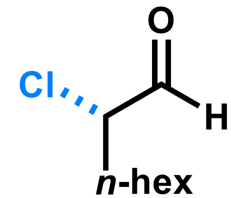
90%, 94% ee.



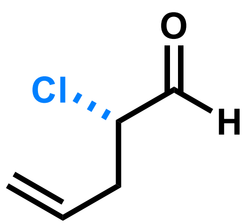
90%, 94% ee.



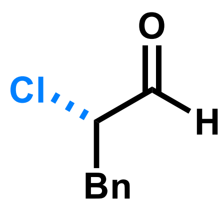
30%[a], 94% ee.



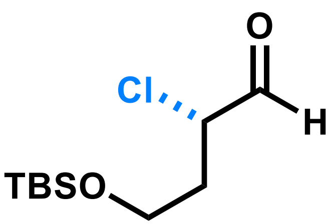
99%, 95% ee.



90%, 95% ee.

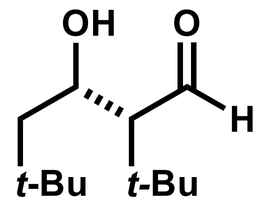


82%, 95% ee.



95%, 81% ee.
(-24 °C, 20 h)

[a] Homo-aldol product was obtained



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

Contents

Dr. Jordi Burès

Dr. Jordi Burès

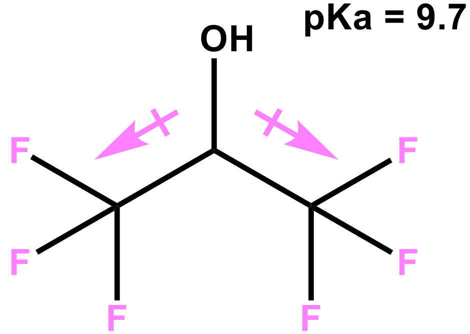
2003	**B.S. @ Barcelona University (Prof. Jaume Vilarrasa)**
2010	**Ph.D @ Barcelona University (Prof. Jaume Vilarrasa)**
2010-	**Postdoctoral fellow @ The Scripps Research Institute (Prof. Donna Blackmond)**
2013-	**IC Junior Research Fellow @ Imperial College London**
2016-	**Lecturer @ The University of Manchester**
2020-	**Senior Lecturer @ The University of Manchester**

Research interest: Development of catalytic reaction

https://jordibures.wixsite.com/buresgroup

HFIP Stabilize Cation

pKa = 9.7



hexafluoroisopropanol
(HFIP)

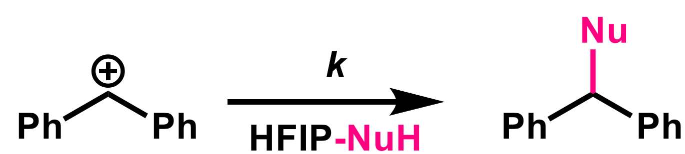
Low nucleophilicity

Nucleophilicity parameter:

N_{OTs}(*i*-PrOH) = 0.2

N_{OTs}(HFIP) = - 4.23

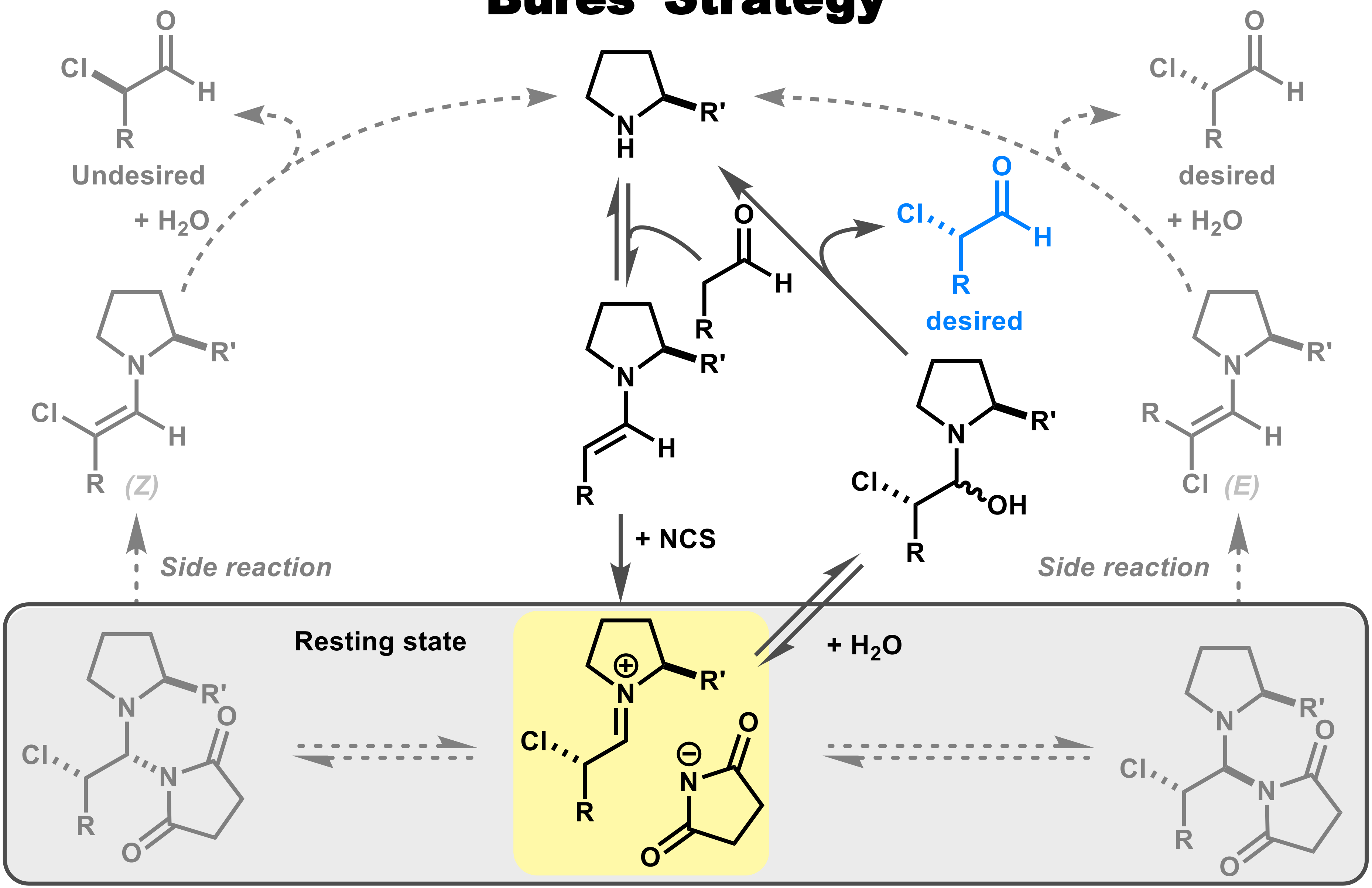
Cation stabilization



HFIP-H_2O (98:2)	k (s^{-1}) = 2.0 x 10^4
HFIP-H_2O (95:5)	k (s^{-1}) = 1.7 x 10^5
HFIP-H_2O (90:10)	k (s^{-1}) = 1.0 x 10^6
HFIP-H_2O (70:30)	k (s^{-1}) = 7.5 x 10^6

1) Colomer, I.; Chamberlain, A. E. R.; Haughey, M. B.; Donohoe, T.J. *Nat. Rev. Chem.* **2017**, *1*, 0088.

Burès' Strategy



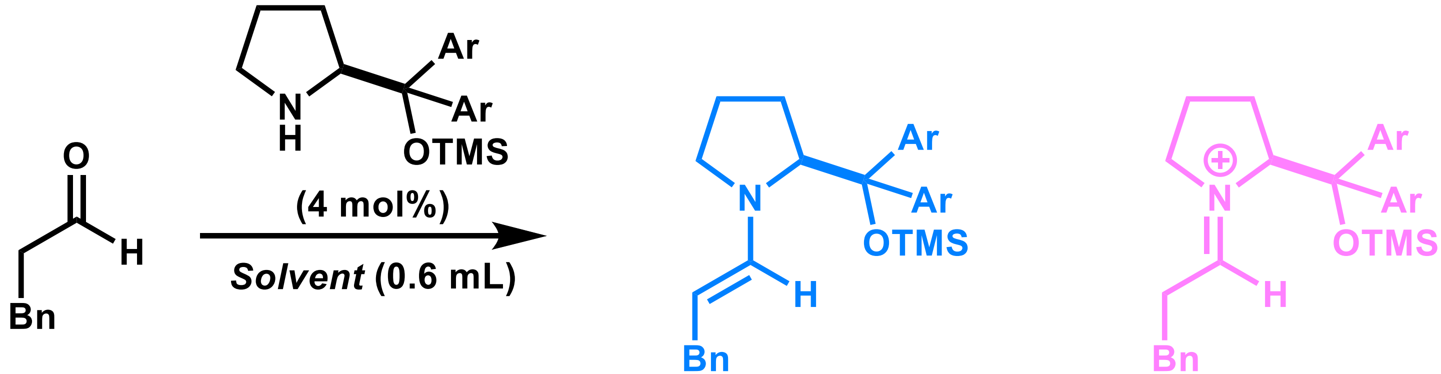
syn-1,2-aminals

Stabilize iminium cation by using HFIP

anti-1,2-aminals

1) Hutchinson, G.; Ferrer, C. A.; Burès, J. *J. Am. Chem. Soc.* **2021**, *143*, 6805-6809.

HFIP vs. Other Solvent

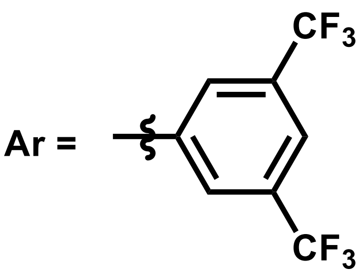


0.37 mmol

Enamine

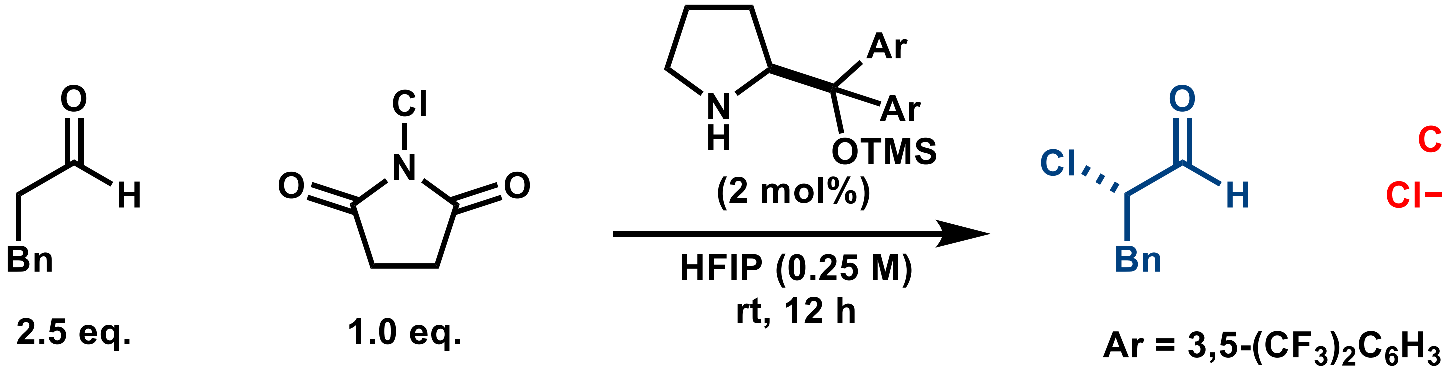
Iminium ion

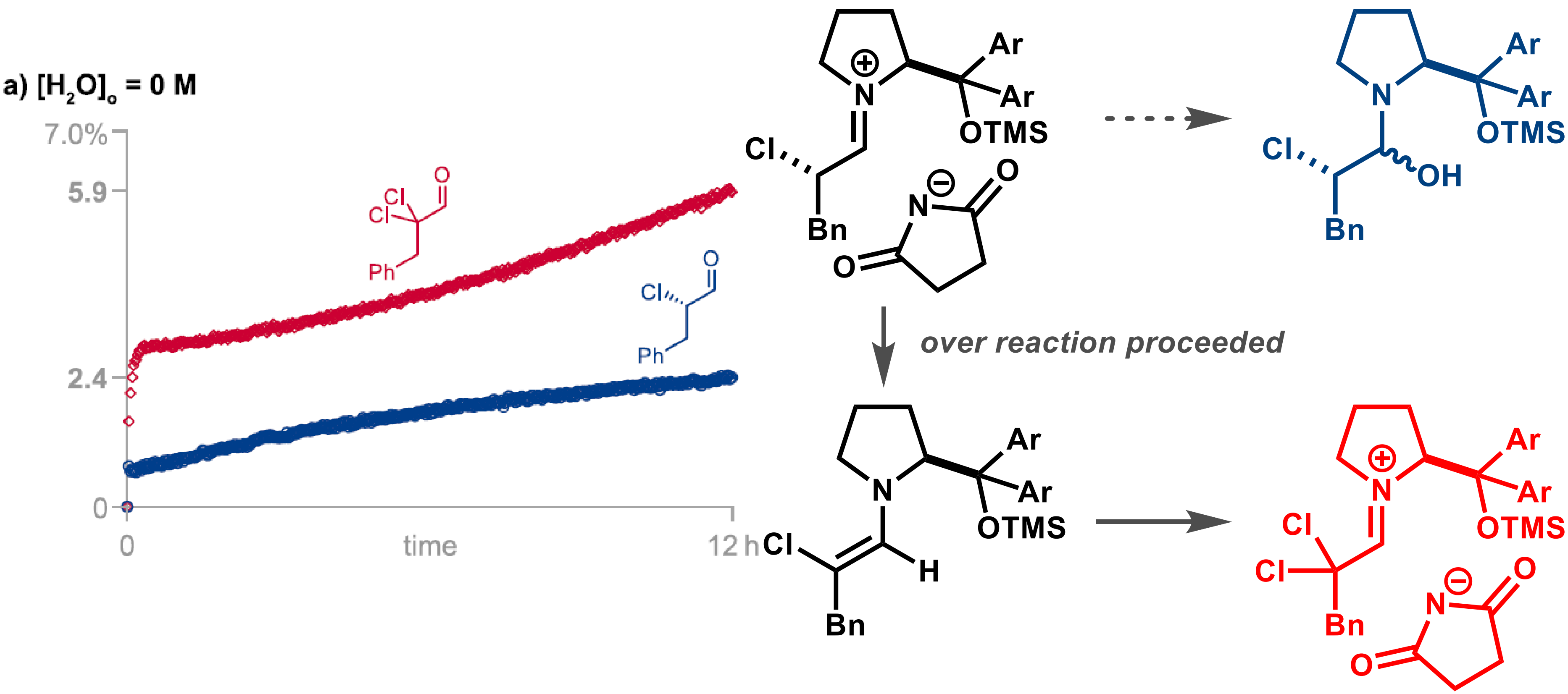
Entry	Solvent	Catalytic species (%)		
		Enamine	Iminium ion	Free catalyst
1	CD_2Cl_2	61	-	39
2	$CDCl_3$	61	-	39
3	MeCN-d_3	92	-	8
4	toluene-d_8	71	-	29
5	methanol-d_4	57	-	43
6	DMSO-d_6	80	-	20
7	THF-d_8	93	-	7
8	*t*-BuOMe	90	-	10
9	*i*-PrOH	66	-	34
10	**HFIP**	-	97	3



1) Hutchinson, G.; Ferrer, C. A.; Burès, J. *J. Am. Chem. Soc.* **2021**, *143*, 6805-6809.

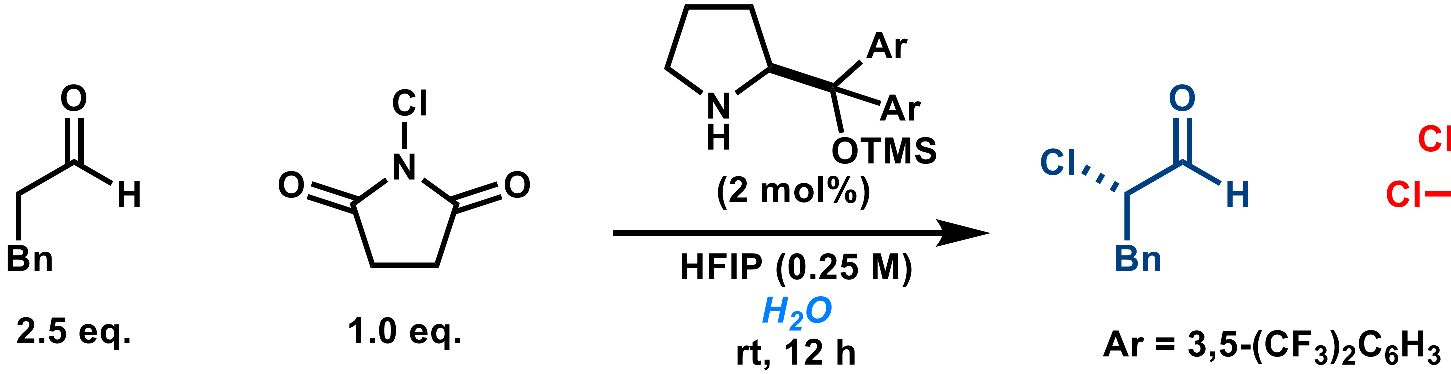
Dichlorination Occurred at the First Trial



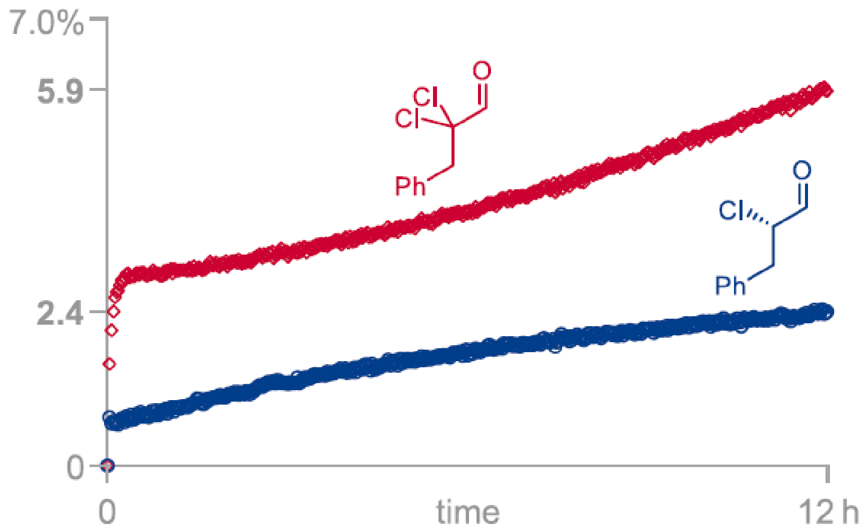


1) Hutchinson, G.; Ferrer, C. A.; Burès, J. *J. Am. Chem. Soc.* **2021**, *143*, 6805-6809.

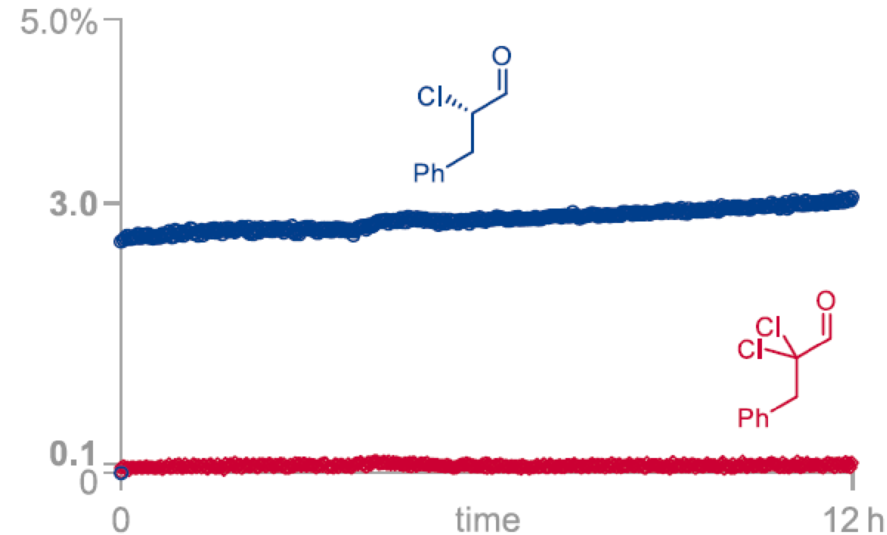
Addition of Water was Insufficient



a) $[H_2O]_o$ = 0 M

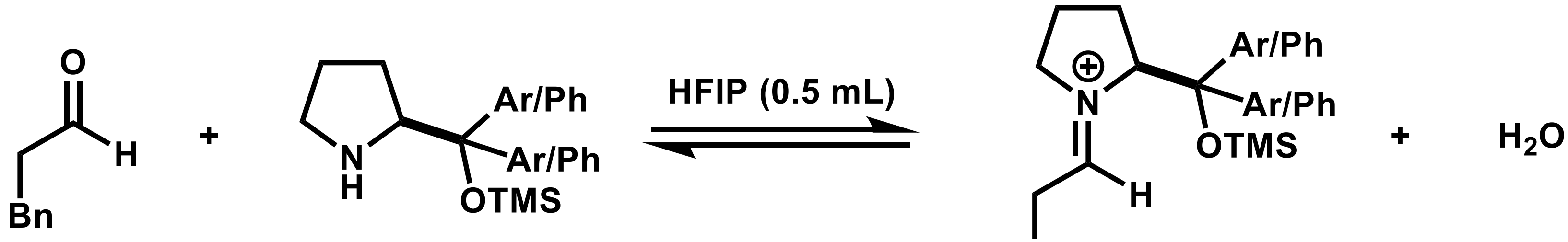


b) $[H_2O]_o$ = 11.15 M



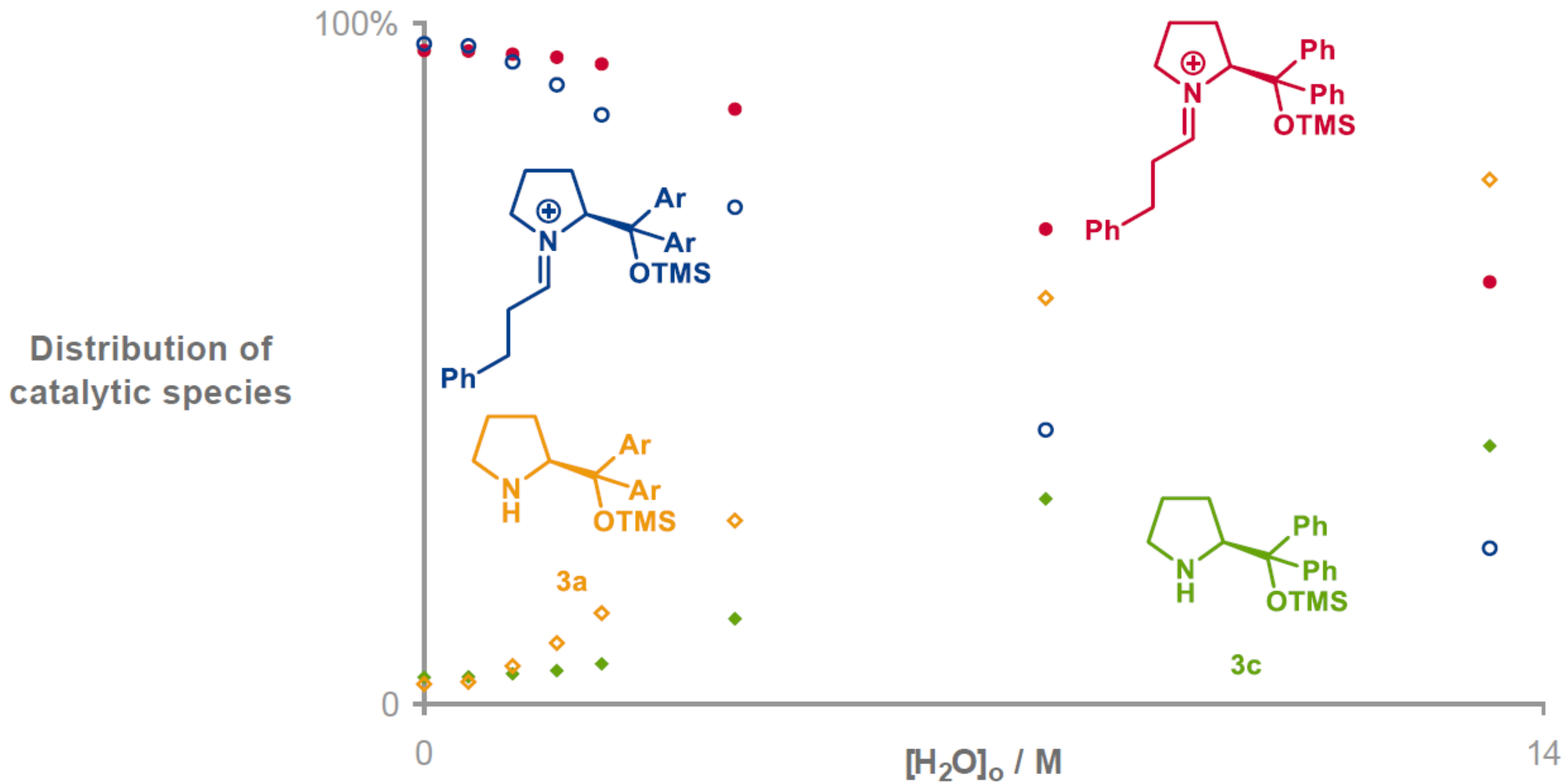
1) Hutchinson, G.; Ferrer, C. A.; Burès, J. *J. Am. Chem. Soc.* **2021**, *143*, 6805-6809.

Water Shifted Equilibrium of Catalyst



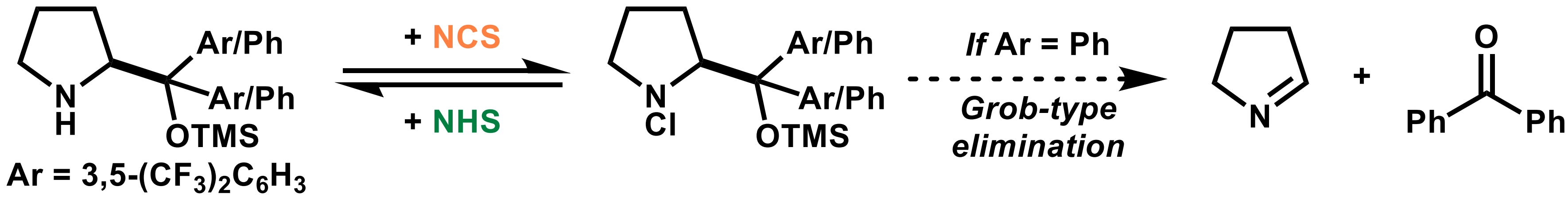
Ar = 3,5-(CF$_3$)$_2$C$_6$H$_3$
Green/ Yellow

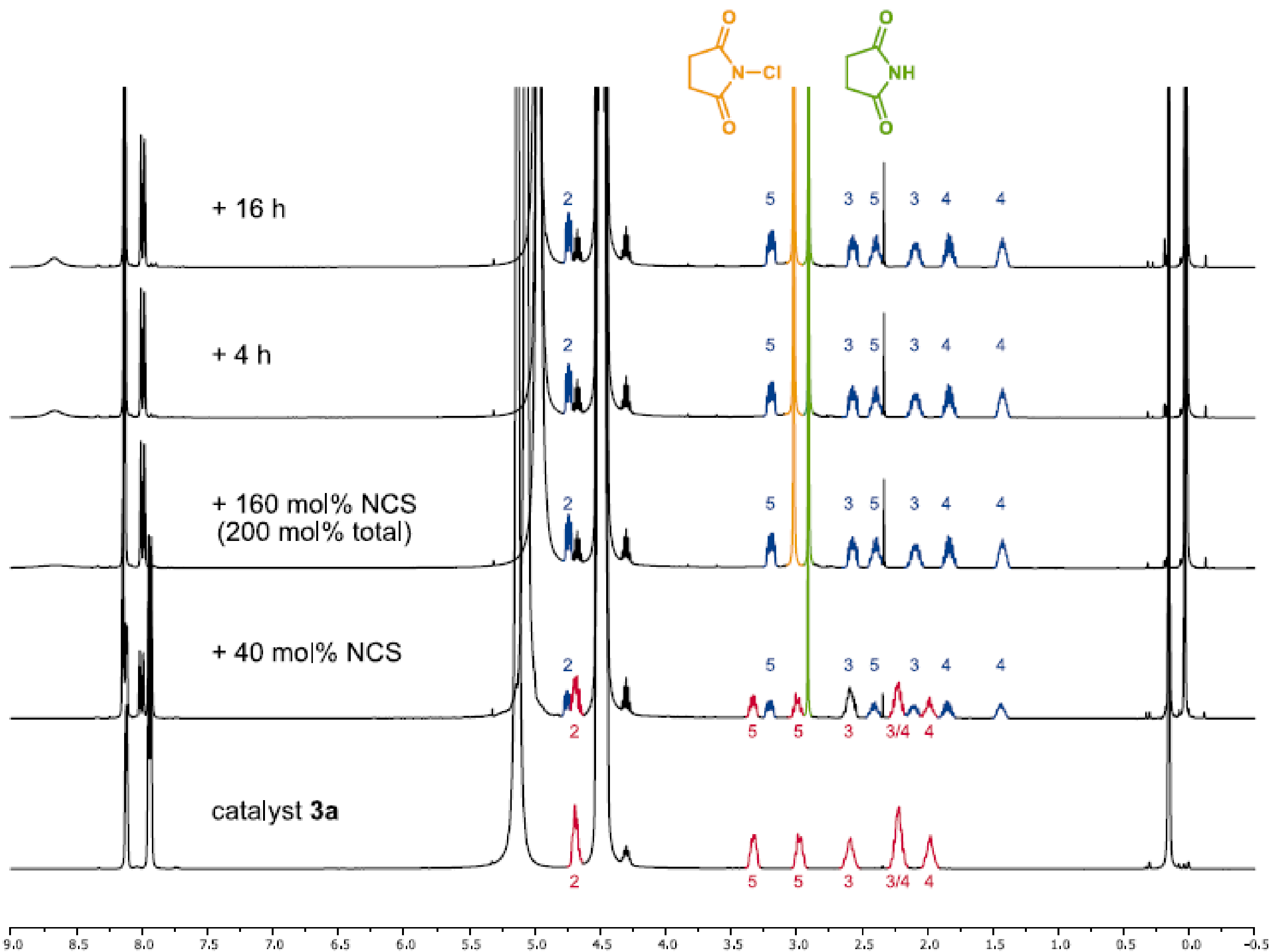
Red/ Blue



1) Hutchinson, G.; Ferrer, C. A.; Burès, J. *J. Am. Chem. Soc.* **2021**, *143*, 6805-6809.

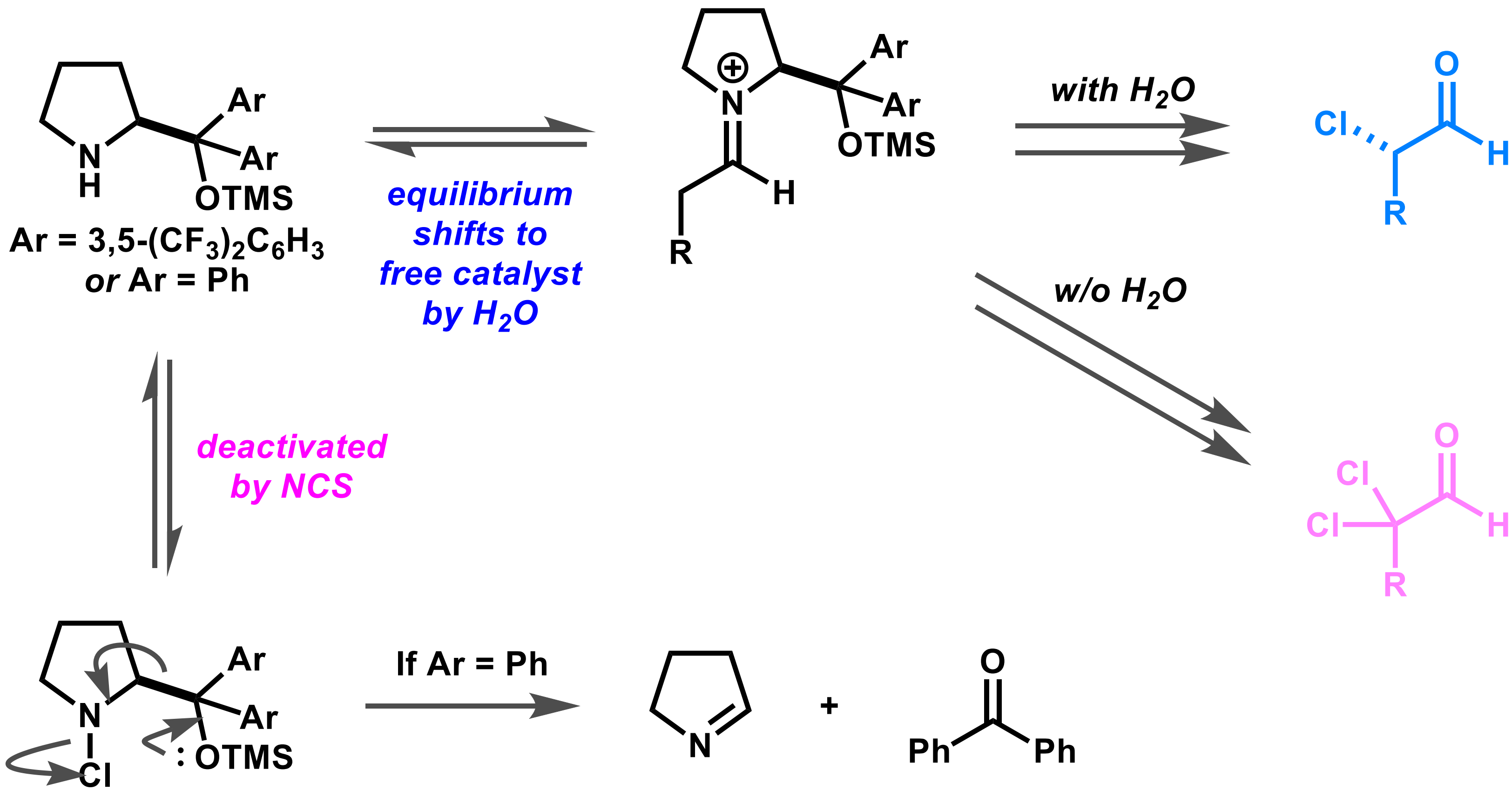
Deactivation of Catalyst





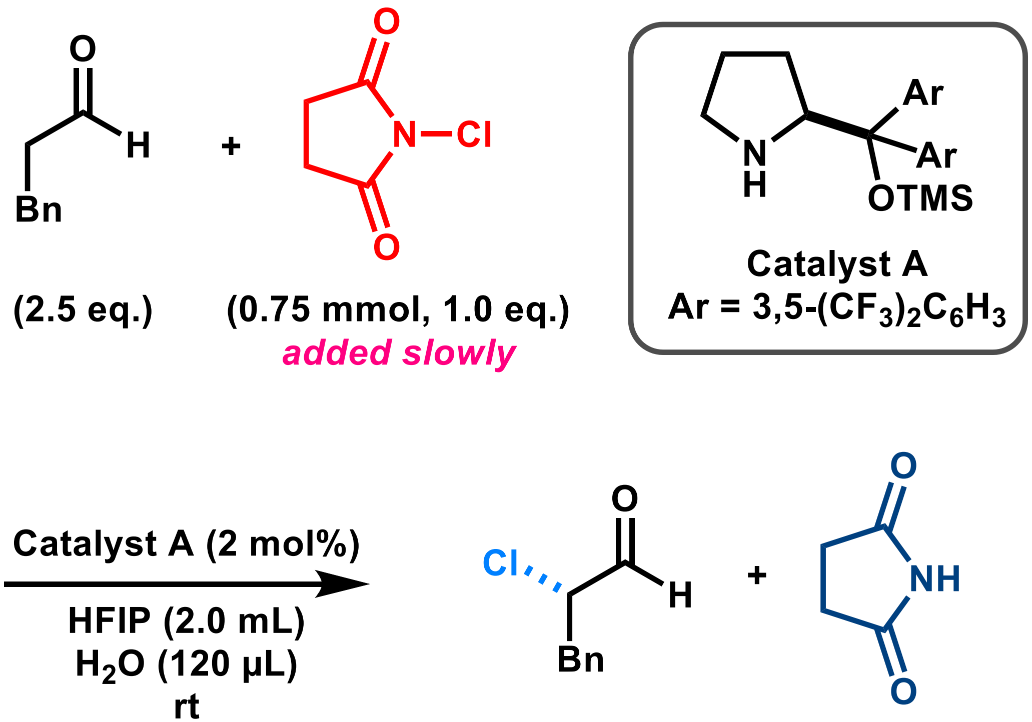
1) Hutchinson, G.; Ferrer, C. A.; Burès, J. *J. Am. Chem. Soc.* **2021**, *143*, 6805-6809.

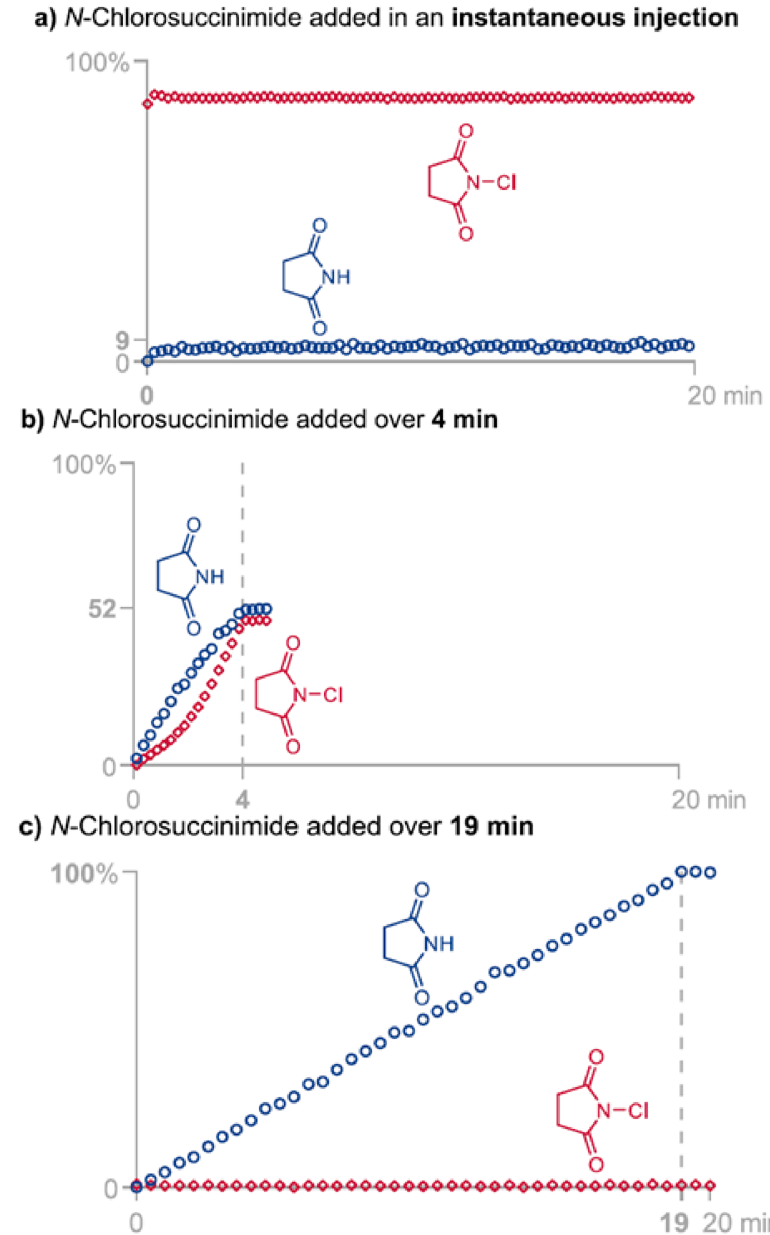
Short Summary of Deactivated Pathway



1) Hutchinson, G.; Ferrer, C. A.; Burès, J. *J. Am. Chem. Soc.* **2021**, *143*, 6805-6809.

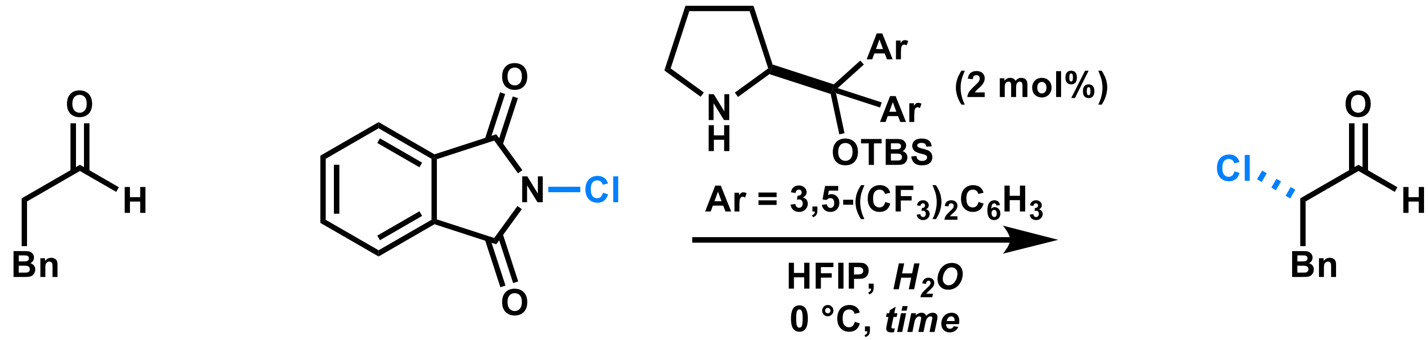
Controlling the Speed of Addition





1) Hutchinson, G.; Ferrer, C. A.; Burès, J. *J. Am. Chem. Soc.* **2021**, *143*, 6805-6809.

Other Conditions

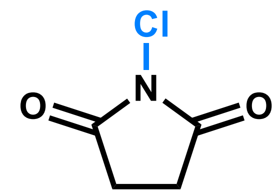


A (1.88 mmol, 2.5 eq.)

NCP (0.75 mmol, 1.0 eq.) added slowly

Entry	Deviation from above	H_2O (μL)	Time of addition of NCP (min)	yield (%)[a]	ee. (%)[b]
1	none	35	60	85	98
2	NCS instead of NCP	35	50	84	94
3	1 mol% of catalyst	10	150	85	96
4	rt instead of 0 °C	30	20	91	94
5[c]	A: NCP = 1: 1.2	40	150	68	94

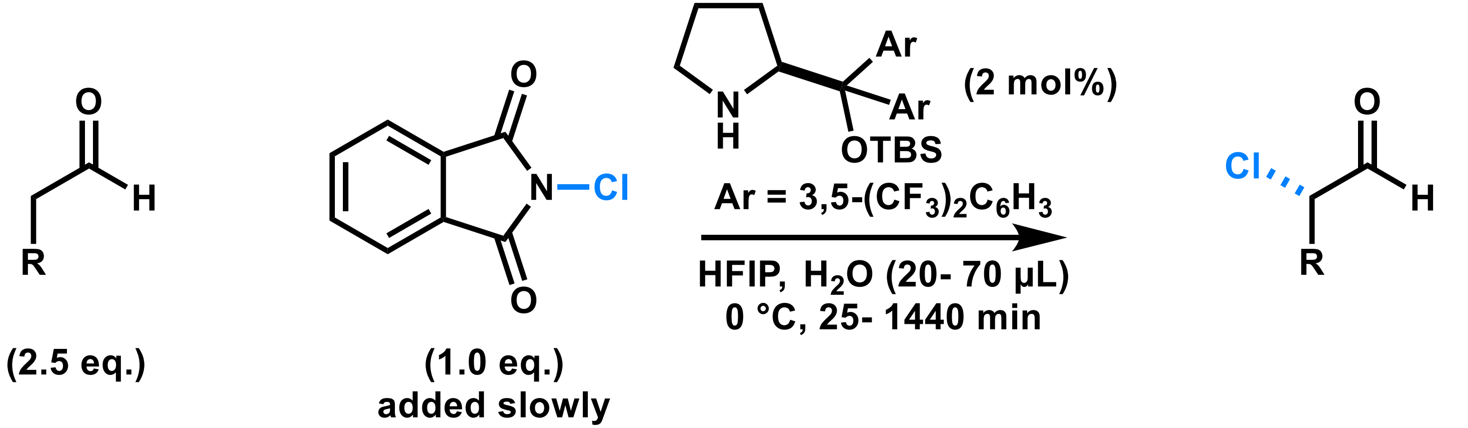
[a] Measured by standard addition with the ReactIR 15[2)]. [b] Determined after reduction of the α-chloroaldehyde to the α-chloroalcohol. [c] A (0.76 mmol) with NCP (0.90 mmol)



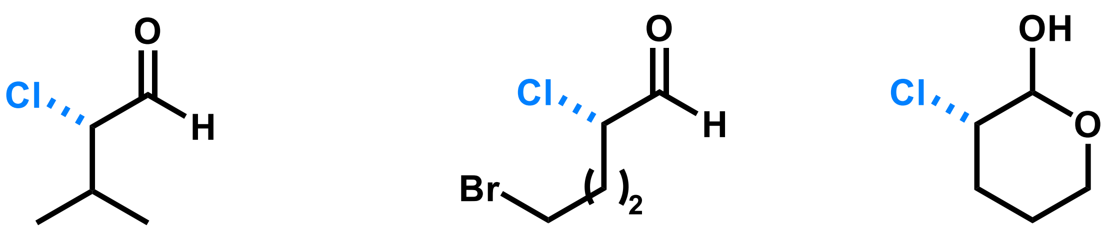
NCS

1) Hutchinson, G.; Ferrer, C. A.; Burès, J. *J. Am. Chem. Soc.* **2021**, *143*, 6805-6809.
2) Hutchinson, G.; Welsh, C. D. M.; Burés, J. *J. Org. Chem.* **2021**, *86,* 2012-2016.

Substrate Scope



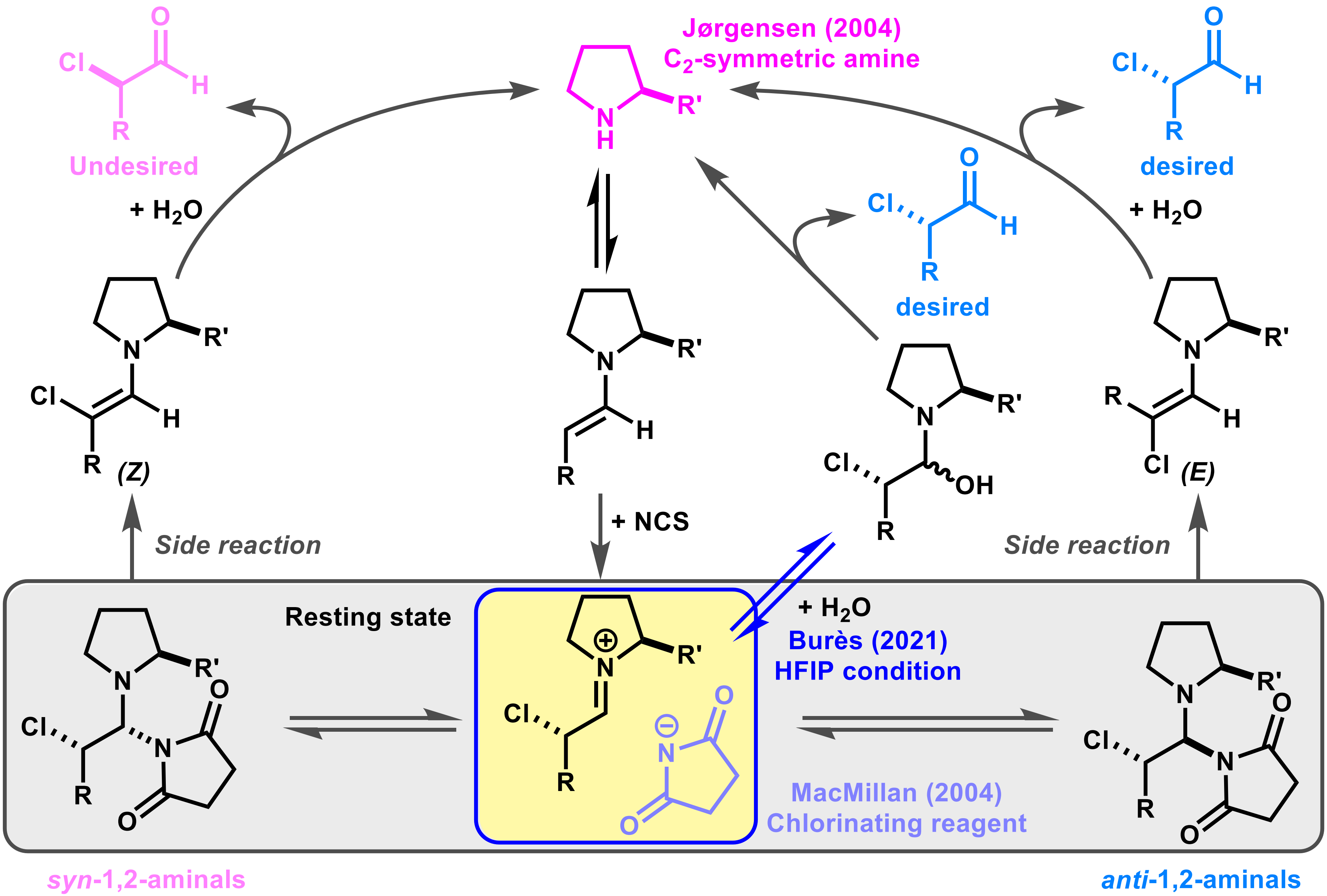
76%, 98% ee. 78%, 96% ee. 77%, 98% ee. 66%, 98% ee.



80%, 98% ee. 80%, 96% ee. 68%, 98% ee.

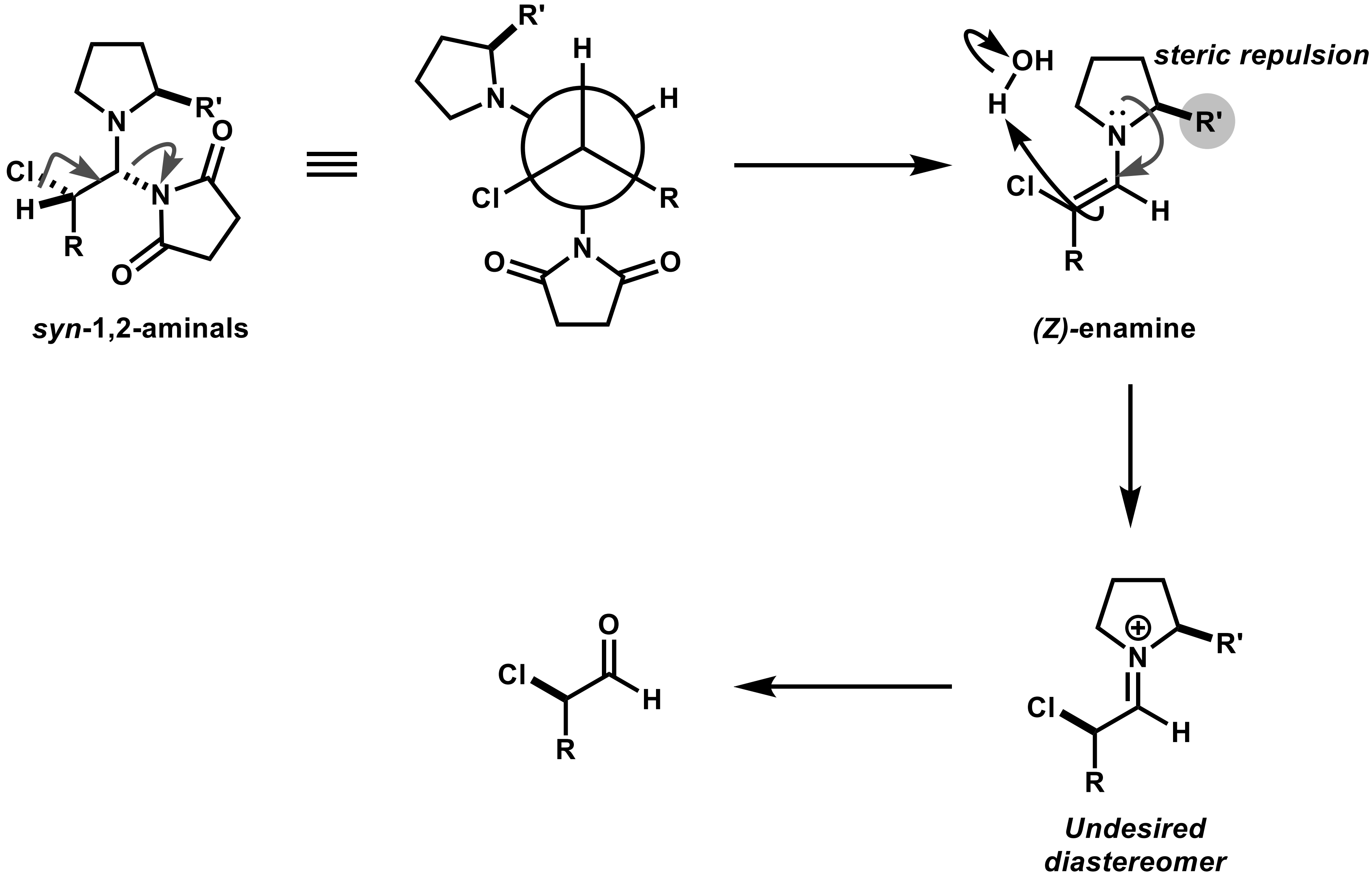
1) Hutchinson, G.; Ferrer, C. A.; Burès, J. *J. Am. Chem. Soc.* **2021**, *143*, 6805-6809.

Summary

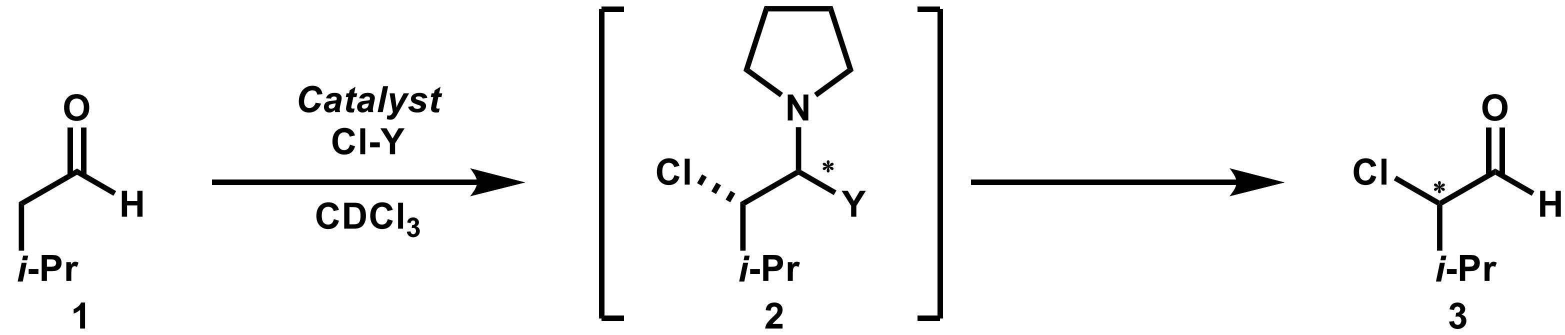

Jørgensen (2004)
C2-symmetric amine
R'
N
H
Cl
O
H
R
Undesired
+ H2O
desired
+ H2O
(Z)
(E)
OH
Side reaction
Side reaction
+ NCS
Resting state
+ H2O
Burès (2021)
HFIP condition
MacMillan (2004)
Chlorinating reagent
syn-1,2-aminals
anti-1,2-aminals

Appendix

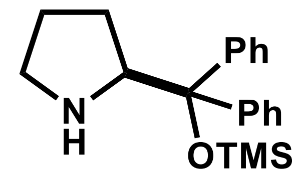
Stereoselectivity of racemization



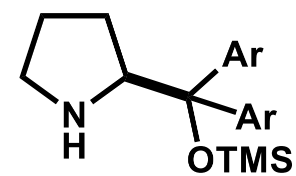
About racemization



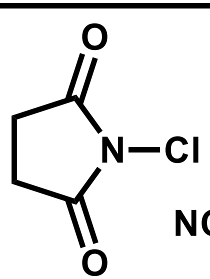
Entry	Catalyst	Cl-Y	dr. *sym*-2: *anti*-2	er. *R*-3: *S*-3
1	A	NCS	30: 70	29: 71
2	B	NCS	16:84	16:84
3	C	NCS	< 5: 95	3: 97
4	A	NCP	26: 74	23: 77
5	B	NCP	21: 79	21: 79
6	C	NCP	< 5: 95	3: 97



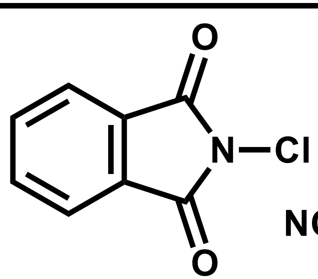
A



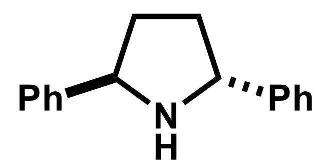
B
(Ar = 3,5-$(CF_3)_2C_6H_3$)



NCS



NCP

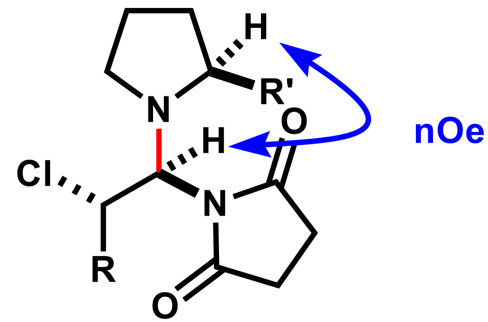


C

1) Burès, J.; Armstrong, A.; Blackmond, G. C.; *J. Am. Chem. Soc.* **2012**, *134*, 6741-6750.

Determination of *anti*-1,2-aminals

C-N bond cannot rotate due to the steric limitation (succinimide and R' are too large to rotate)



equilibrium.

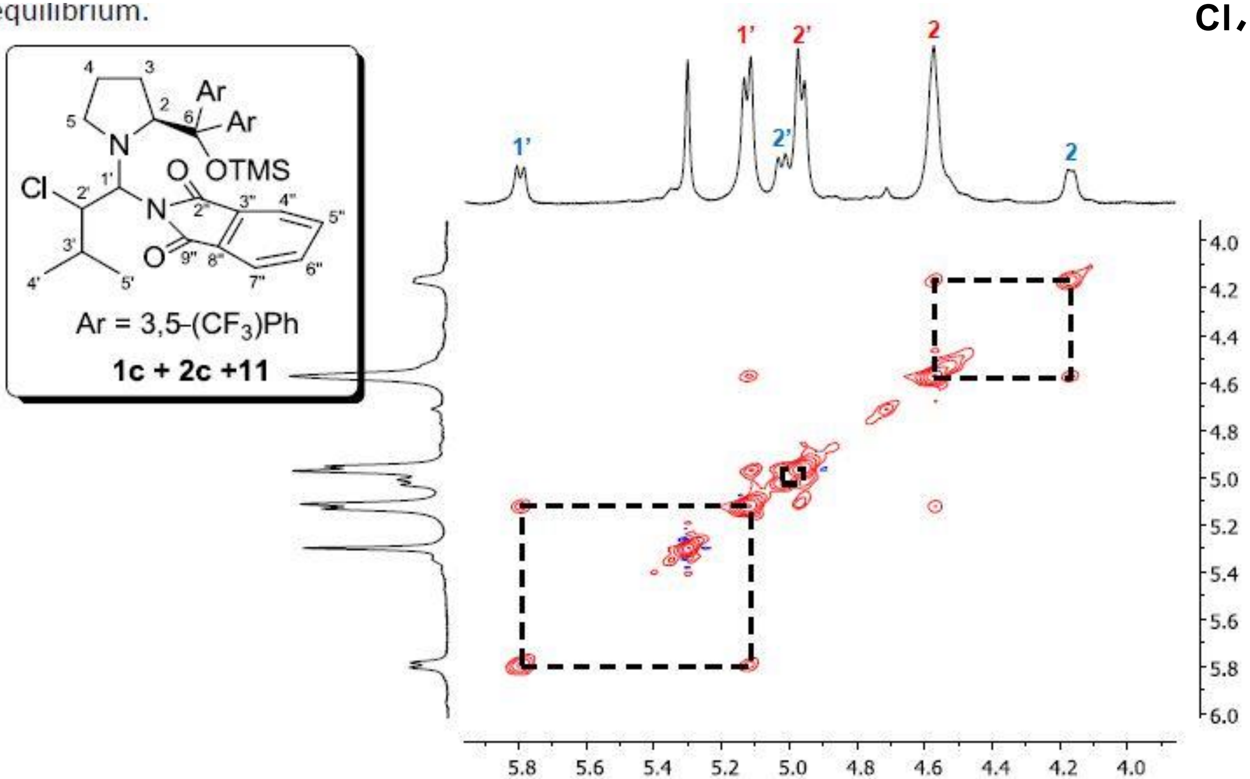
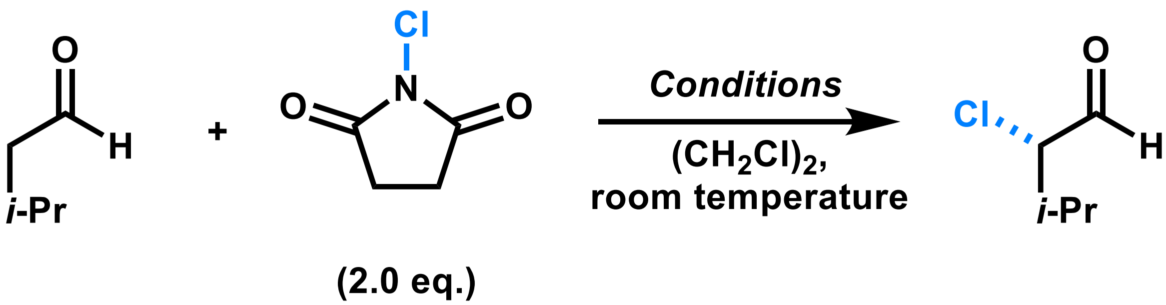
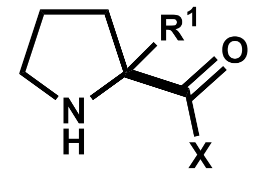


Figure 25. EXSY cross-peaks in the NOESY of intermediates from 1c + 2c + catalyst 11 at −54 °C.

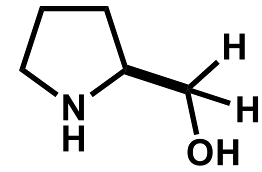
1) Burès, J.; Armstrong, A.; Blackmond, G. C.; *J. Am. Chem. Soc.* **2012**, *134*, 6741-6750.

Other Catalysts in Jørgensen's experiment

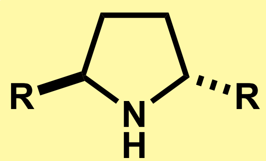




1c: R^1 = Me, X = OH
1d: R^1 = H, X = NH*i*-Pr
1e: R^1 = H, X = NHGly



2c



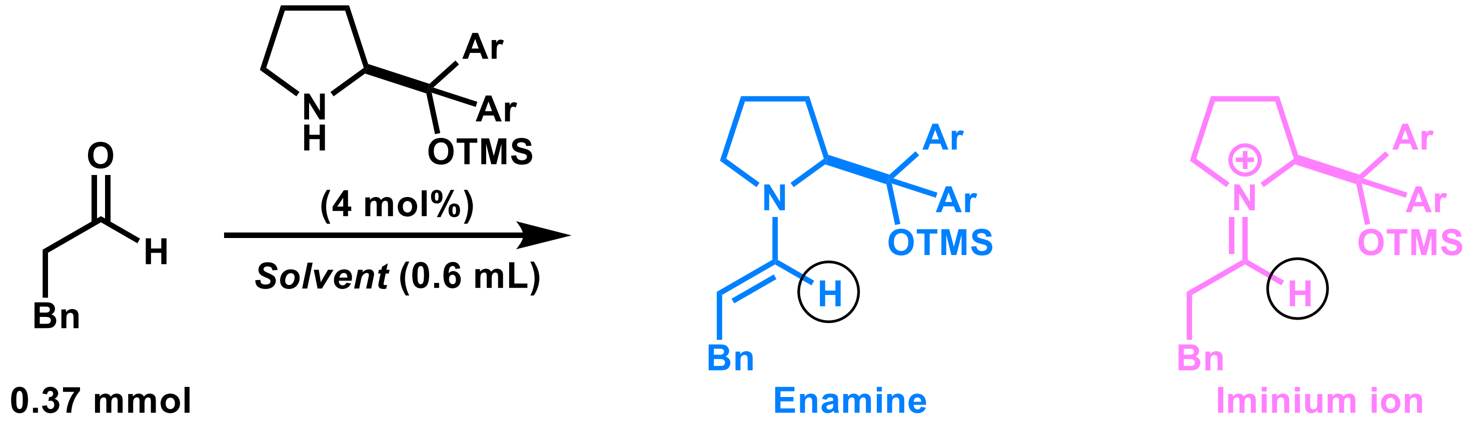
3a: R = Ph
3b: R = Bn

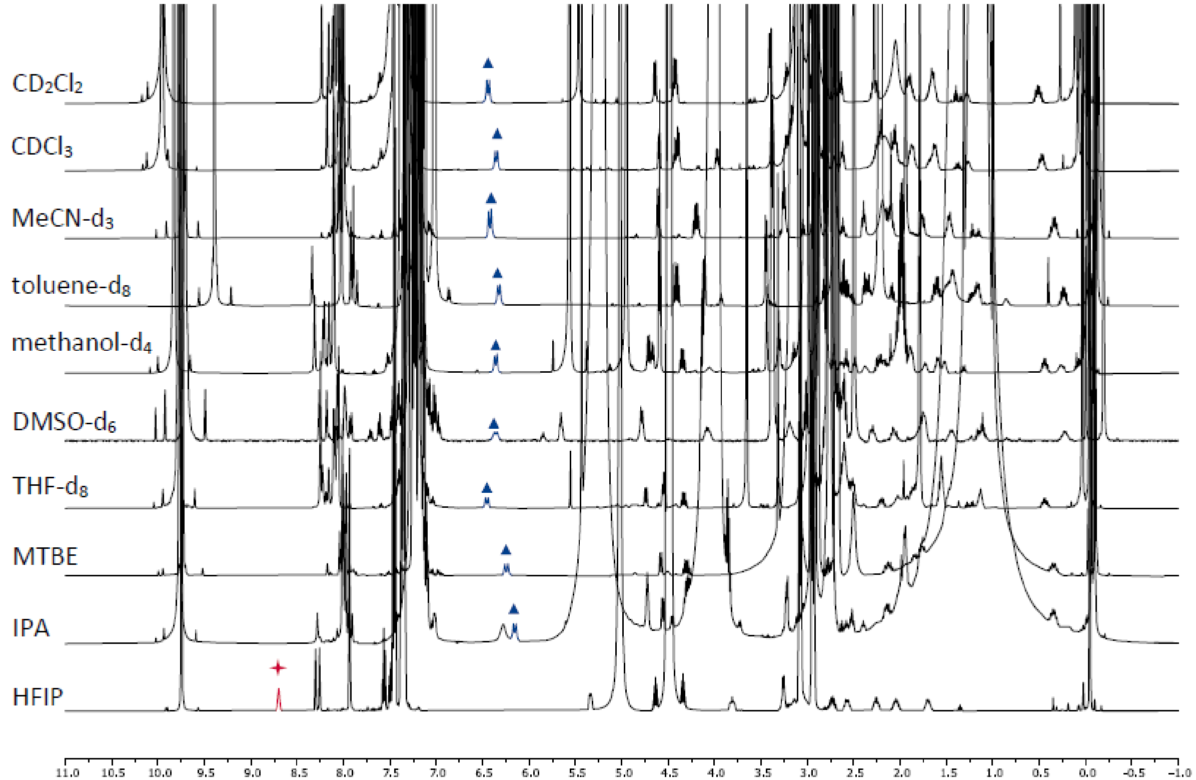
Entry	Catalyst (mol%)	Time (h)	Conversion (%)[a]	ee. (%)[b]
1	1c (20)	5.0	76	60
2	1d (20)	0.5	> 95	54
3	1e (20)	1.0	33	81
4	2b (20)	0.5	92	64
5	3a (20)	0.5	> 95	94
6	3a (10)	1.0	> 95	94
7	3a (5)	1.0	78	94
8	3b (20)	1.0	< 10	78

[a] Measured by ^1H NMR of the crude reaction mixture and confirmed by GC, due to the high volatility of the products. [b] ee determined by GSP-GC.

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

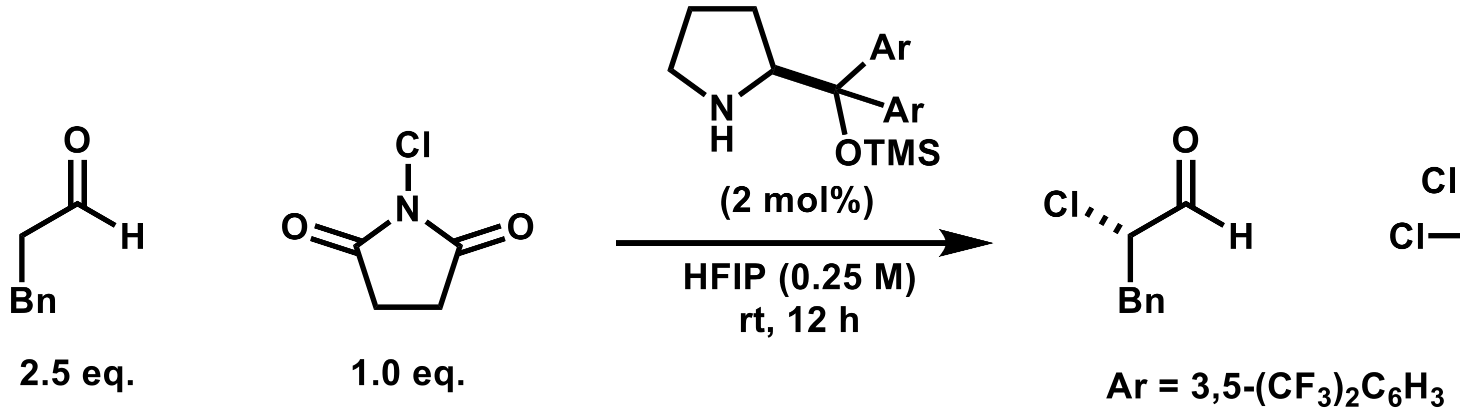
1H NMR Data of Enamine/Iminium cation

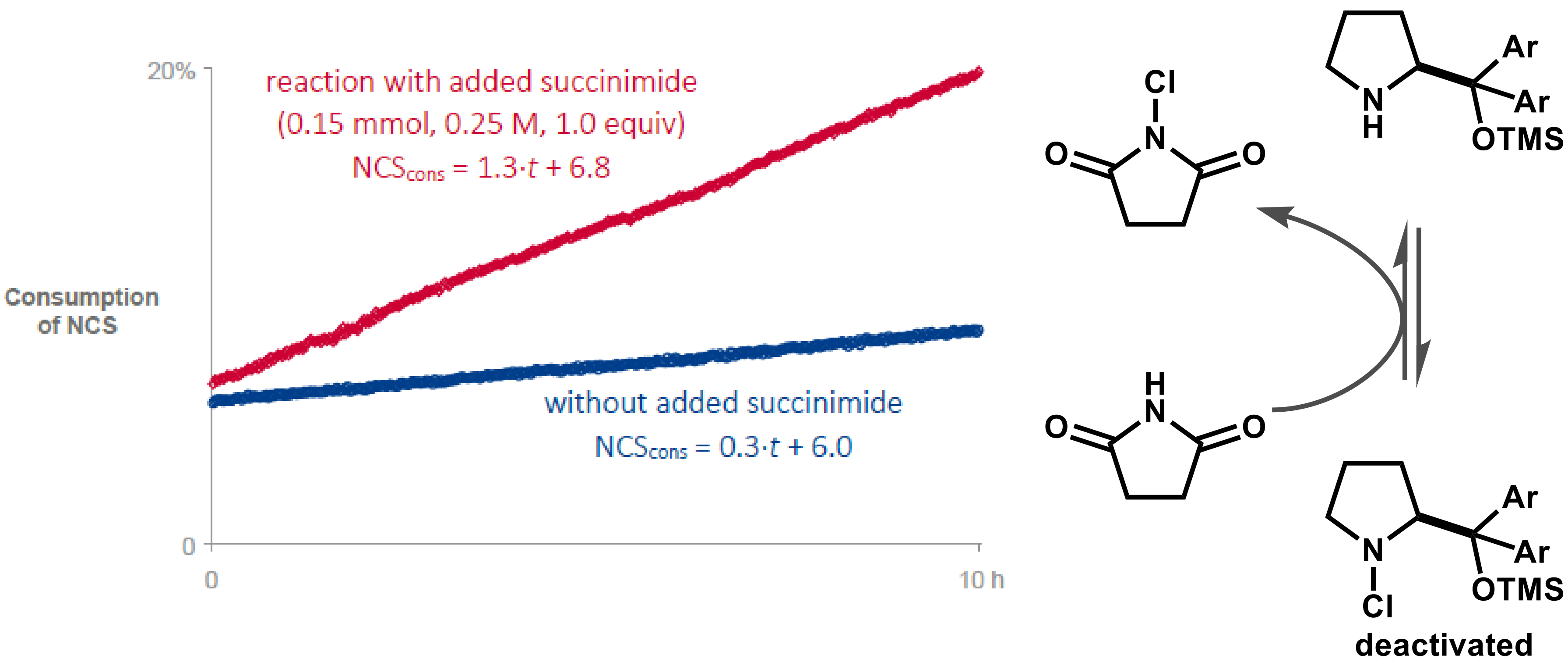




1) Hutchinson, G.; Ferrer, C. A.; Burès, J. *J. Am. Chem. Soc.* **2021**, *143*, 6805-6809.

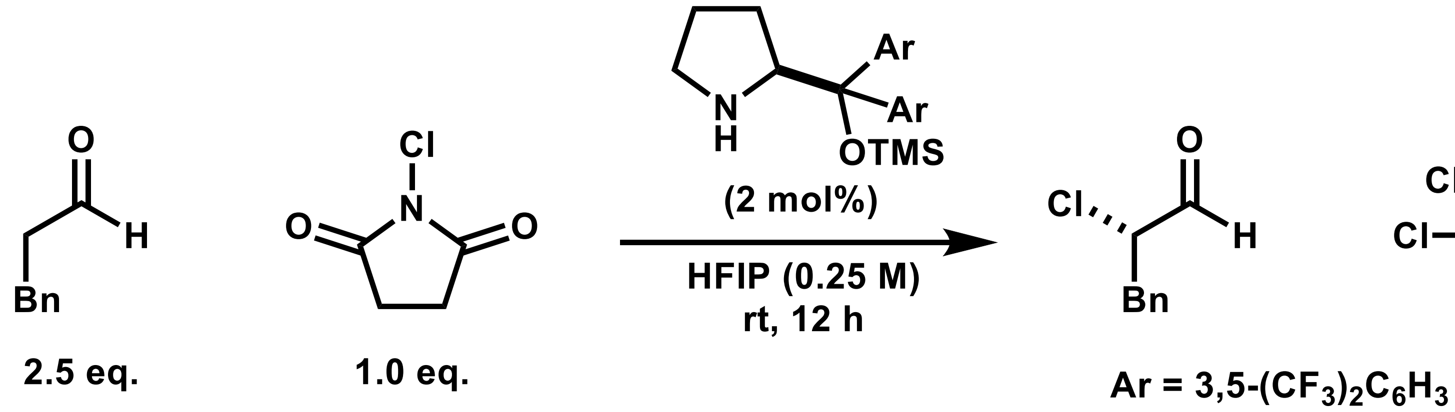
Investigation of deactivation process (1)

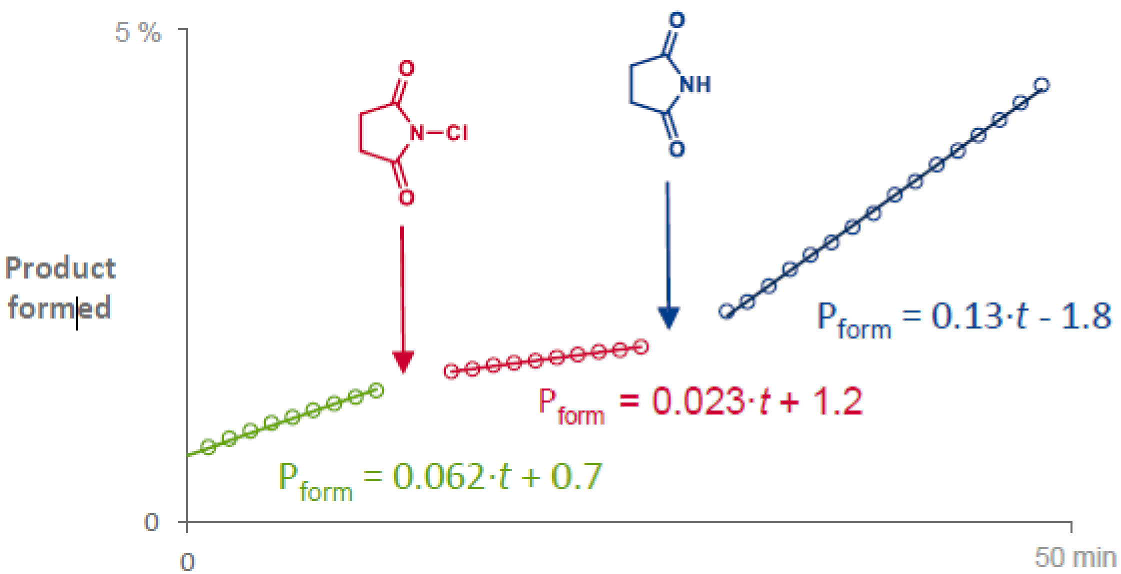


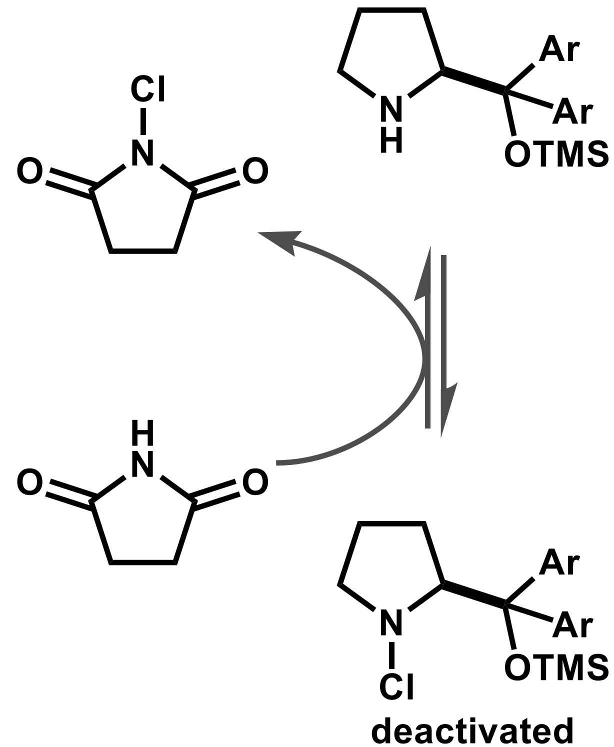


1) Hutchinson, G.; Ferrer, C. A.; Burès, J. *J. Am. Chem. Soc.* **2021**, *143*, 6805-6809.

Investigation of deactivation process (2)

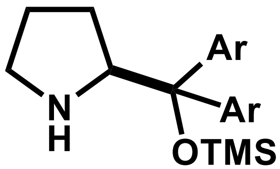


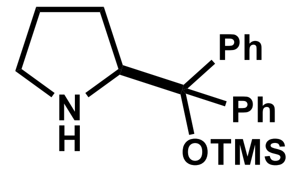


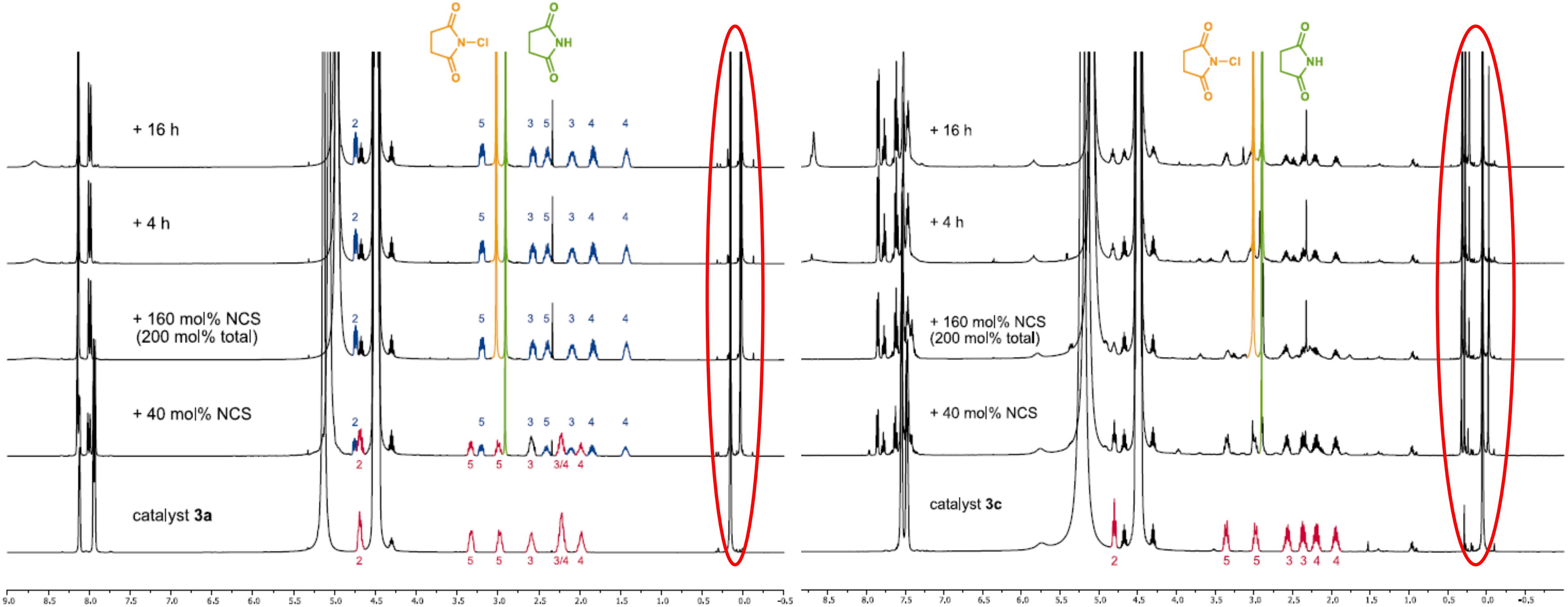


1) Hutchinson, G.; Ferrer, C. A.; Burès, J. *J. Am. Chem. Soc.* **2021**, *143*, 6805-6809.

Investigation of deactivation process (3)

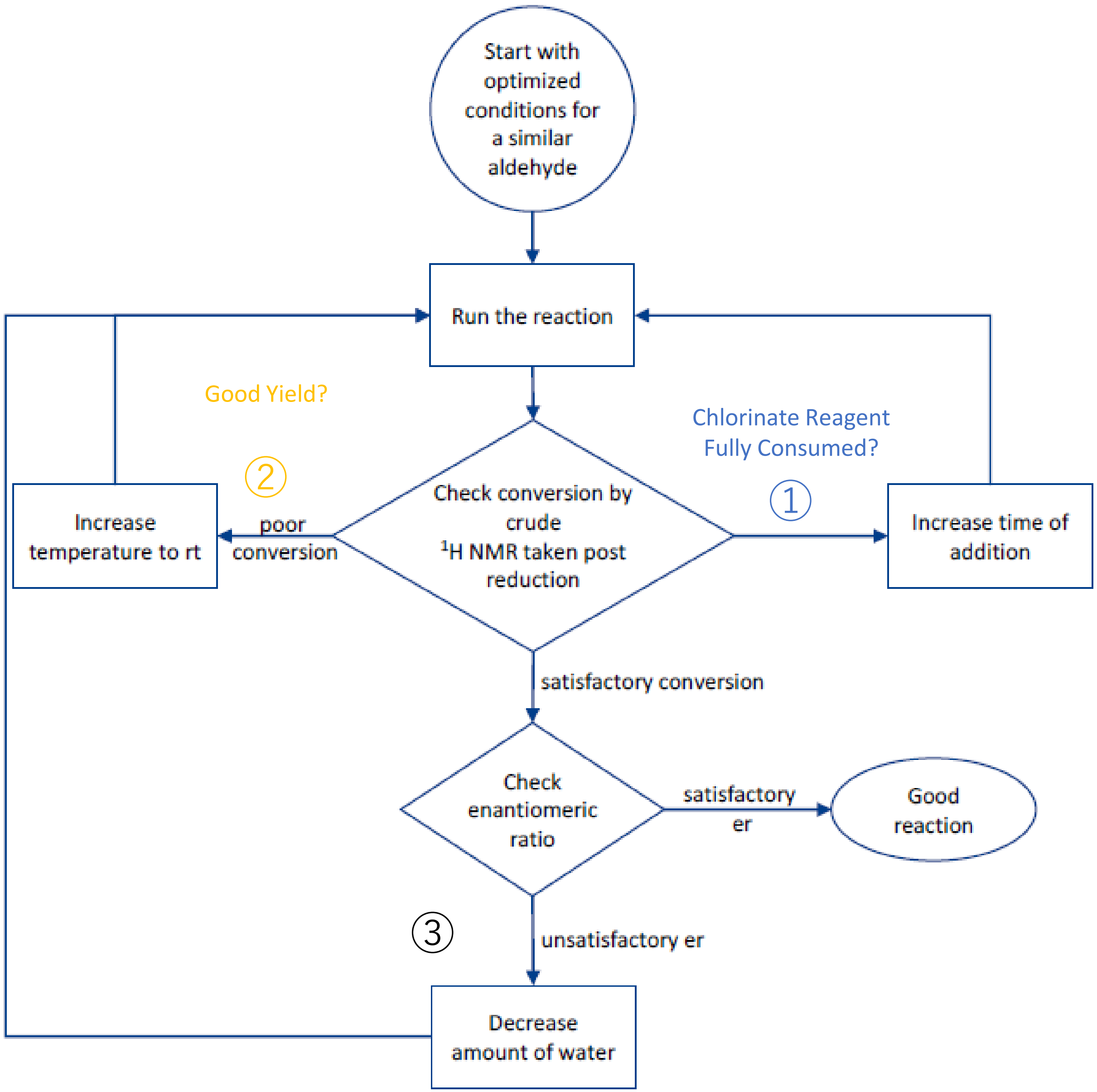


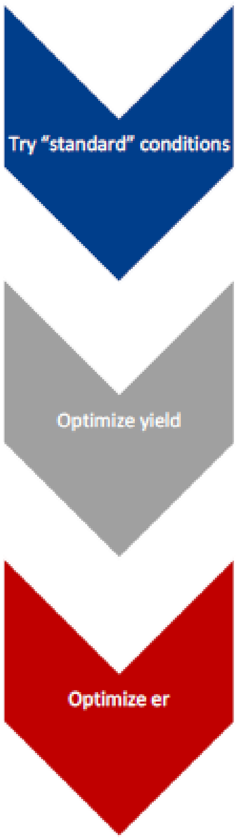




1) Hutchinson, G.; Ferrer, C. A.; Burès, J. *J. Am. Chem. Soc.* **2021**, *143*, 6805-6809.

Optimization procedure for chlorination





1) Hutchinson, G.; Ferrer, C. A.; Burès, J. *J. Am. Chem. Soc.* **2021**, *143*, 6805-6809.