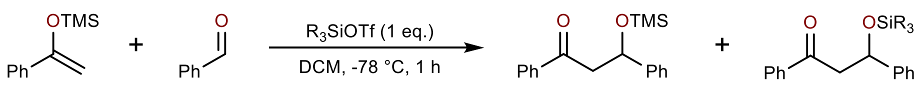
Super Silyl Group in Organic Synthesis

Introduction:

- super silyl = $Si(TMS)_3$ or $Si(TES)_3$
- Unless otherwise noted, Si = $Si(TMS)_3$
- Useful for synthesis of polyketide-like units
- Diastereoselectivity follows Felkin-selectivity

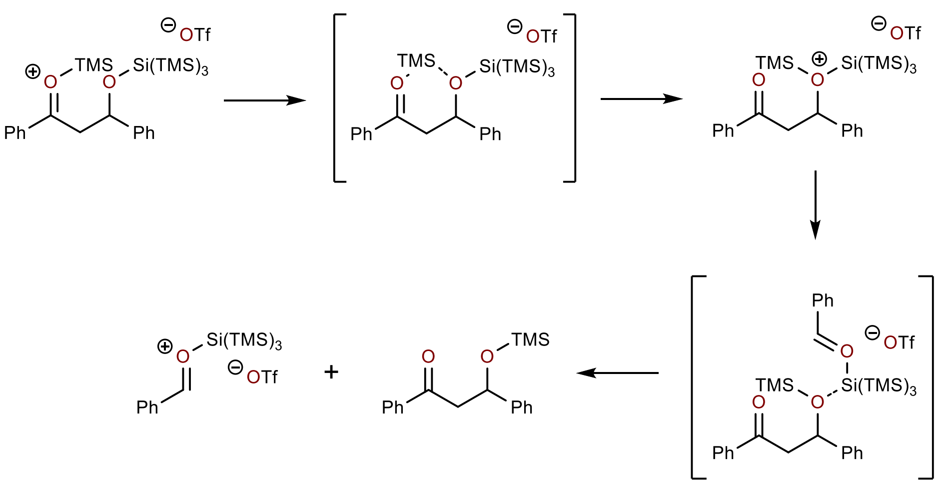
Mukaiyama Aldol Reactions:

Chemoselective Silyl Transfer



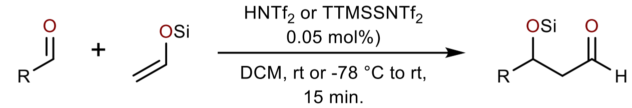
R_3Si	Yield	Yield
TBS	71%	27%
TIPS	86%	10%
$(TMS)_3$	95%	0%
$(TES)_3$	94%	0%

- Exclusive formation of the TMS aldolate via intramolecular TMS^+ transfer
- Addition of aldehyde to $(TMS)_3Si^+$ energetically more favored than TMS^+

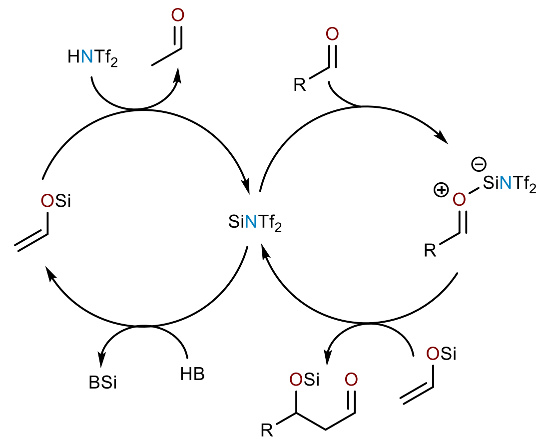


Yamamoto, H. *Chem. Chem.* **2014**, *50*, 15206. https://doi.org/10.1039/c4cc05807k

Acetaldehyde Derived



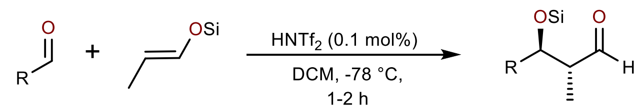
R = alkyl, allyl, aryl



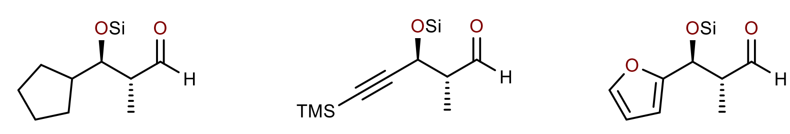
- Consistently high yields of desired 1:1 aldol adduct with aliphatic, branched, aromatic, and α,β-γ,δ-unsaturated aldehydes

Yamamoto, H. *JACS* **2007**, *129*, 2762. https://doi.org/10.1021/ja0693542

α-Substituted



R = alkyl, aryl, alkynyl, allyl



Si	Yield	dr
$Si(TMS)_3$	82%	86:14
$Si(TES)_3$	86%	96:4

Si	Yield	dr
$Si(TMS)_3$	67%	79:21
$Si(TES)_3$	63%	94:6

Si	Yield	dr
$Si(TMS)_3$	95%	>97:3

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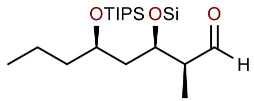
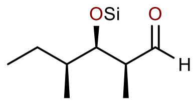
R = alkyl, aryl, alkynyl, allyl

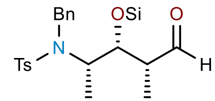


Si	Yield	dr
$Si(TMS)_3$	76%	88:12



Si	Yield	dr
$Si(TMS)_3$	85%	83:13:3:2

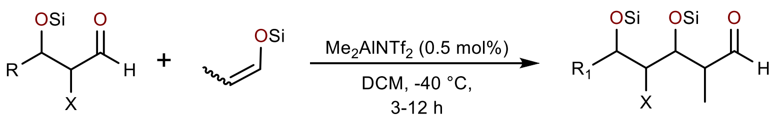
er = 96:4



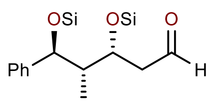
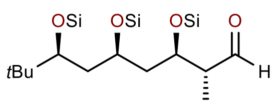
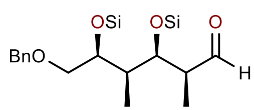
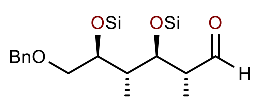
Si	Yield	dr
$Si(TMS)_3$	78%	>97:3

er = 99:1

- Higher reactivity with <0.5 mol% $AlMe_2NTf_2$ for consecutive additions

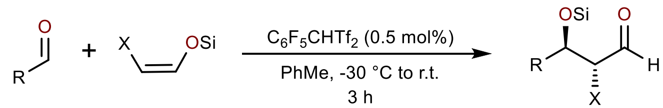


R = alkyl, aryl, alkynyl, allyl

R	X	enol ether	Product	dr	Yield
Ph	Me	*E* then acetone		96:4	86% (67% using $HNTf_2$)
*t*Bu	H	acetaldehyde then *E*		-	45%
$BnOCH_2$	Me	*Z*		89:7:2:2	48%
$BnOCH_2$	Me	*E*		86:14	63%

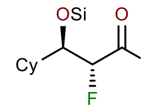
Yamamoto, H. *ACIE* **2012**, *51*, 1942. https://doi.org/10.1002/anie.201108325

α-Halogenated

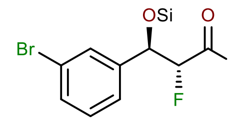


R = alkyl, aryl, alkynyl, allyl, heteroaryl

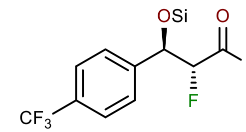
X = F



Yield	dr
58%	91:9

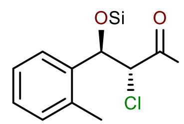


Yield	dr
82%	96:4

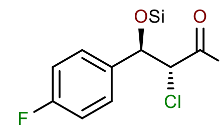


Yield	dr
74%	95:5

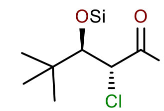
X = Cl



Yield	dr
68%	99:1

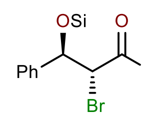


Yield	dr
75%	>99:1

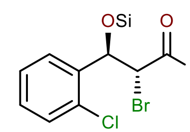


Yield	dr
73%	>99:1

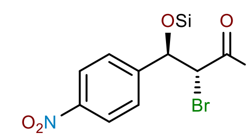
X =Br



Yield	dr
77%	97:3

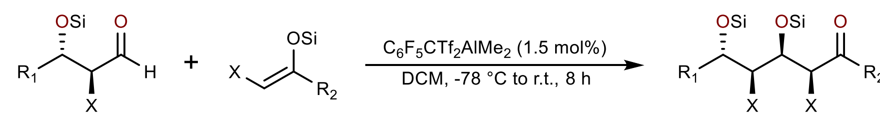


Yield	dr
85%	96:4



Yield	dr
89%	95:5

- Triflimide catalyst only effective for aromatic aldehydes, while pentafluorophenylbis(triflyl)methane can also catalyze aliphatic aldehydes

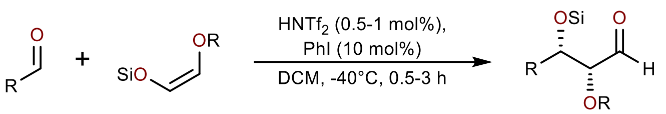


R = alkyl, aryl, alkynyl, allyl, heteroaryl

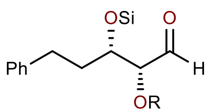
Yamamoto, H. *Chem. Eur. J.* **2011**, *19*, 3842. https://doi.org/10.1002/chem.201204493

Super Silyl Group in Organic Synthesis

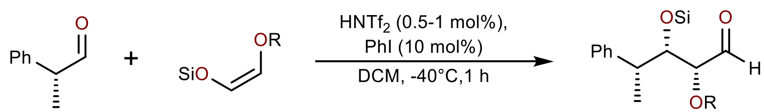
Bis(silyloxy) Enol Ethers



R = alkyl, aryl, heteroaryl, allyl, alkynyl



R	Yield	dr
$Si(TMS)_3$	68%	91:9
Bn	79%	97:3
TES	50%	98:2
allyl	42%	98:2
Me	55%	97:3



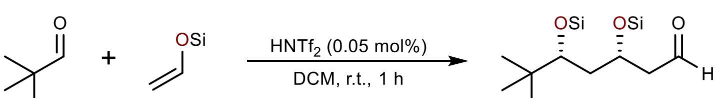
1,2-stereodirecting

R	Yield	dr
$Si(TMS)_3$	32%	65:35
Bn	53%	>99:1
allyl	62%	98:2

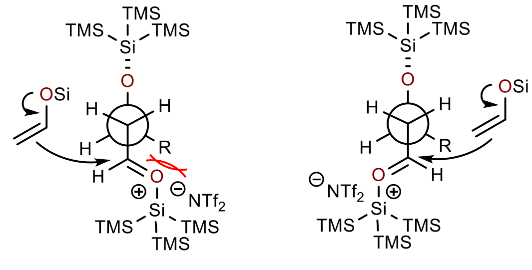
- Phenyl iodide activates silyl triflimide by stabilizing silylium cation
  - $[PhI\text{-}Si(TMS)_3]^+$ active catalyst
- Yields may improve upon use of $Si(TES)_3$
- Electron withdrawing groups on heteroaryls necessary for reaction to occur

Yamamoto, H. *Chem. Sci.* **2016**, *7*, 394. https://doi.org/10.1039/c5sc03307a

Sequential Aldol-Aldol Reactions:

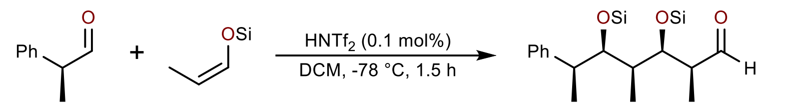


syn-product

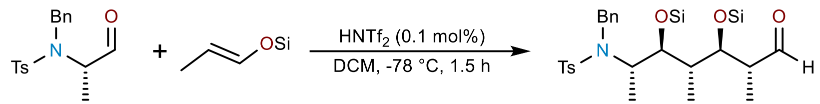


anti ***syn***

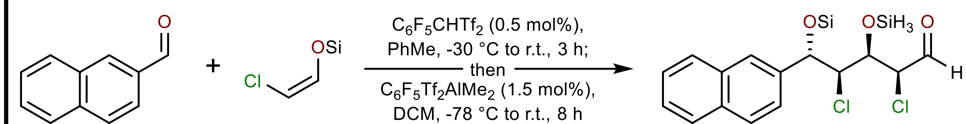
- Use of ketone gives *anti* via methyl becoming the more sterically disfavored group
- Can achieve 2,3,4,5-*syn* with *Z* enolate (*anti* with *E*)
- Process stops after 3rd addition due to steric bulk



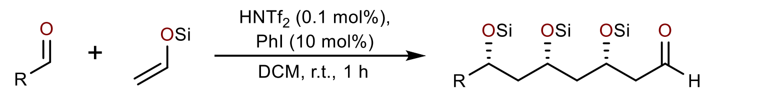
72%, dr = 94:4:1:1



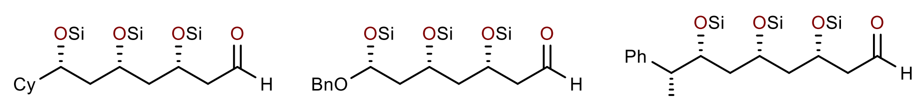
74%, dr = 97:3



82%, dr = 95:5



1,3-*syn*-adduct



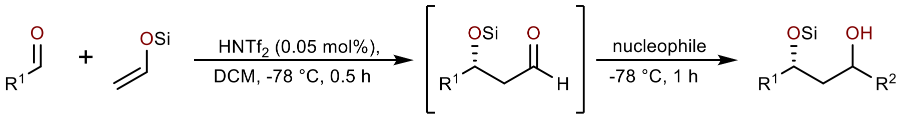
87% dr = 81:9:8:<2 — 75% dr = 81:9:8:<2 — 54% dr = not determined

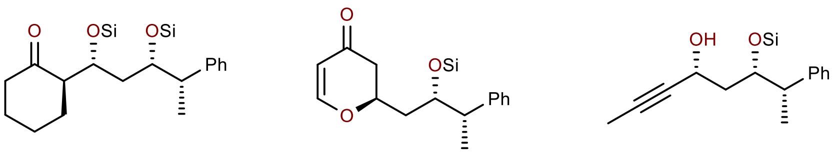
Yamamoto, H. *ACIE* **2012**, *51*, 1942. https://doi.org/10.1002/anie.201108325
Yamamoto, H. *Chem. Sci.* **2016**, *7*, 394. https://doi.org/10.1039/c5sc03307a

Super Silyl Group in Organic Synthesis

Sequential Aldol-Carbanion Addition Reactions:

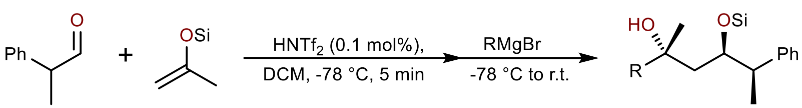
- High *dr* one-pot sequential strong-acid, strong-base system





80% dr = 97:2:<1:<1 | 63% dr = 95:4:<1:<1 | 79% dr = 86:13:<1:<1

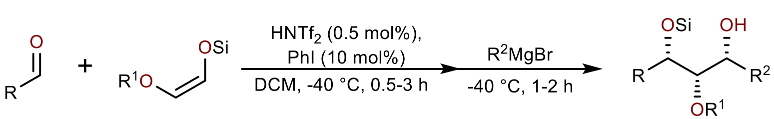
Yamamoto, H. *JACS* **2007**, *129*, 2763. https://doi.org/10.1021/ja0693542

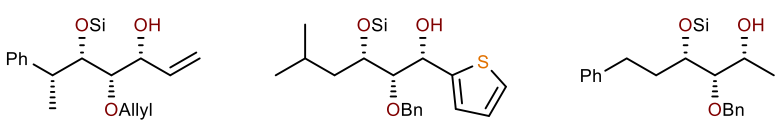


85% dr = 95:5

- Preference for *anti* isomer by 2.6 kcal/mol in TS via DFT calculations
- Super silyl creates large umbrella-like structure under which rest of molecule aligns, restricting conformational freedom
- Can differentiate between methyl and ethyl

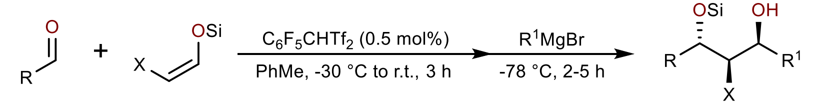
Yamamoto, H. *JACS* **2008**, *130*, 1580. https://doi.org/10.1021/ja7102586

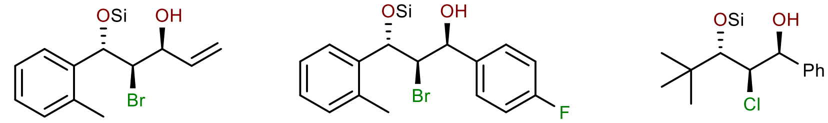




63%, dr >99:1:0 | 75%, dr >99:1:0 | 84%, dr >99:1:0

Yamamoto, H. *Chem. Sci.* **2016**, *7*, 394. https://doi.org/10.1039/c5sc03307a

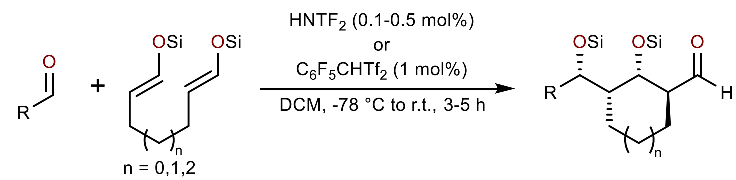


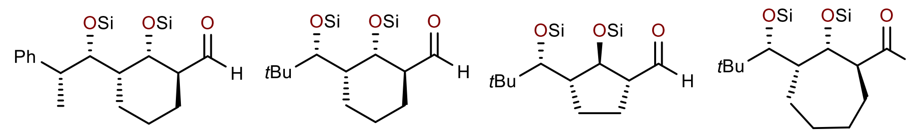


71%, dr = 94:1:<1:<1 | 73%, dr = 97:3:<1:<1 | 84%, dr = 99:1:<1:<1

Yamamoto, H. *JACS* **2011**, *133*, 14248. https://doi.org/10.1021/ja2066169

Inter/Intramolecular Sequential Aldol Reactions:



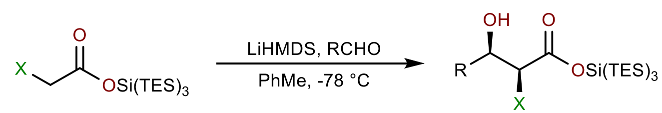


72%, dr = 100:0 | 86%, dr = 100:0 | 66%, dr = 100:0 | 52%, dr = 100:0

Yamamoto, H. *JACS* **2014**, *136*, 1308. https://doi.org/10.1021/ja413008a

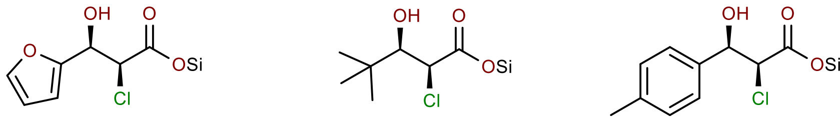
β-Hydroxy-α-Haloesters:

- *Syn*-selective
- Tolerates electron withdrawing and electron donating substituents

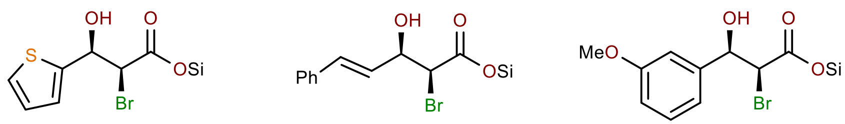


X = Cl, Br
R = aryl, alkyl, vinyl, allyl, heteroaryl

Super Silyl Group in Organic Synthesis



Yield	dr	Yield	dr	Yield	dr
78%	87:13	74%	90:10	85%	97:3



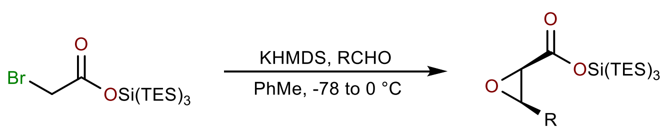
Yield	dr	Yield	dr	Yield	dr
57%	97:3	56%	90:10	58%	96:4

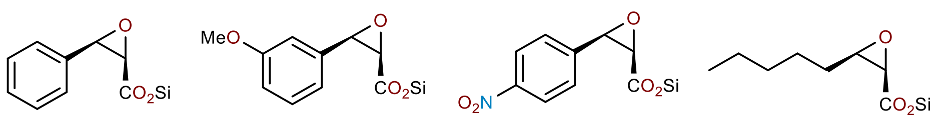
- HMPA necessary for *ortho*-substituted aryl aldehydes to have high diastereoselectivity

Yamamoto, H. *Org. Lett.* **2013**, *15*, 1308. https://doi.org/10.1021/ol402928p

Cis-Selective Darzens Reactions:

- Alternative to the typical *trans*-selective using a super silyl

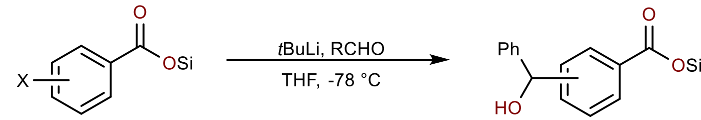


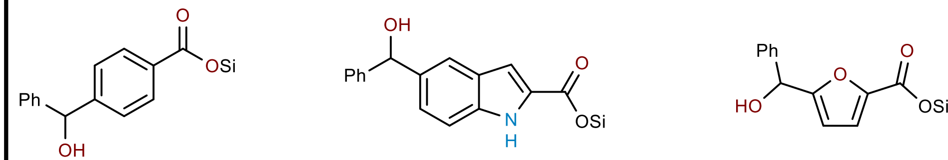


Yield	dr	Yield	dr	Yield	dr	Yield	dr
43%	87:13	48%	90:10	50%	95:5	45%	86:16

Yamamoto, H. *Org. Lett.* **2013**, *15*, 1308. https://doi.org/10.1021/ol402928p

Lithiations:





X	Yield
I	80
Br	87

X	Yield
Br	78

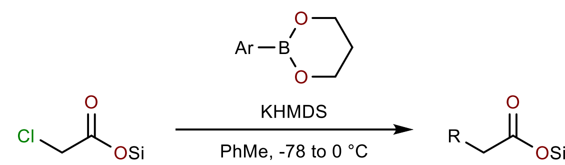
X	Yield
H	77

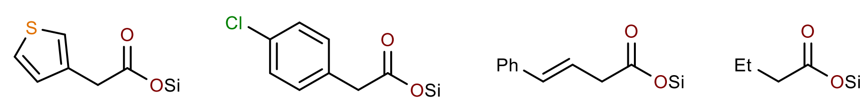
- Super silyl group is a strong and robust protecting group against highly reactive anionic species

Yamamoto, H. *ACIE* **2013**, *52*, 8165. https://doi.org/10.1002/anie.201304225

Matteson Rearrangements:

- Protects intermediates during reaction by inhibiting their condensation





74%	55%	53%	83% with LiHMDS, BR_3

Yamamoto, H. *ACIE* **2013**, *52*, 8165. https://doi.org/10.1002/anie.201304225