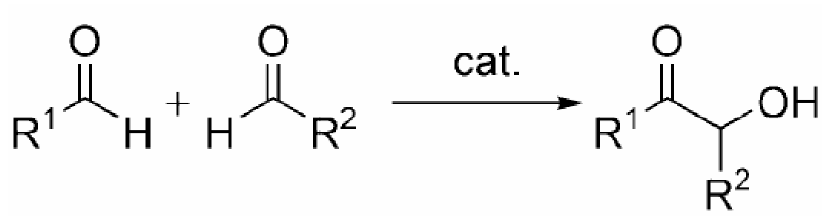
Recent Development in Catalytic Benzoin Reaction

- Some Adventures in “Umpolung Chemistry ” of Aldehydes



Leading References:

Linghu, X.; Potnick, J. R. Johnson, J. S. *JACS*, **2004**, *126*, 3070.
(Highlights) Johnson, J. S. *Ang*. **2004**, *43*, 1326.
Linghu, X.; Johnson, J. S. *Ang*. **2003**, *42*, 2534.
Enders, D.; Kallfass, U. *Ang*. **2002**, *41*, 1743.
(Review) Enders, D. et al. *Comprehensive Asymm. Catalysis*, Vol 3, **1999**, pp 1093

Yu Zhang

March, 2004

Introduction

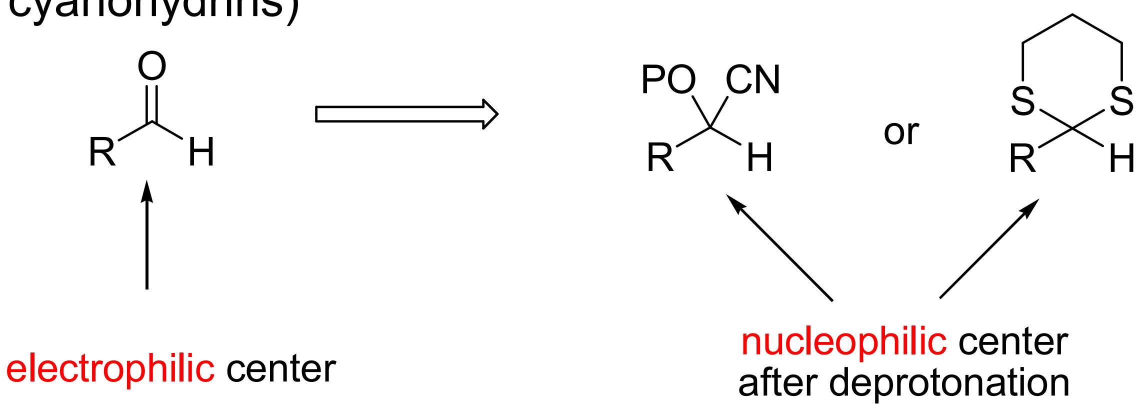
- **Umpolung**

  Any process by which the normal alternating donor and acceptor reactivity pattern of a chain, which is due to the presence of O or N heteroatoms, is interchanged.

  The original meaning of the term has been extended to the reversal of any commonly accepted reactivity pattern. For example, reaction of R–C≡ CX (X = halide) as a synthon for ‘R–C≡C$^+$ (i.e. *electrophilic* acetylene) is an umpolung of the normal more common acetylide, R–C≡C$^-$ (i.e. *nucleophilic*) reactivity.

  IUPAC Compendium of Chemical Terminology 2nd Edition (1997)

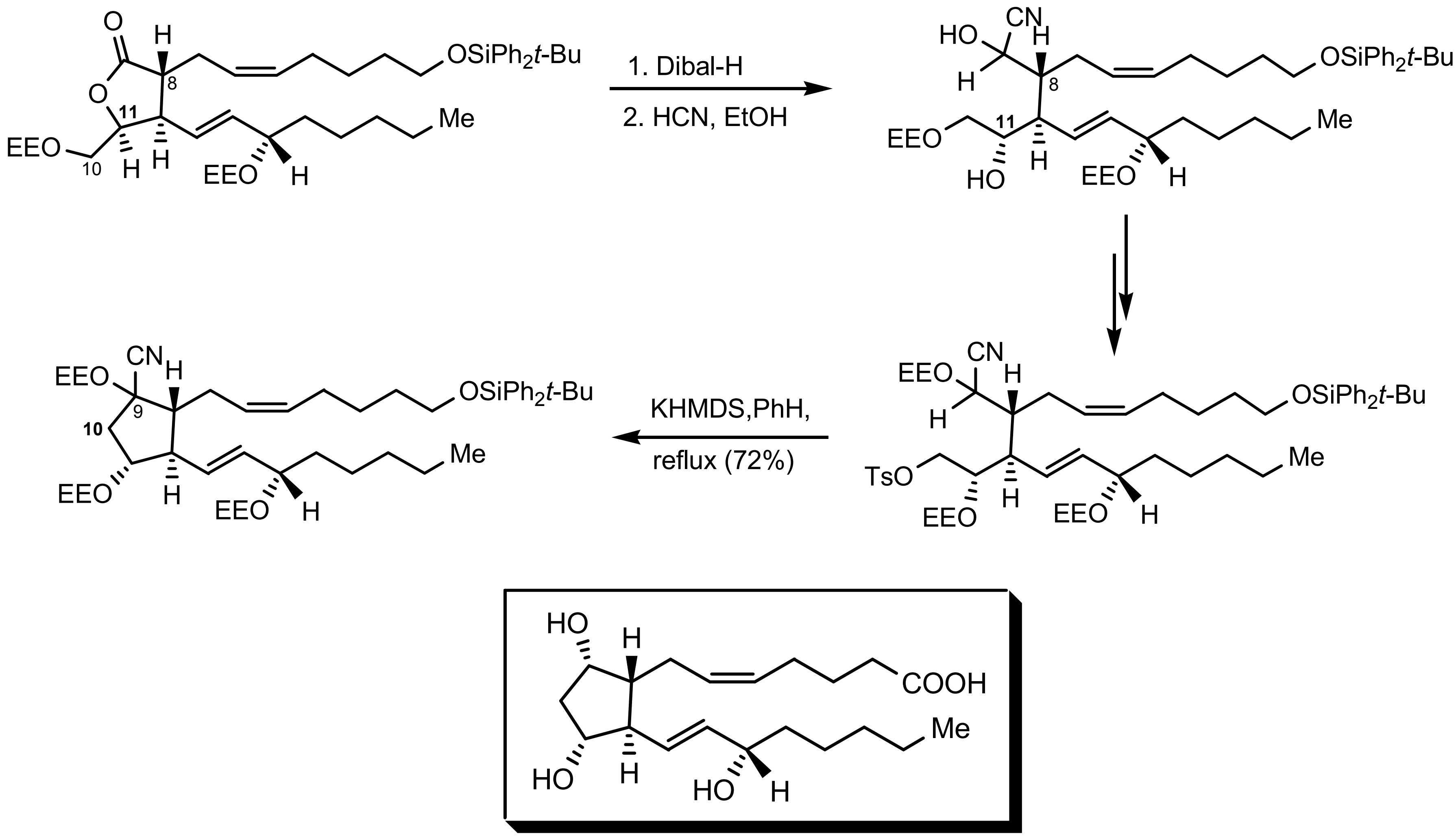
- “Umpolung Chemistry ” of Aldehydes
  – Conversion of an aldehyde into a nucleophic center (such as dithianes and protected cyanohydrins)



Enders, D. et al. *Comprehensive Asymm. Catalysis*, Vol 3, **1999**, pp 1093
Johnson, J. S. *Ang*. **2004**, *43*, 1326.

“Umpolung Chemistry ” of Aldehydes – Early Examples

- Cyanohydrin as aldehyde umpolung:

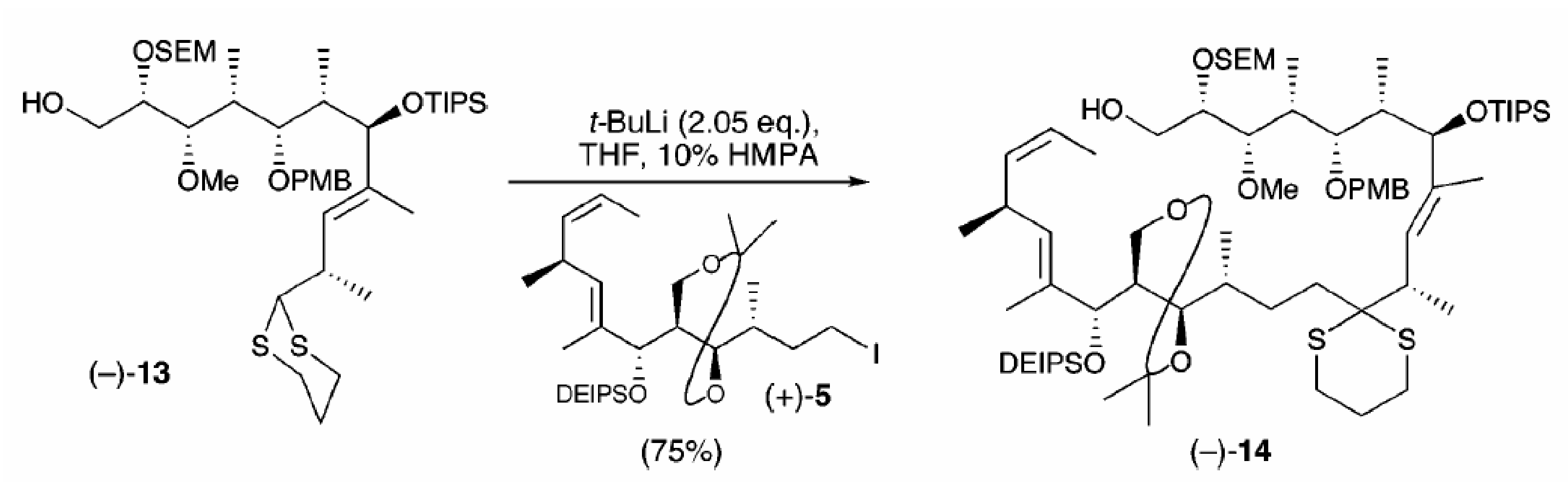


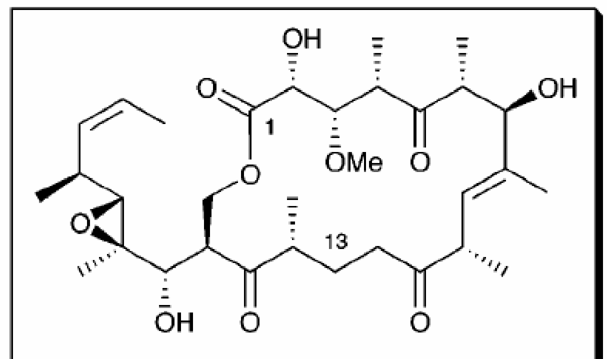
Prostaglandin $F_{2\alpha}$

Stork, G. et al. *JACS*. **1978**, *100*, 8272.

"Umpolung Chemistry " of Aldehydes – Early Examples

- Dithiane as aldehyde umpolung:

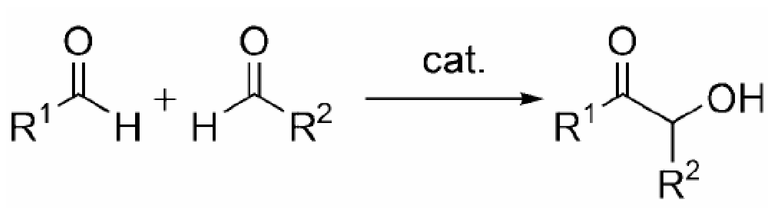


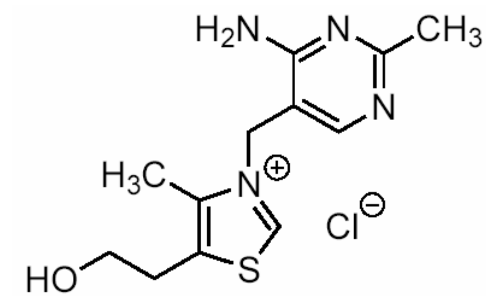


(+)-13-Deoxytedanolide

Smith, A. B. et al. *JACS*. **2003**, *125*, 350.

Introduction to Benzoin Reaction



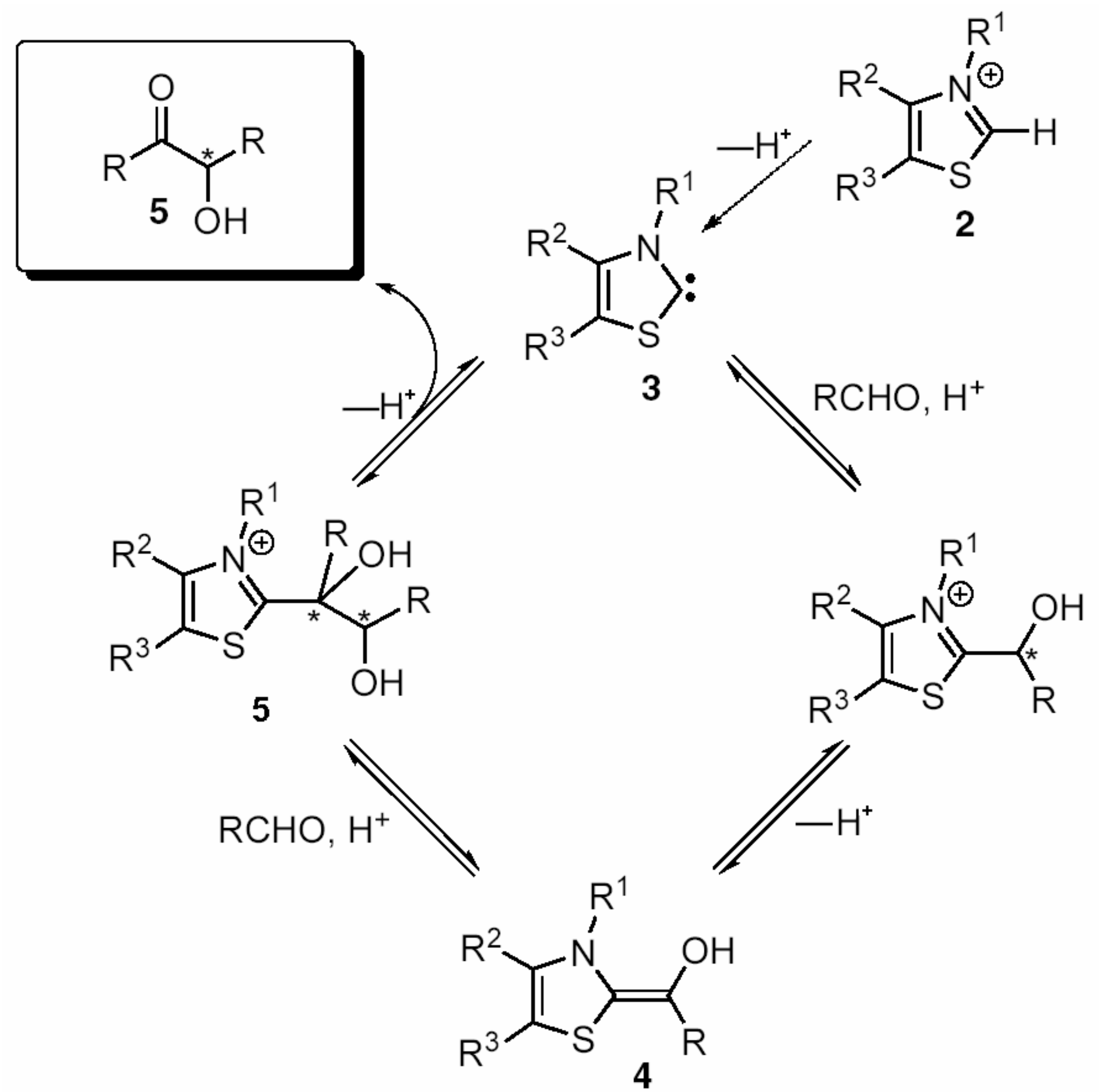


A

- Benzoin Reaction: Originally developed by nature (million years ago)
  -- Nucleophilic acylation reactions catalyzed by lyases in the presence of coenzyme thiamine **A**.

Enders, D. et al. *Comprehensive Asymm. Catalysis*, Vol 3, **1999**, pp 1093

Mechanism of Heterazolium Catalyzed Benzoin Reaction

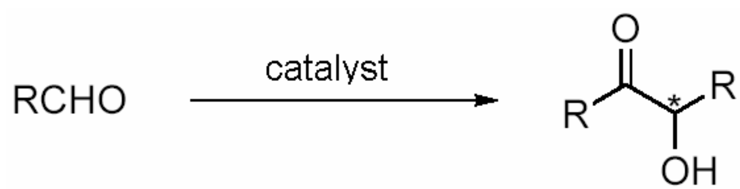


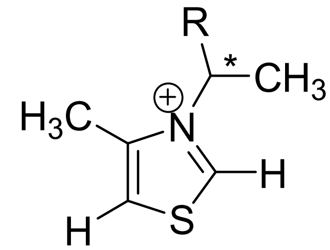
Breslow, R. *JACS*, **1958**, *80*, 3719

Enders, D. et al. *Comprehensive Asymm. Catalysis*, Vol 3, **1999**, pp 1093

Thiazolium Catalyzed Benzoin Reaction

- Thiazolium catalysis: Just limited success





4a, R = Bn
4b, R = 1-naphthyl
4c,d R = Ph

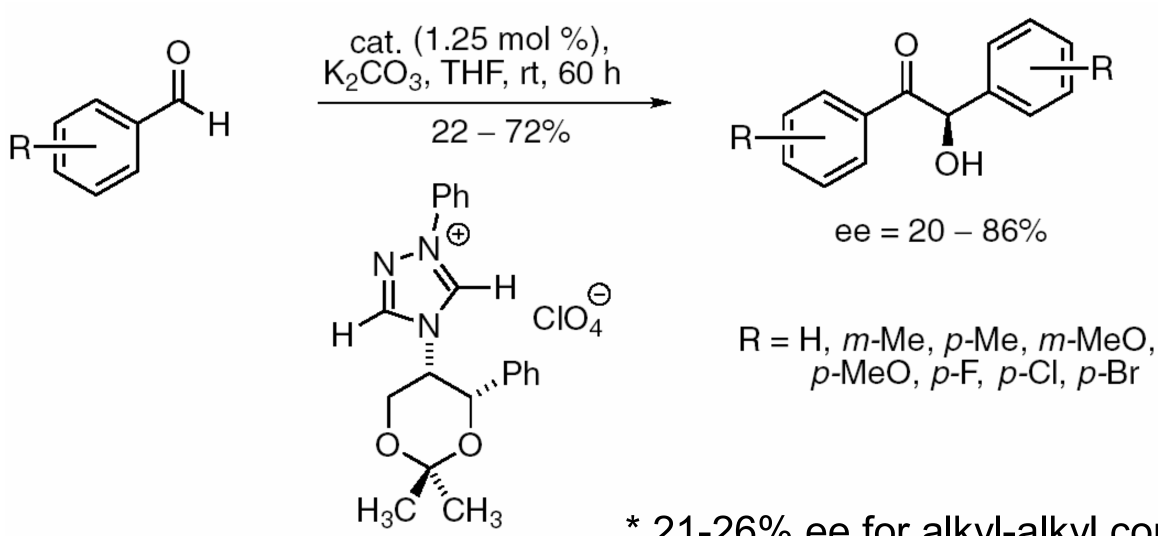
Salt	Reaction conditions,[a] solvent, base, time in hr	Yield,[b] %	Optical purity,[d] %
(*R*)-(−)-**4a**	MeOH, Et_3N 6	12	0
(*S*)-(+)-**4b**	MeOH, Et_3N 6	6.1	51.5
(*R*)-(−)-**4b**	MeOH, Et_3N 24	21	38.5
		17	37.5
	MeOH, Et_3N 48	26	29.4
	MeOH–H_2O, NaOH 24	22	31.0
(*S*)-(+)-**4c**	MeOH, Et_3N 25	78	7.8
(*S*)-(+)-**4d**	MeOH, Et_3N 25	68	7.1

-- The culprits: Low acitivity of thiazolium & bulky N-substitution.

Sheehan, J. C. et al. *JOC*, **1974**, *39*, 1196.

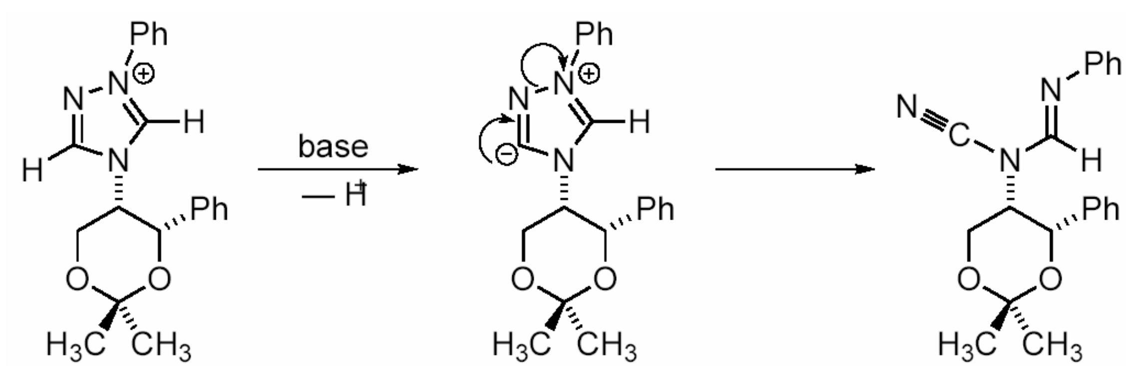
Triazolium Catalyzed Benzoin Reaction

- Triazolium salts: more active catalyst



* 21-26% ee for alkyl-alkyl condensation

- Catalyst deactivation pathway:



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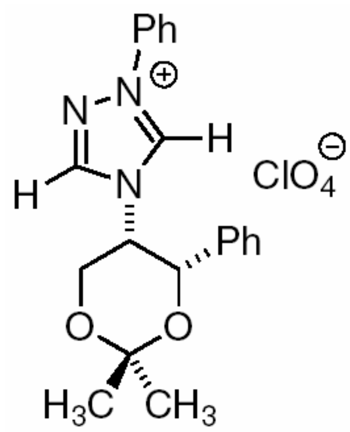
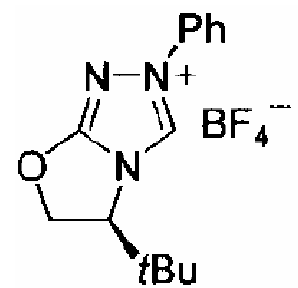
Enders, D. et al. *Helv* Chim. Acta, **1996**, *79*, 1899.

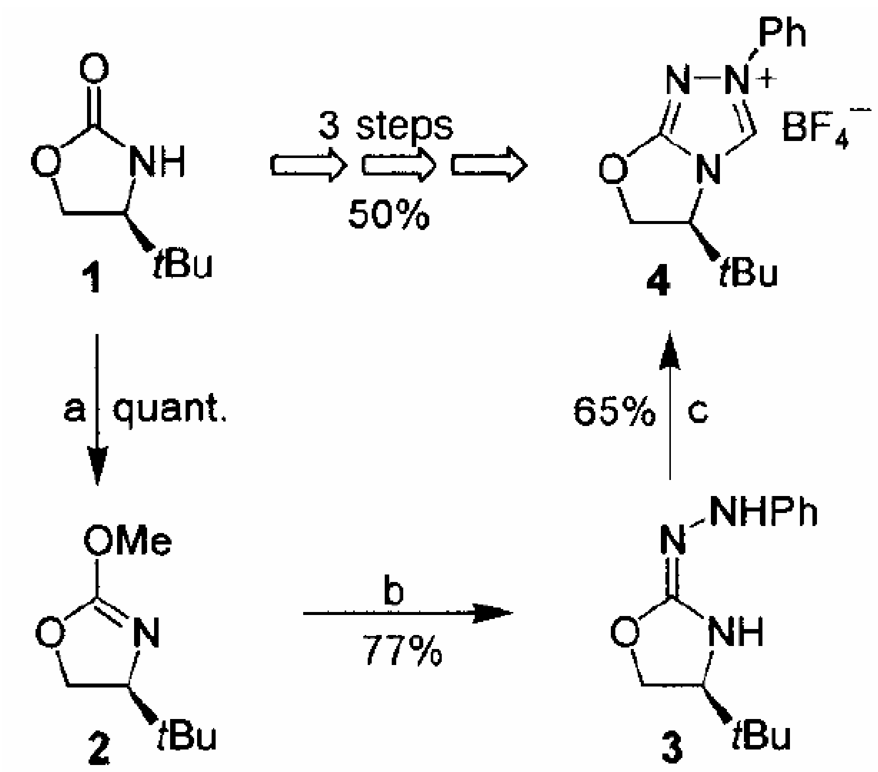
Design and Preparation of New Catalyst



Enders, 1996



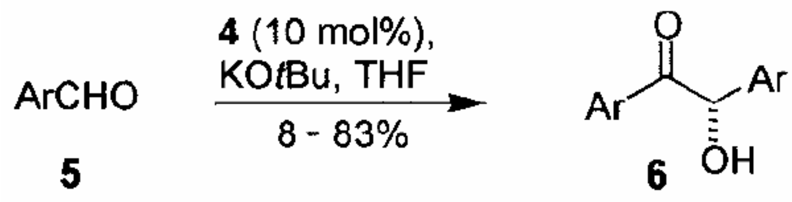
Enders, 2002



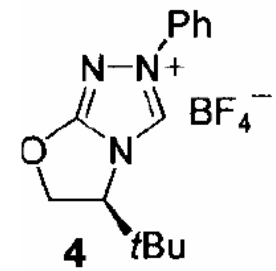
a) Me_3OBF_4 (1.2 equiv), CH_2Cl_2 , RT, 15 h;
b) $PhNHNH_2$ (1 equiv), NEt_3 (1 equiv), THF, 80°C, 7 d;
c) HBF_4 (1 equiv) in diethyl ether, CH_2Cl_2 , RT; $HC(OMe)_3$ (20 equiv), MeOH, 80°C, 12 h.

Enders, D. et al. *Ang.*, **2002**, *41*, 1743.

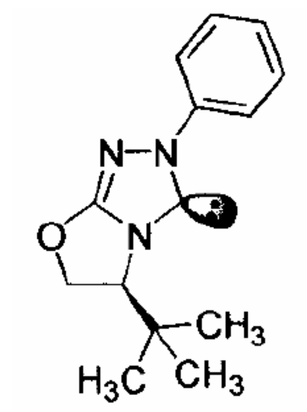
Triazolium Carbene Catalyzed Benzoin Reaction



6	Ar	T [°C]	Yield [%]	*ee* [%][c]
a	Ph	18	83	90
b	4-FC_6H_4	18	81	83
b′	4-FC_6H_4	0	61	91
c	4-ClC_6H_4	18	80	64
c′	4-ClC_6H_4	0	44	89
d	4-BrC_6H_4	18	82	53
d′	4-BrC_6H_4	0	59	91
e	3-ClC_6H_4	18	92	62
e′	3-ClC_6H_4	0	85	86
f	4-MeC_6H_4	18	16	93
g	3-MeC_6H_4	18	70	86
g′	3-MeC_6H_4	0	36	91
h	4-$MeOC_6H_4$	18	8	95
i	2-furyl[e]	0	100	64
i′	2-furyl	– 78	41	88
j	2-naphthyl	18	69	80



4



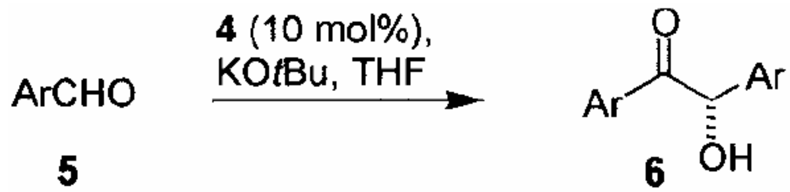
4'

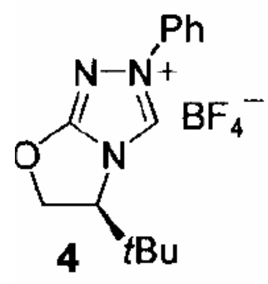
General reaction conditions: aldehyde (10 mmol), **4** (10 mol%), KOtBu (10 mol%), absolute THF (11 mL), 16 h.

Enders, D. et al. *Ang.*, **2002**, *41*, 1743.

Triazolium Carbene Catalyzed Benzoin Reaction

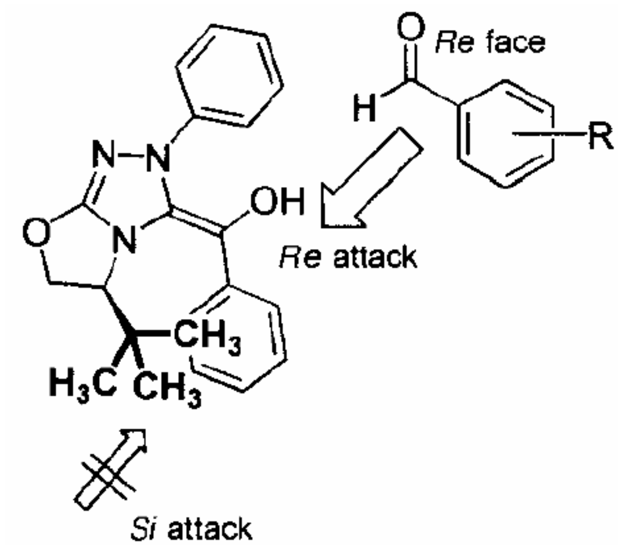
♦ Influence of the reaction conditions on the yield and ee (Ar = Ph).





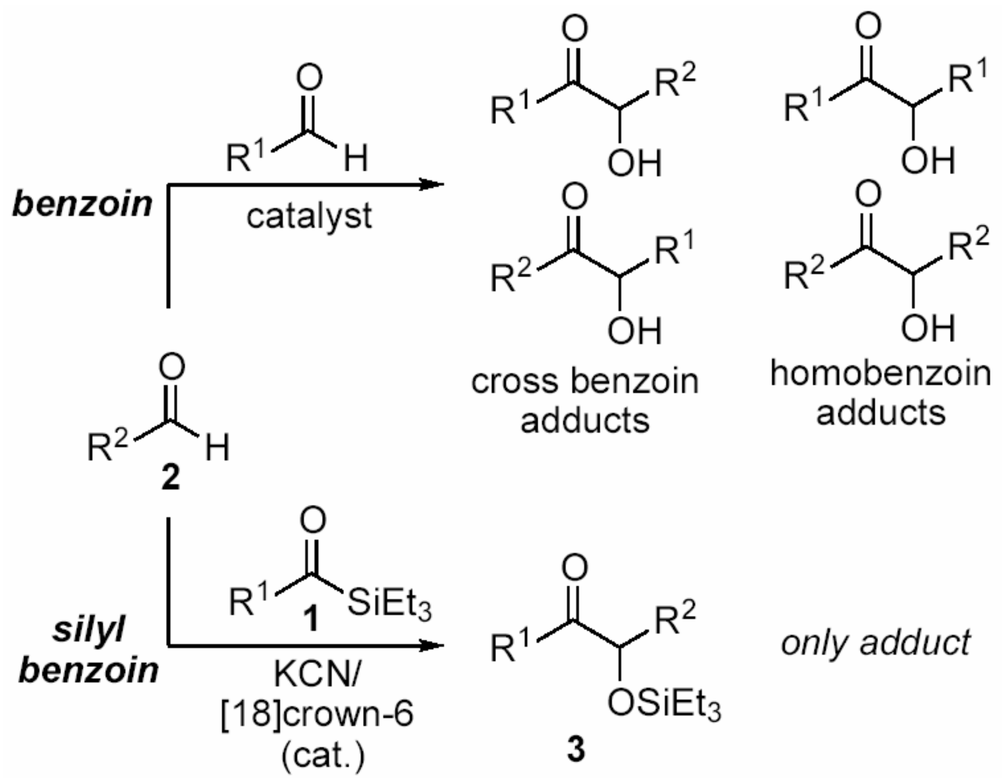
4 [mol %]	KO*t*Bu [mol %]	Yield [%]	*ee* [%][b]
2.5	2.5	33	99
5.0	5.0	46	93
10.0	10.0	83	90

♦ Postulated transition-state model (Breslow intermediate)



Enders, D. et al. *Ang*. **2002**, *41*, 1743.

Cyanide Ion Catalyzed Benzoin Reaction

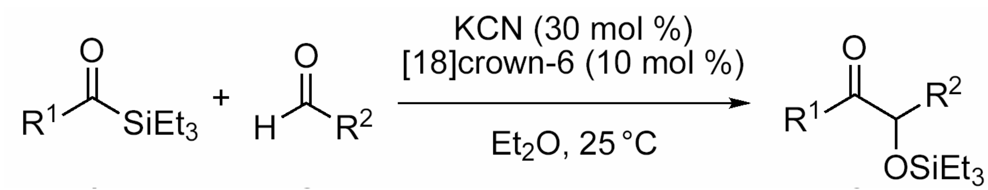


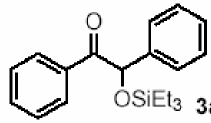
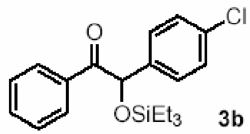
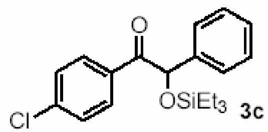
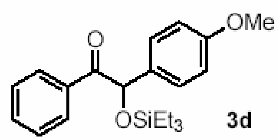
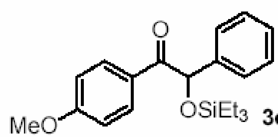
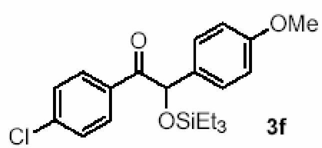
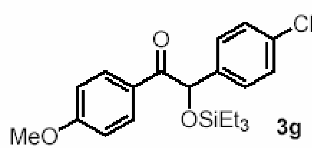
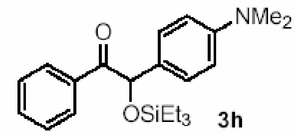
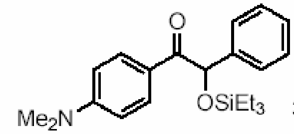
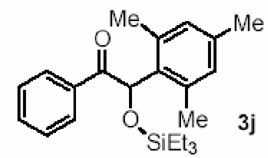
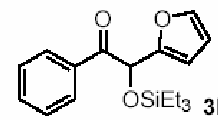
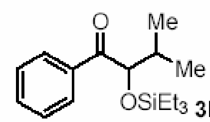
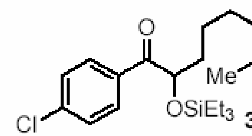
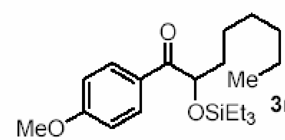
♦ Cross Benzoin reaction: selectivity determined by relative stablity of four pdts.

♦ Silyl Benzoin reaction: Kinetic control, regiospecific, (but need to make **1**!)

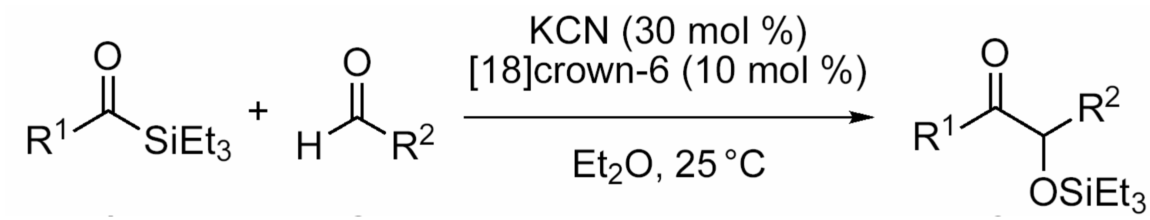
Johnson, J. S. et al. *Ang*. **2003**, *42*, 2534.

Cyanide Ion Catalyzed Benzoin Reaction

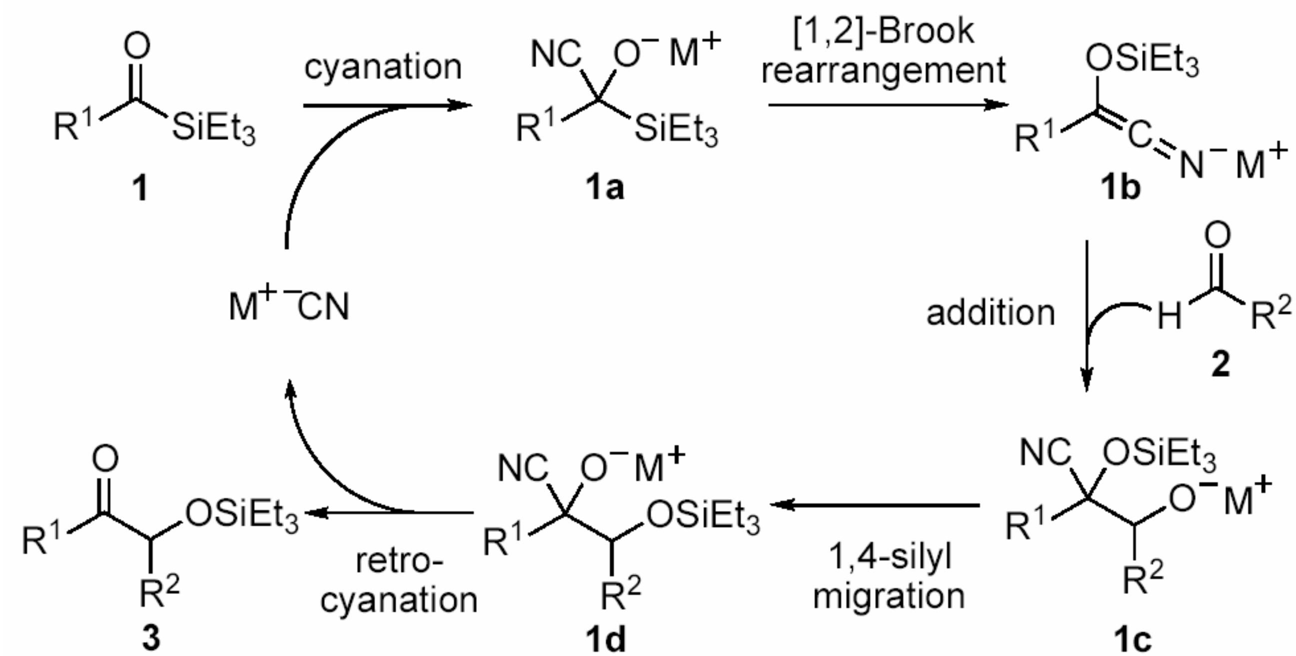


Entry	R^1	R^2	Product	Yield [%][b]
1	Ph	Ph	 **3a**	90
2	Ph	4-ClPh	 **3b**	82
3	4-ClPh	Ph	 **3c**	86
4	Ph	4-MeOPh	 **3d**	79
5	4-MeOPh	Ph	 **3e**	85
6	4-ClPh	4-MeOPh	 **3f**	80
7	4-MeOPh	4-ClPh	 **3g**	80
8	Ph	4-Me_2NPh	 **3h**	66[c]
9	4-Me_2NPh	Ph	 **3i**	95[c]
10	Ph	mesityl	 **3j**	85
11	Ph	2-furyl	 **3k**	75
12	Ph	isopropyl	 **3l**	66
13	4-ClPh	*n*-hexyl	 **3m**	75
14	4-MeOPh	*n*-hexyl	 **3n**	51

Cyanide Ion Catalyzed Benzoin Reaction



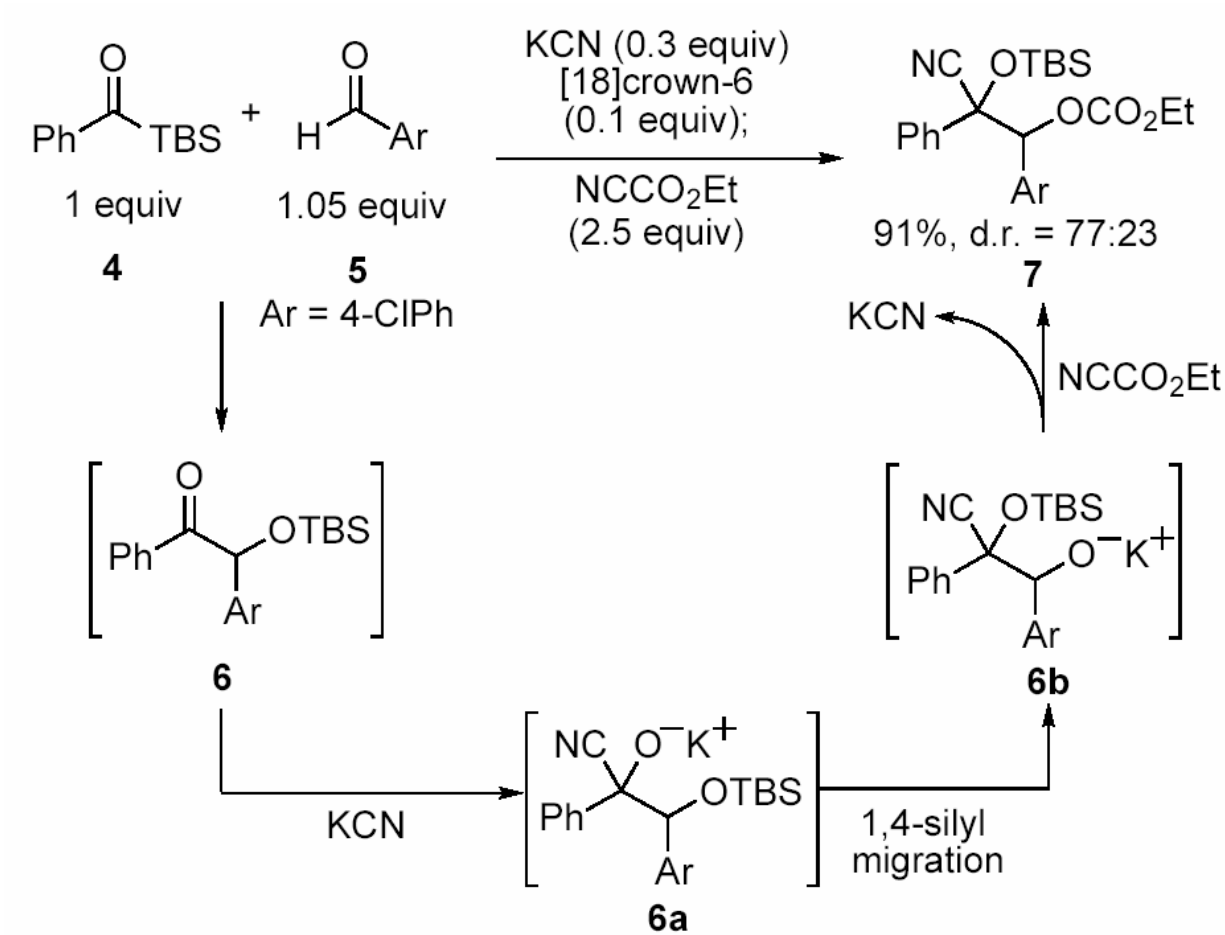
- Proposed mechanism for the cross silyl benzoin reaction:



Johnson, J. S. et al. *Ang*. **2003**, *42*, 2534.

Cyanide Ion Catalyzed Benzoin Reaction

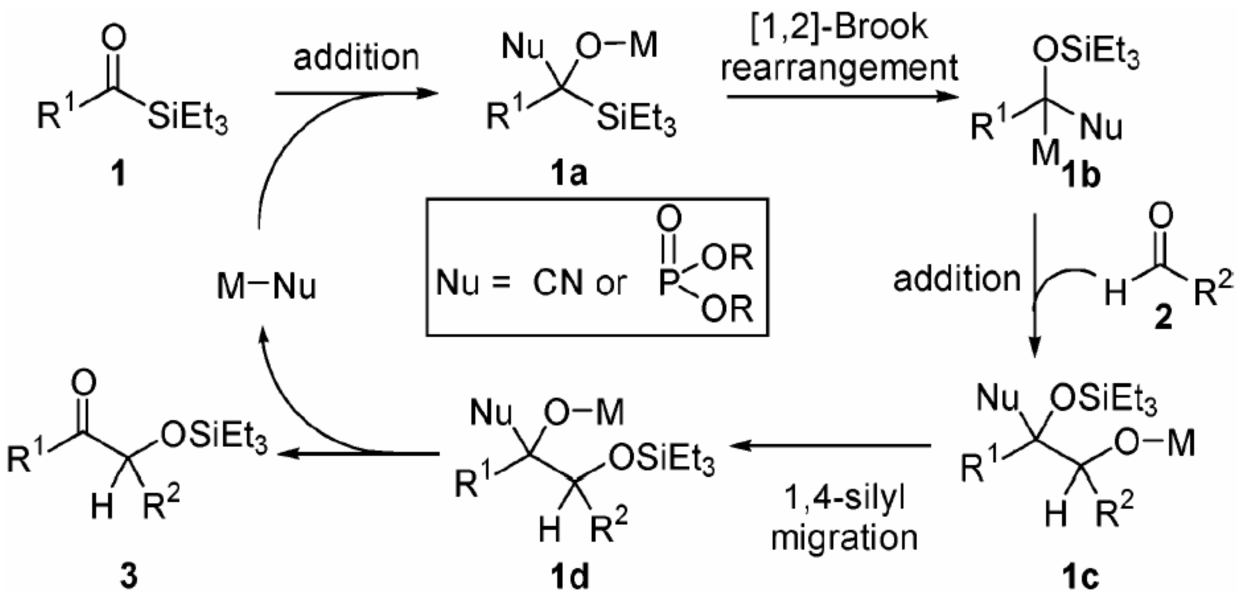
♦ Sequential one-pot silyl benzoin addition-cyanation-acylation reaction:

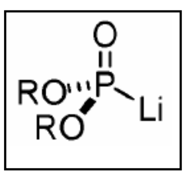


Johnson, J. S. et al. *Ang*. **2003**, *42*, 2534.

Metallophosphite Catalyzed Asymmetric Benzoin Reaction

♦ Proposed Mechanism:



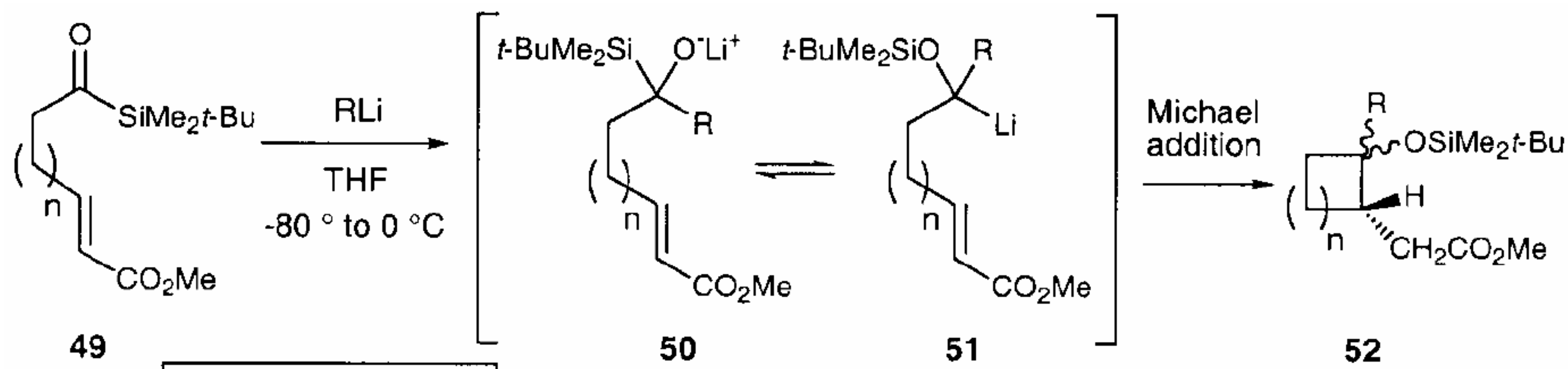


Must function as nucleophile (**1**-**1a**), anion stablizing group (**1a**-**1b**), and leaving group (**1d**-**3**). Or can it?

Johnson, J. S. et al. *JACS*, **2004**, *126*, 3070.

Metallophosphite Catalyzed Asymmetric Benzoin Reaction

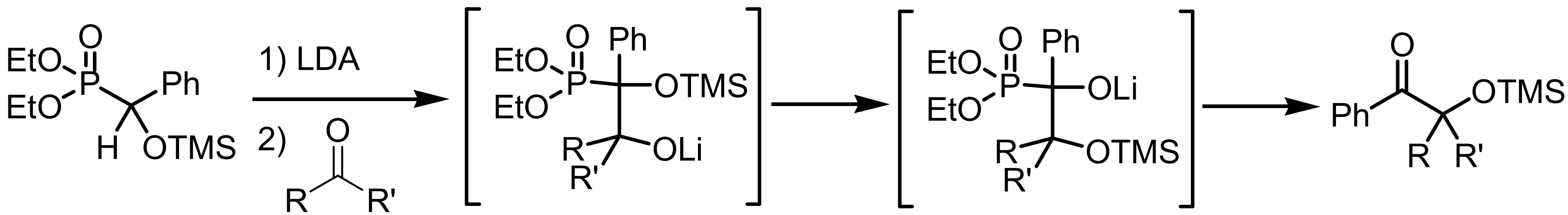
♦ Literature precedent One (1,2-Brook):



R = Ph, P(O)(OMe)$_2$
n = 1-3

Takeda et al. *Synlett* **1999**, 705

♦ Literature precedent Two (1,4-silyl migration):

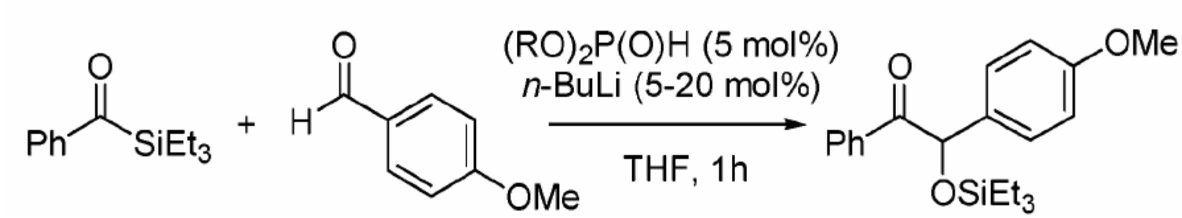


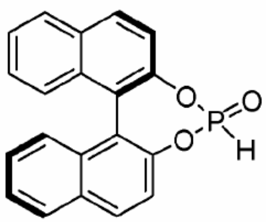
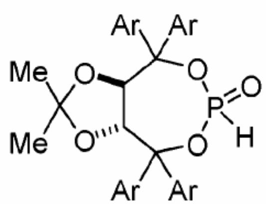
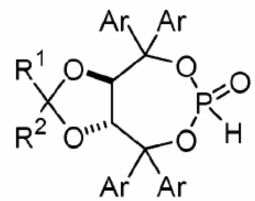
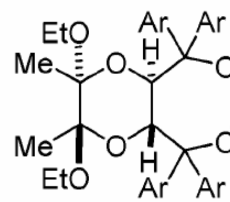
Zimmer, H. et al. *TL* **1980**, 1017

Johnson, J. S. et al. *JACS*, **2004**, *126*, 3070.

Metallophosphite Catalyzed Asymmetric Benzoin Reaction

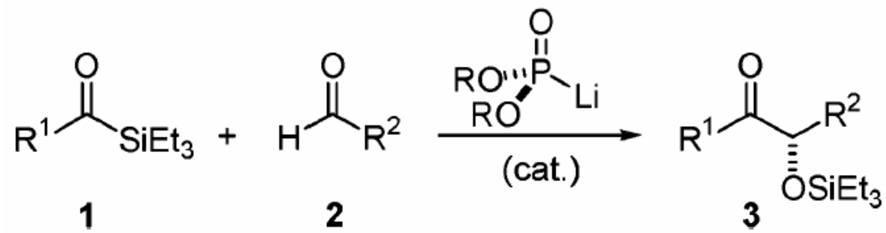
- Evaluation of phosphite catalysts:

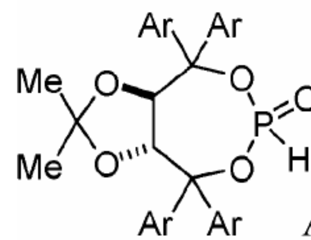


entry	phosphite			% ee[a]	% conv.[b]
1	$(EtO)_2P(O)H$	**4a**		-	100 (60)[c]
2		**4b**		-	<5
3	 **4c-i**	**4c**	Ar = Ph	41	100
4		**4d**	Ar = 2-MePh	77	<20
5		**4e**	Ar = 2-naphthyl	58	<20
6		**4f**	Ar = 2-FPh	90	100
7		**4g**	Ar = 2,6-F_2Ph	74	<60
8		**4h**	Ar = F_5Ph	-	<5
9		**4i**	Ar = 2-CF_3Ph	-	<5
10	 **4j-l** (Ar = 2-FPh)	**4j**	R^1 = Me, R^2 = Ph	75	<80
11		**4k**	R^1,R^2 = $(CH_2)_4$	86	100
12		**4l**	R^1,R^2 = $(CH_2)_5$	88	100
13	 **4m-n**	**4m**	Ar = Ph[d]	76	100
14		**4n**	Ar = 2-FPh	66	100

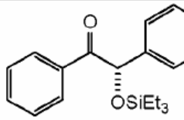
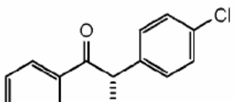
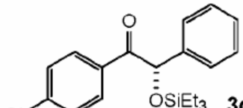
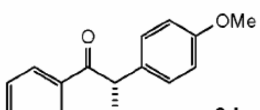
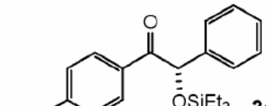
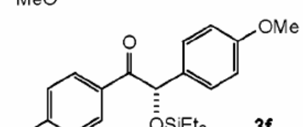
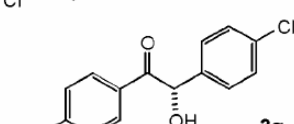
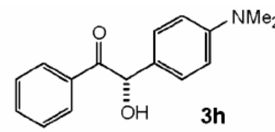
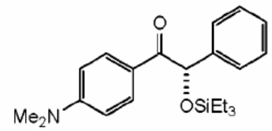
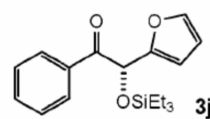
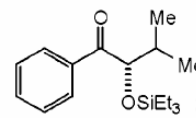
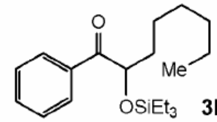
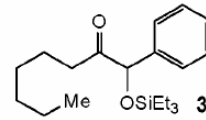
Johnson, J. S. et al. *JACS*, **2004**, *126*, 3070.

Metallophosphite Catalyzed Asymmetric Benzoin Reaction





Ar = 2-FPh

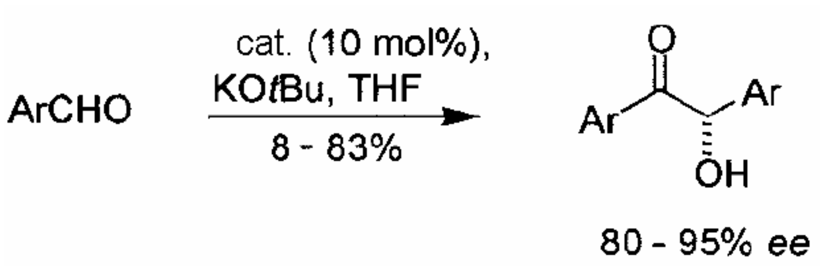
entry	product[b]	cat. **4f** (mol %)	% ee[c]	% yield[d]
1	 3a	7.5	82	84
2	 3b	7.5	82	75
3	 3c	7.5	87	82
4	 3d	5	91	87
5	 3e	7.5	88	83
6	 3f	7.5	90	83
7	 3g	10	83[e]	79
8	 3h	5	81[e]	80
9	 3i	12.5	86	86
10	 3j	7.5	85[e]	65
11	 3k	15	73	78
12	 3l	20	41	88
13	 3m	20	67	72

$R^1C(O)SiEt_3$ (1.0 equiv), R^2CHO (1.5 equiv), ligand, and *n*-BuLi (0.2-0.4 equiv) in THF from 0 to 25 ° C. Reaction time 0.5 h.

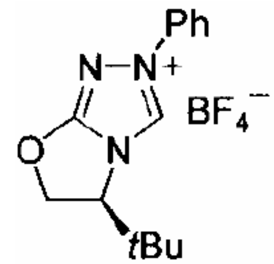
Johnson, J. S. et al. *JACS*, **2004**, *126*, 3070.

Catalyzed Benzoin Reactions – Now and Future

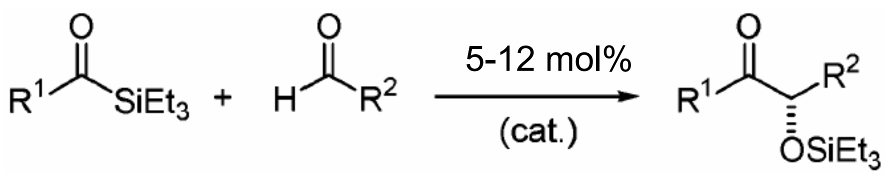
♦ Enders' system:



Cat. =

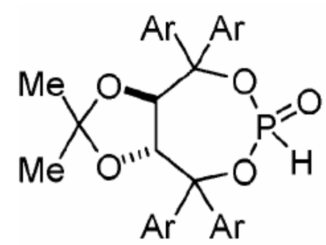


♦ Johnson's systems:



81-91% ee for aryl-aryl
41-73% ee for alkyl-aryl

Cat. =



+ BuLi

or

KCN/
[18]crown-6 (racemic)

♦ Now:
--Idea, starting material, yield and/or ee, regioselectivity, condition – Who's better?

♦ Future Challenges:
-- More active catalyst (low loading)
-- Expanded functional group compatibility (alkyl-aryl & alkyl-alkyl condensation)