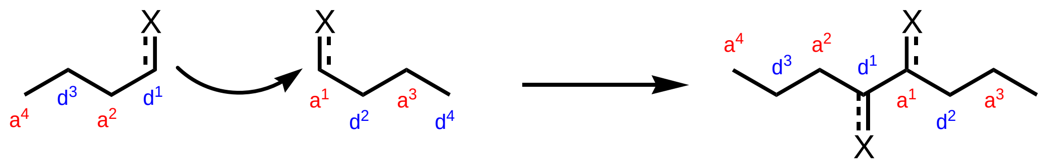
Umpolung Chemistry: Recent Developments in the Benzoin and Stetter Reaction



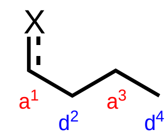
Reviews:

Umpolung:	**Seebach** *ACIEE* **1979**, *18*, 239
Stetter Reaction:	**Stetter** *ACIEE* **1976**, *15*, 639
Acyl Anion Equivalents:	**Johnson** ACIEE **2004**, *43*, 1326
Asymmetric Stetter:	**Christmann** *ACIEE* **2005**, *44*, 2632
Nucleophilic Carbenes:	**Enders** *Acc. Chem. Res.* **2004**, *37*, 534 **Zeitler** *ACIEE* **2005**, 44, 7506

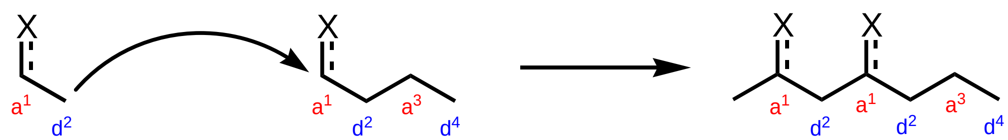
Kristy Tran
Leighton Group
October 16, 2006

The Synthetic Problem

Heteroatoms impose an alternating acceptor (a) and donor (d) reactivity pattern

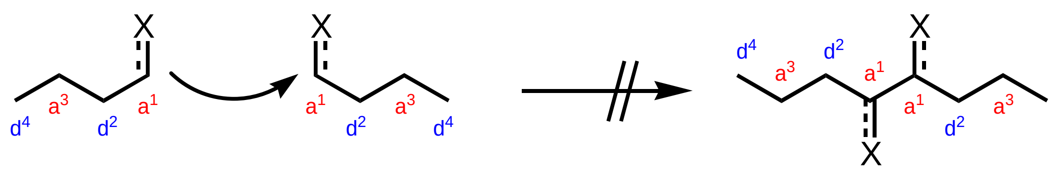


Since most organic reactions are polar in nature (*ie* a nucleophile attacks and electrophile), there is a synthetic limitation: *only an odd number of carbons* may be placed between functional groups

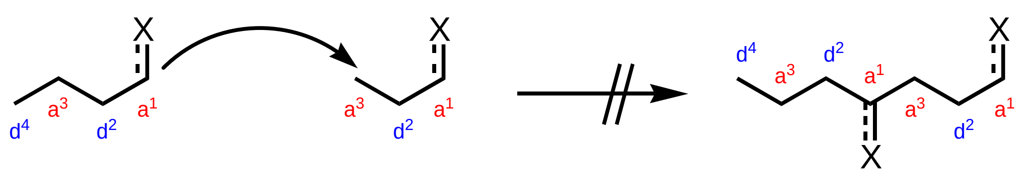


1,3 disubstitution

Coupling of components with the **same** polarity are required to synthesize a molecule with **even number of carbons** in between functional groups



1,2 disubstitution



1,4 disubstitution

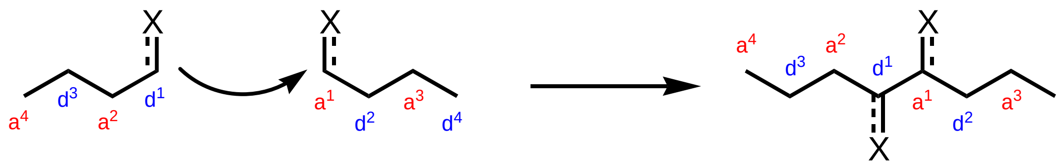
Seebach *ACIEE* **1979**, *18*, 239

Umpolung

Umpolung –

a reversal in polarity *or*

any process in which donor and acceptor reactivities are interchanged



1,2 disubstitution

Outline

Benzoin Reaction

Cyanide Catalyzed
N-Heterocyclic Carbene Catalyzed
Asymmetric Benzoin Reactions

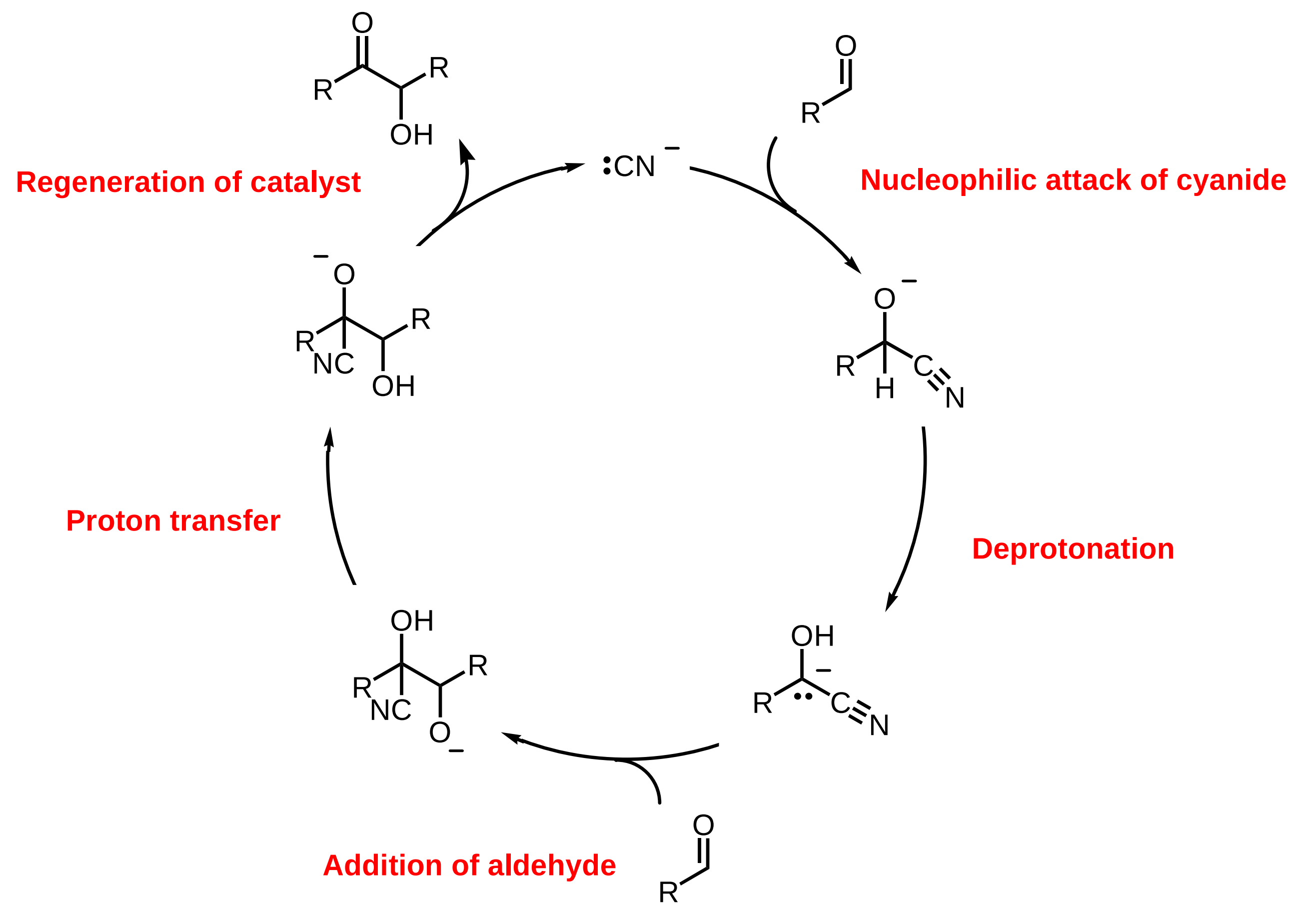
Stetter Reaction

Thiazolium Catalyzed
Intramolecular Asymmetric Stetter Reaction
Variations of the Asymmetric Stetter

Other uses of N Heterocyclic Carbenes

Seebach *ACIEE* **1979**, *18*, 239

Cyanide Catalyzed Benzoin Reaction



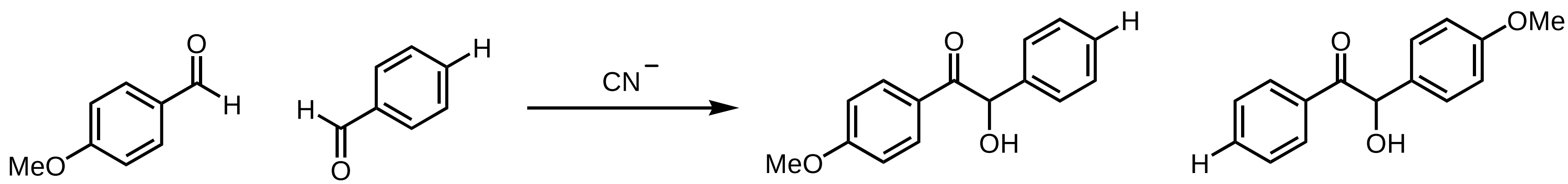
- Must use aromatic aldehydes; aliphatic aldehydes tend to undergo an aldol condensation
- Cannot selectively cross couple of two different aldehydes

- Stoichiometric umpolung reagents required to selectively cross couple (ie dithianes, protected cyanohydrins) and require an extra deprotection step

Seebach *ACIEE* **1979**, *18*, 239

Cross Benzoin Reaction

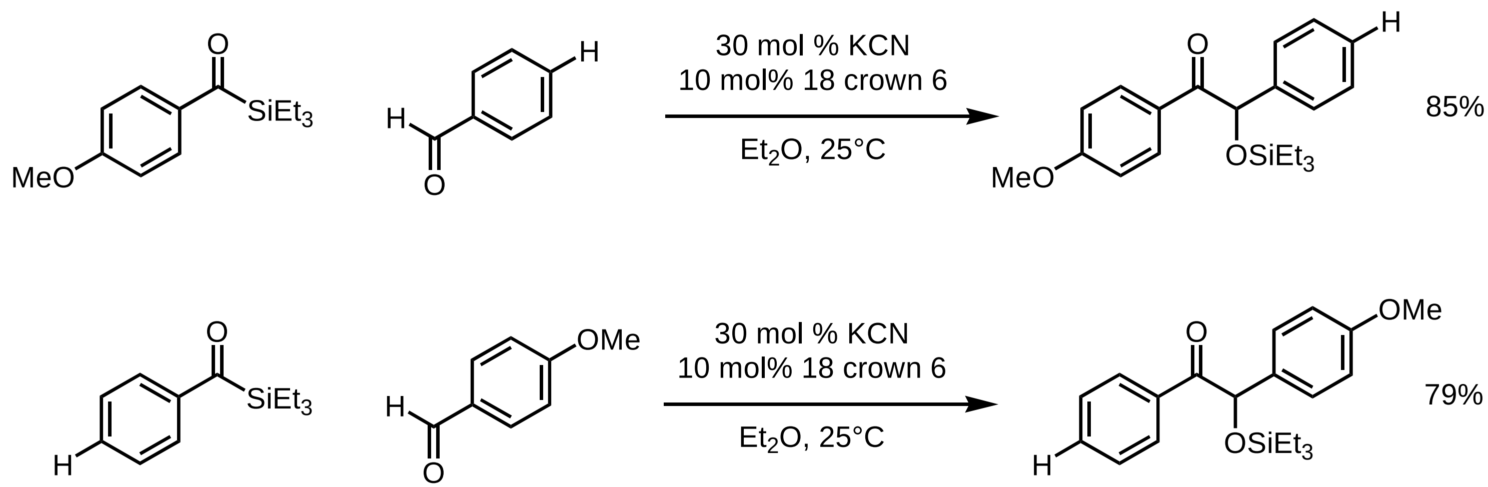
When both components are aldehydes



Thermodynamic Product

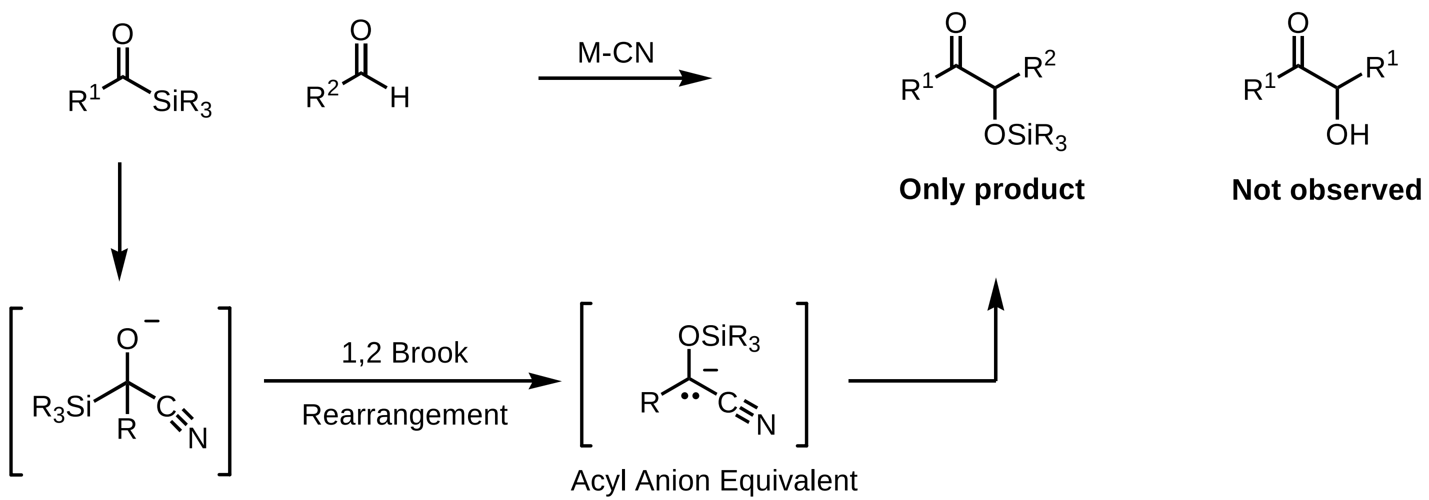
Not Formed

With acyl silanes, BOTH products are possible

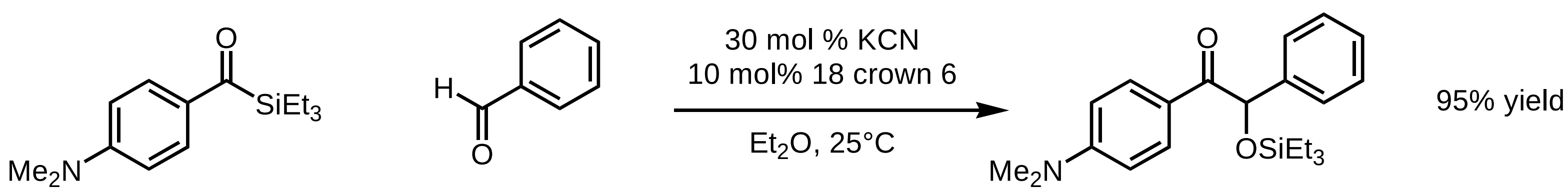


Johnson *JACS* **2005**, *127*, 1833

Cyanide Catalyzed Cross Silyl-Benzoin Reaction

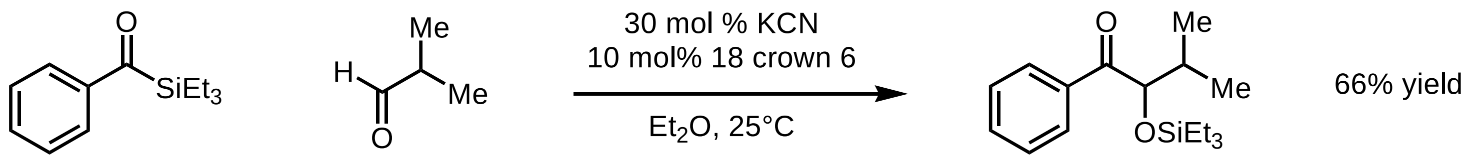


An alternate method of acyl anion formation!

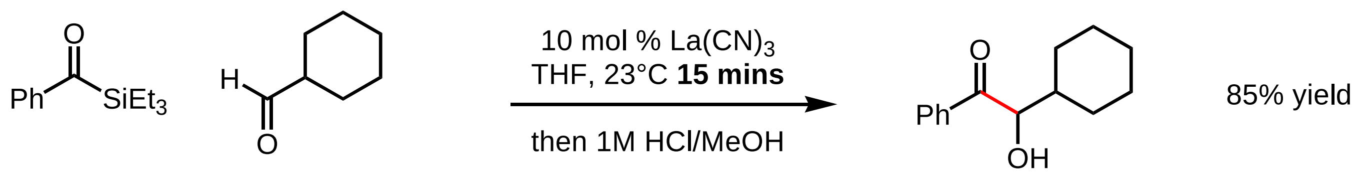


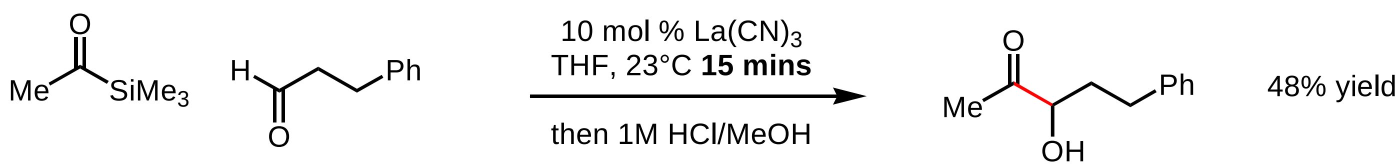
Johnson *JACS* **2005**, *127*, 1833

Limitation: Aliphatic Aldehydes



Lower yields often result from aliphatic aldehydes; <20% yields from alkyl-alkyl´ benzoin reactions

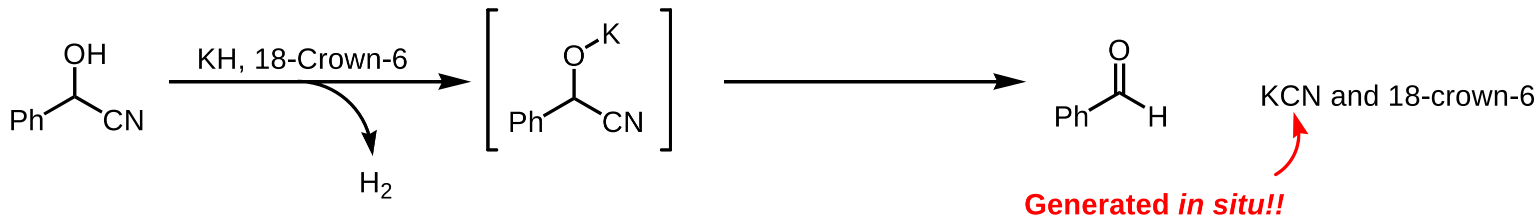


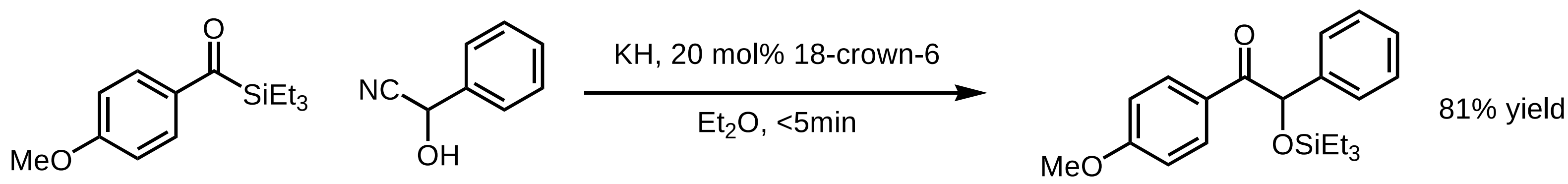


Faster reaction times, lower catalysts loadings and provides alkyl-alkyl´ benzoin adducts

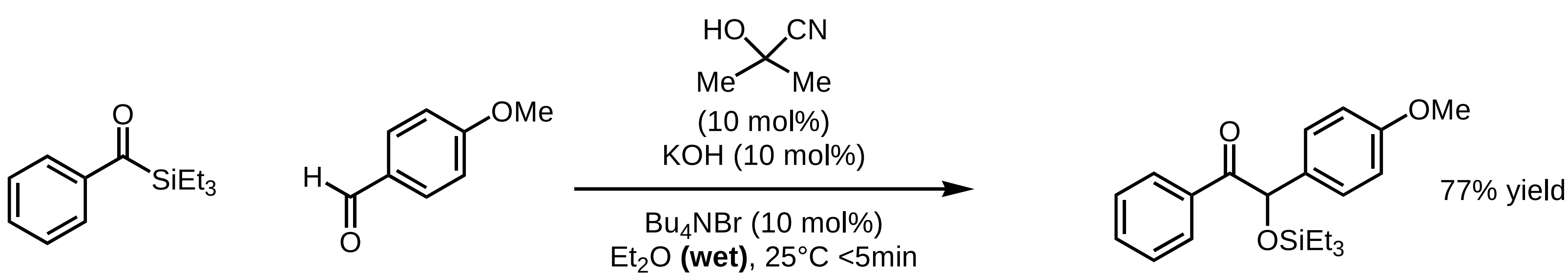
Johnson *JACS* **2005**, *127*, 1833

Reversibility of Formation of Cyanohydrin





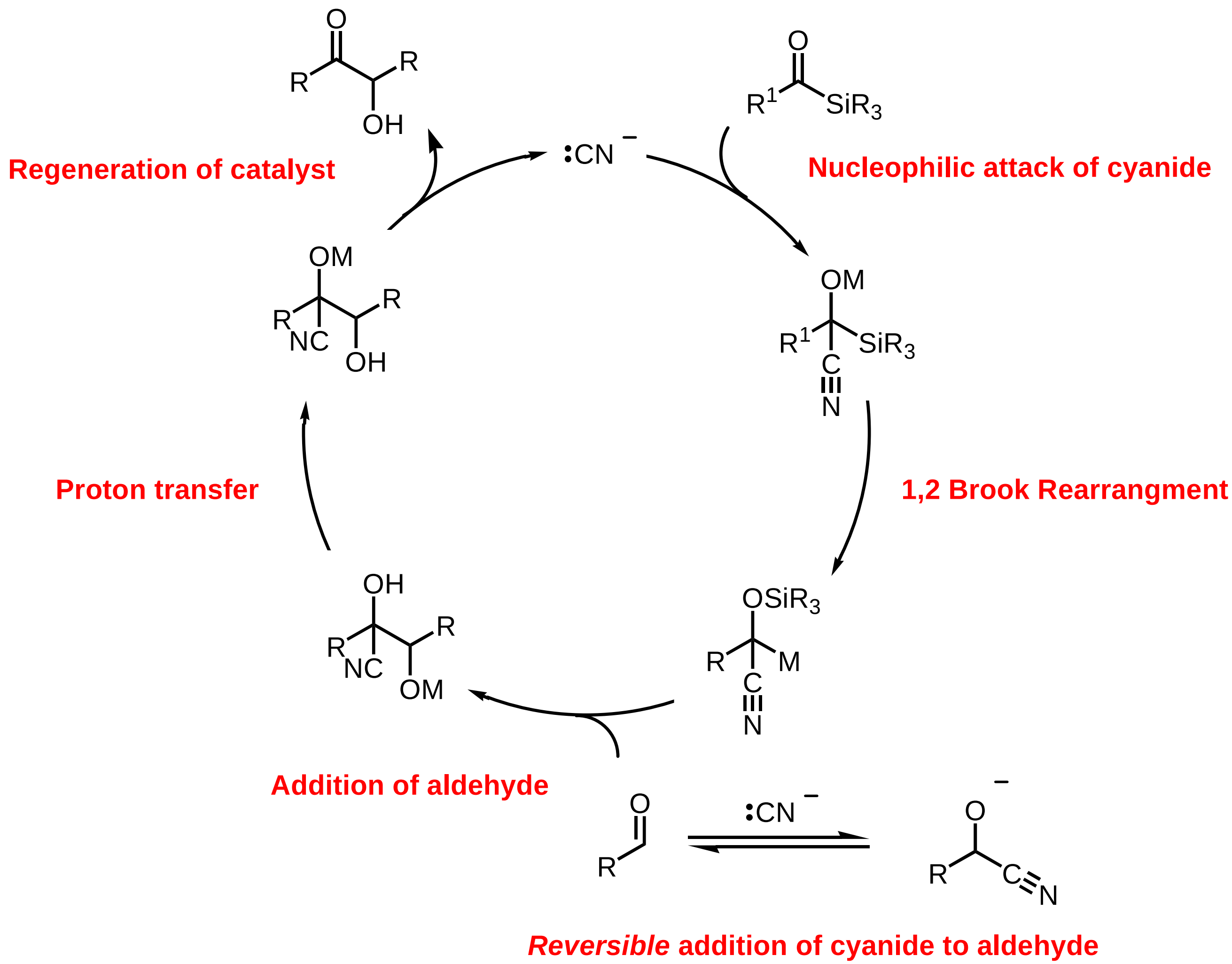
Addition to aldehyde is reversible!



Cheap and stable cyanohydrins may be used as latent cyanide ions

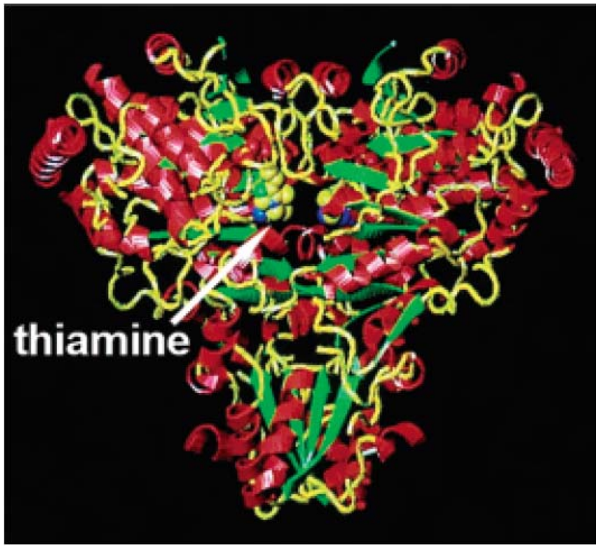
Johnson *JACS* **2005**, *127*, 1833

Cross Silyl Benzoin Catalytic Cycle

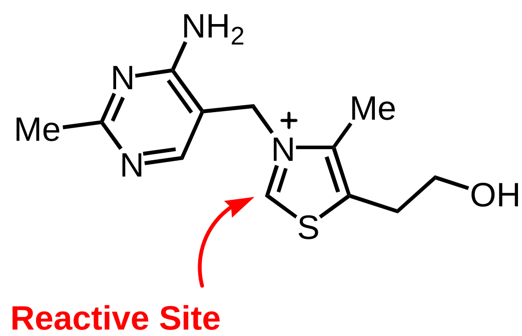


Johnson *JACS* **2005**, *127*, 1833

N-Heterocyclic Carbenes Catalyzed Umpolung



Thiamine (vitamin B_1)



1943 Ukai – thiazolium catalyzed benzoin reaction

1958 Breslow – mechanistic model for thiazolium catalyzed benzoin reactions

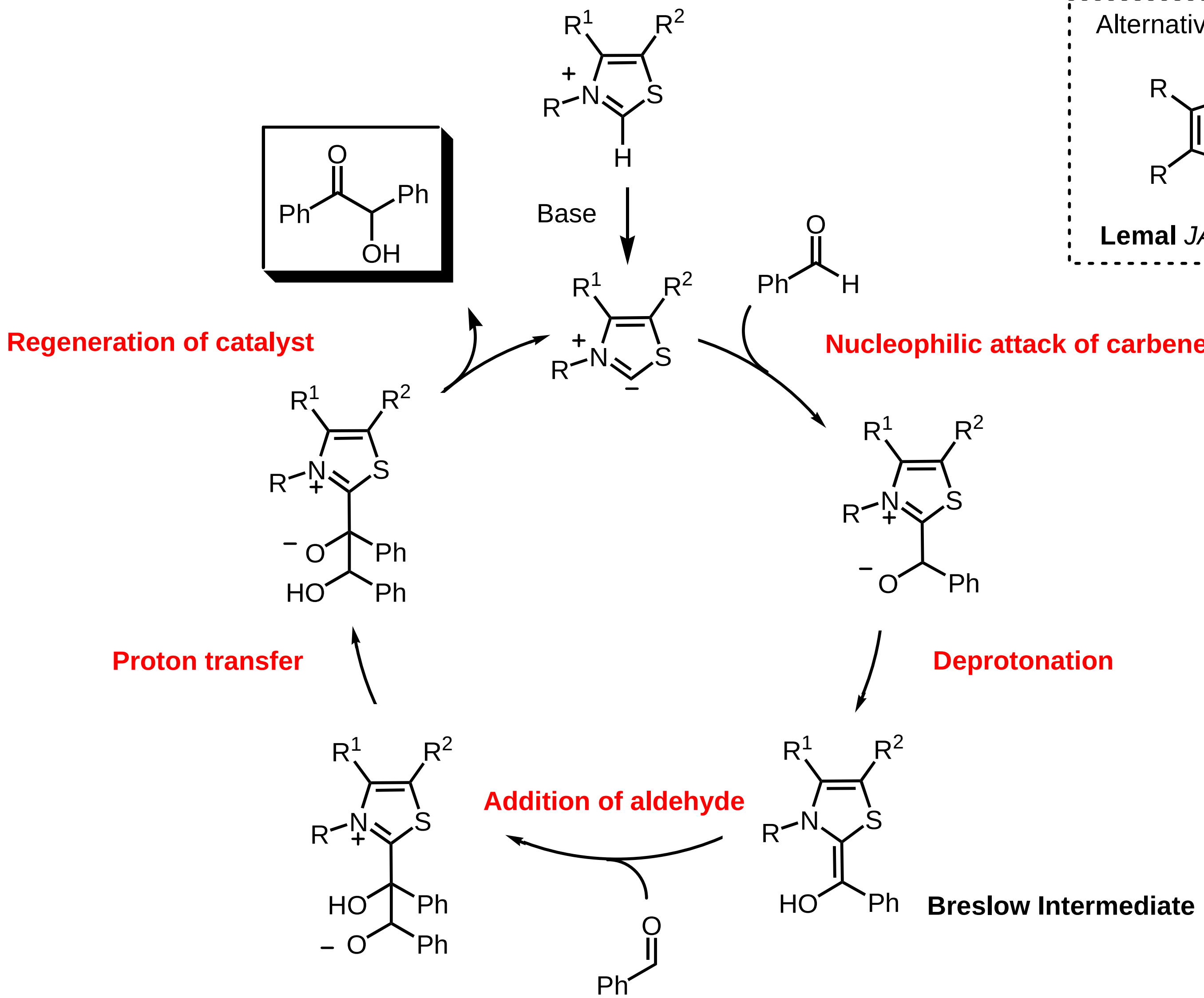
1973 Stetter – thiazolium catalyzed additions of aldehydes to α,β unsaturated carbonyls

1966 Sheehan – asymmetric benzoin

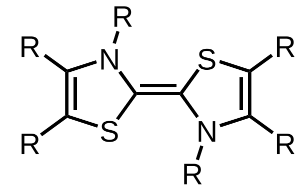
1996 Enders – asymmetric Stetter

Enders *Acc. Chem. Res.* **2004**, *37*, 534

Thiamine Catalyzed Benzoin Reaction



Alternative Mechanistic Model



Lemal *JACS* **1964** , *86, 2518*

(a) **Breslow** *JACS* **1958**, *80,* 3719. (b) **Enders** *Acc. Chem. Res.* **2004**, *37*, 534.

Kinetics of Thiamine Catalyzed Benzoin

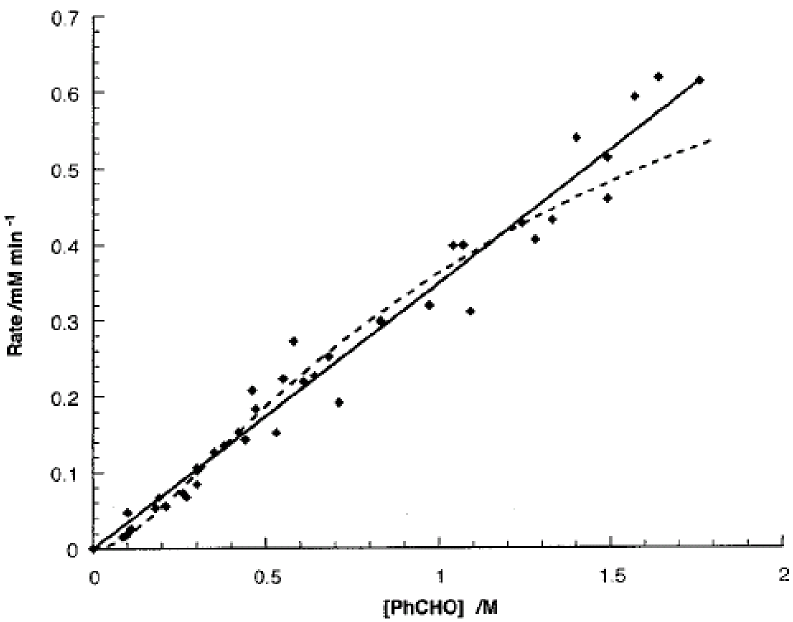


Figure 1. Rate of benzoin formation at different concentrations of PhCHO. The solid line (—) is the best fit of the first-order equation, rate = k[PhCHO]. The dashed line (– –) is the calculated rate using $k_1 = 0.14\ M^{-1}\ min^{-1}$, $k_2 = 0.035\ min^{-1}$, $k_{-1} = 0.025\ min^{-1}$, $k_{-3} = 0.01\ M^{-1}\ min^{-1}$, and $k_3/k_{-2} = 1\ M^{-1}$.

- Previous studies which concluded 2nd order kinetics are involved may be incorrect due to (1) catalyst degradation over time (2) side product interference (3) reversibility of the benzoin reaction.

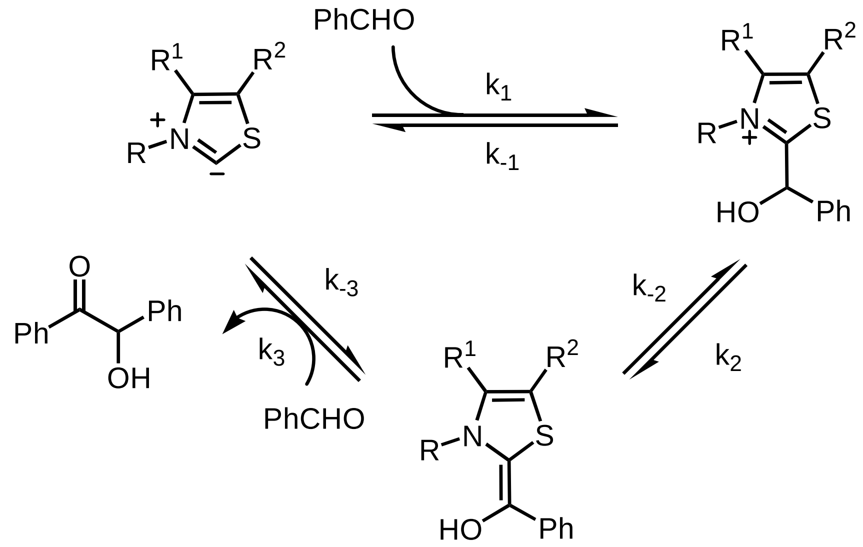
- Determined by using initial rates of reaction at different concentrations of benzaldehyde

- ***No dimerization of catalyst observed when benzaldehyde is present***
- ***Reaction is essentially first order with respect to PhCHO.*** However…

For detailed kinetic study see Leeper *JOC* **2001**, *66*, 5124 and references therein

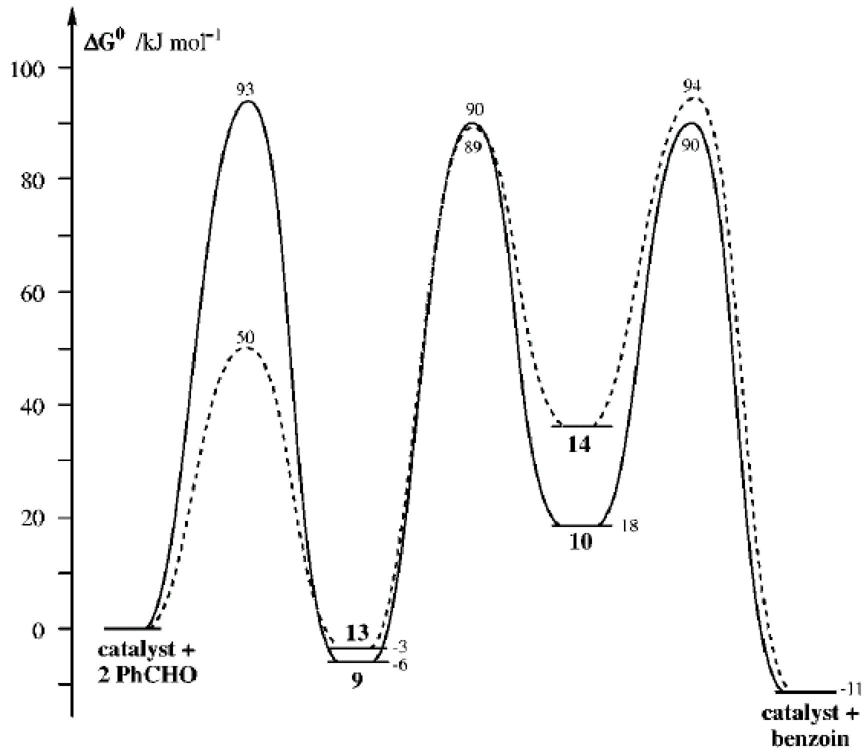
Free Energy Profile of Benzoin Condensations

Kinetic model



- At high concentrations of aldehyde, C-C bond formation fast and deprotonation is the rate determining step (first order)

- At low concentrations, C-C bond formation is slow and deprotonation is fast (second order)



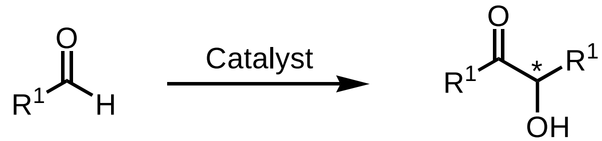
– Thiazolium -- Cyanide

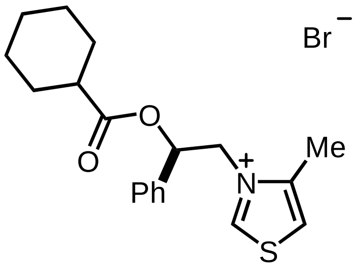
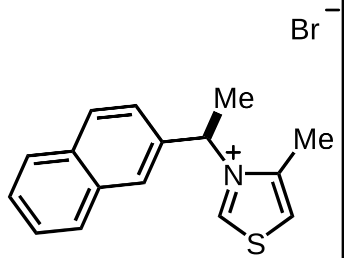
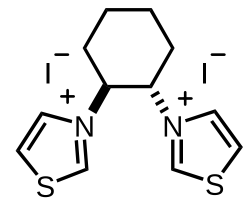
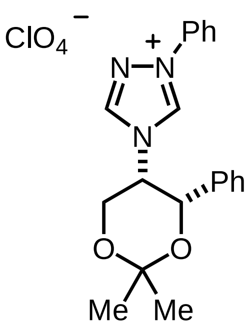
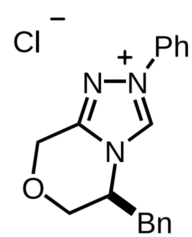
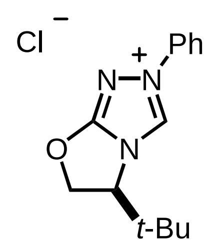
*Free energies are relative to starting materials.
Relative free energy of 14 unknown.

•No step is fully rate determining, all three steps are partially rate determining

For detailed kinetic study see Leeper *JOC* **2001**, *66*, 5124 and references therin

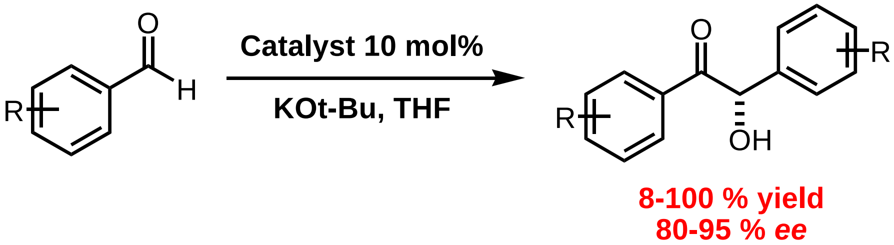
Asymmetric Benzoin Reactions



Catalyst	Result	Catalyst	Result	Catalyst	Result
 Sheehan (1966)	**9 % Yield** **22 % ee**	 Sheehan (1974)	**6 % Yield** **52 % ee**	 Lopez Calahorra (1993)	**21 % Yield** **27 % ee**
 Ender (1996)	**22-72 % Yield** **20-86 % ee**	 Leeper (1998)	**11-45 % Yield** **76-83 % ee**	 Enders (2002)	**8-100 % Yield** **80-95 % ee**

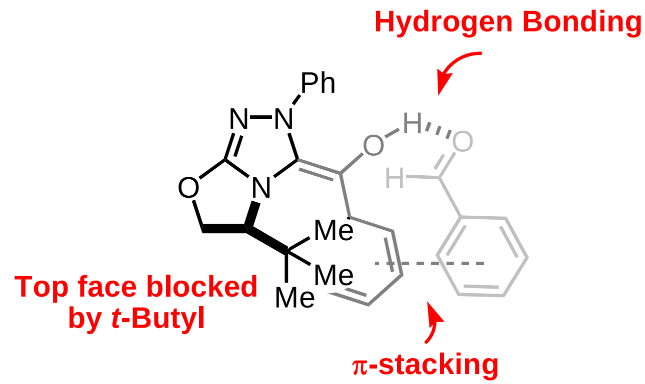
For a review see Enders *Acc. Chem Res.* **2004**, *37*, 534

Transition States of Asymmetric Benzoin

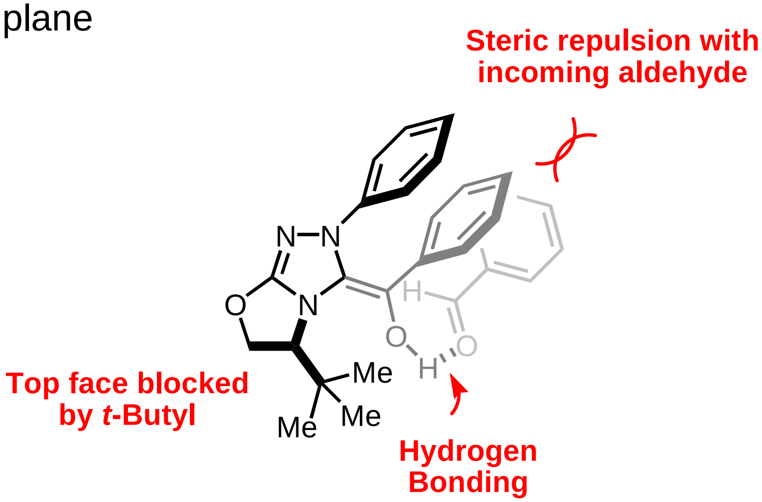


- *Though undefined, E/Z geometry of Breslow's intermediate is important in facial selectivity of the incoming aldehyde*
- Note: Facial attack designation is with respect to the incoming aldehyde

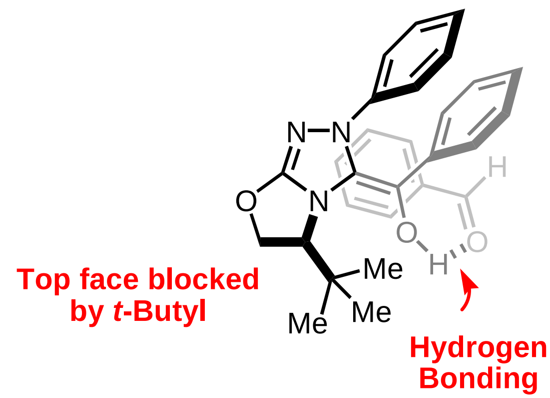
- **E Olefin – Favored *Re* facial attack**



- **Z Olefin – Disfavored *Si* facial attack**
  A-1,3 Strain forces aryl groups to rotate out of the plane

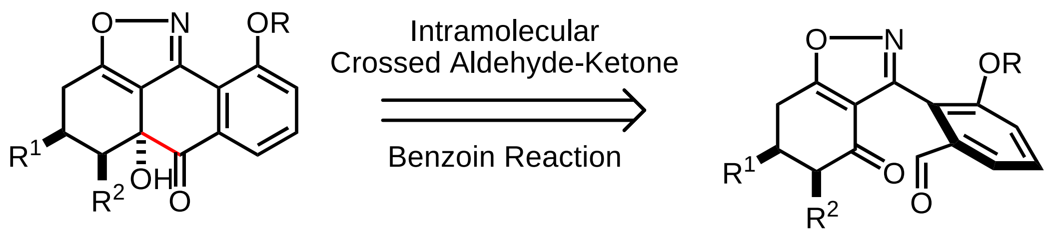


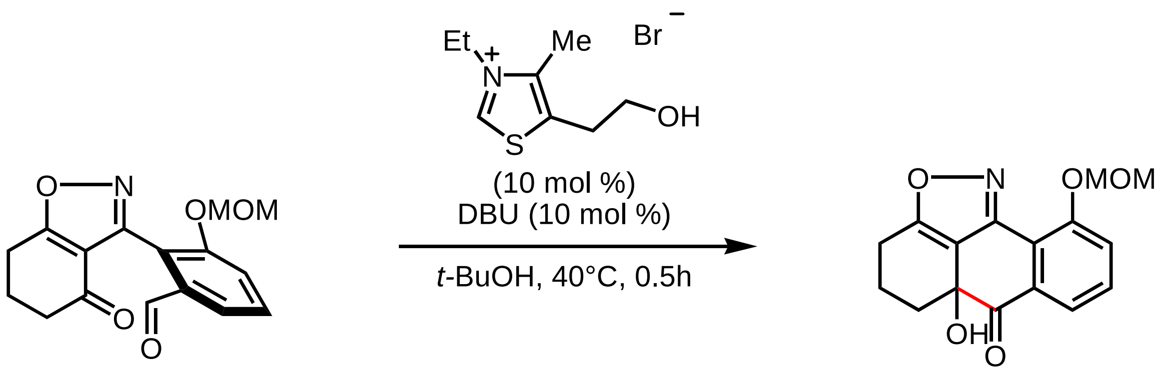
- **Z Olefin – Favored *Re* facial attack**
  A-1,3 Strain forces aryl groups to rotate out of the plane



(a) **Enders** *Acc. Chem Res.* **2004**, *37*, 534 (b) **Houk** *Proc. Natl. Acad. Sci.* **2004**, *101*, 5770

Intramolecular Crossed Aldehyde-Ketone Benzoin

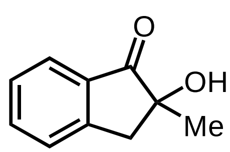




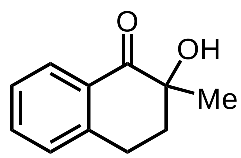
94 % yield

Cyanide gave low yields.

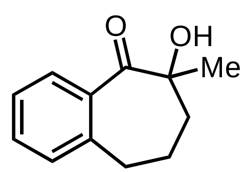
Intermolecular aldehyde-aldehyde benzoin side products were not observed



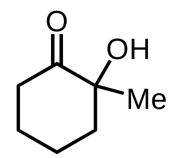
73 % yield[b]



89 % yield[b]



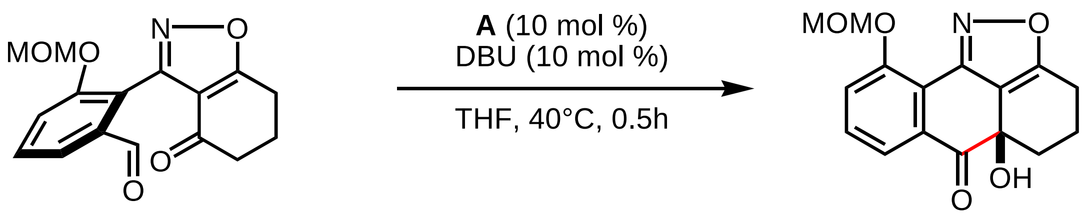
0 % yield[b]



42 % yield[b]

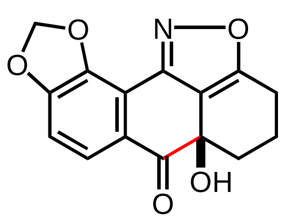
(a) **Suzuki** *JACS* **2003**, *125*, 8432. (b) **Suzuki** *Adv. Synth. Cat.* **2004**, *45*, 3492. (c) **Suzuki** *ACIEE* **2006**, *45*, 3492

Enantioselective Crossed Aldehyde-Ketone

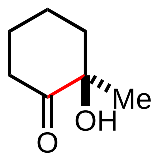


87 % yield
99 %ee

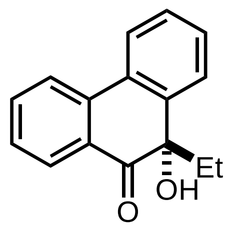
Generally, good yields and selectivities for aliphatic, aromatic intramolecular crossed benzoin!



73% yield
99%*ee*

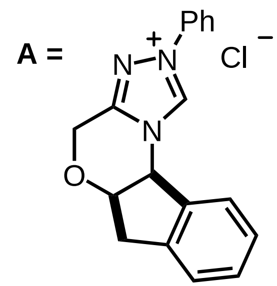


44% yield
96%*ee*

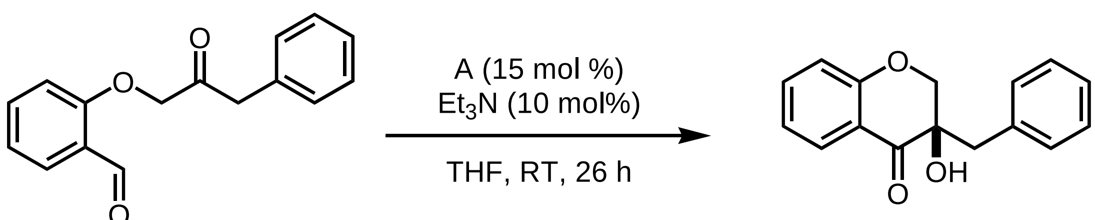


47% yield
90%*ee*

Biaryl systems give opposite enantioselectivities



Rovis *JACS* **2002**, *124*, 10298

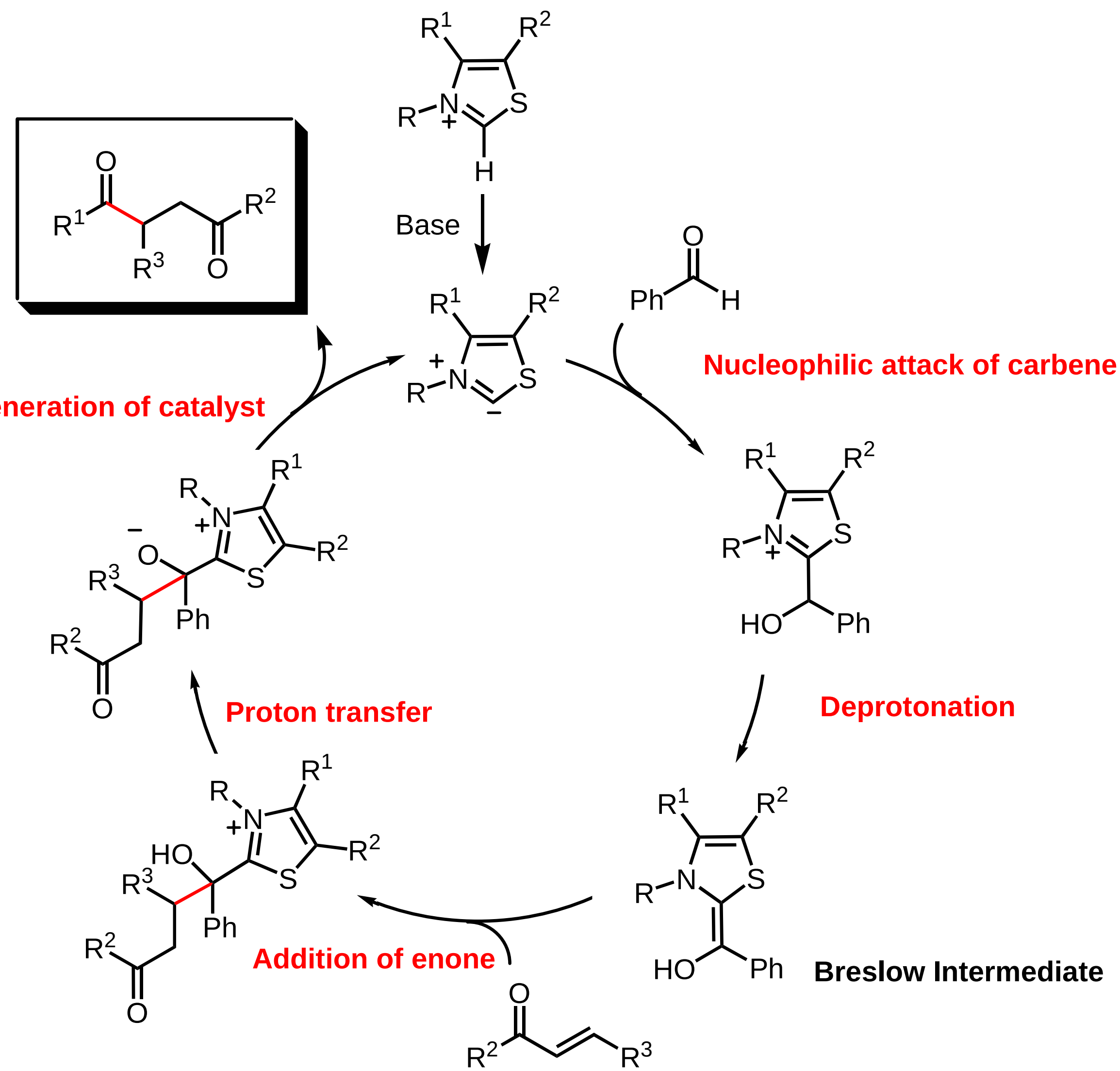


56% yield
88% ee

Eucomol structural core

(a) **Suzuki** *JACS* **2003**, *125*, 8432. (b) **Suzuki** *Adv. Synth. Cat.* **2004**, *45*, 3492. (c) **Suzuki** *ACIEE* **2006**, *45*, 3492

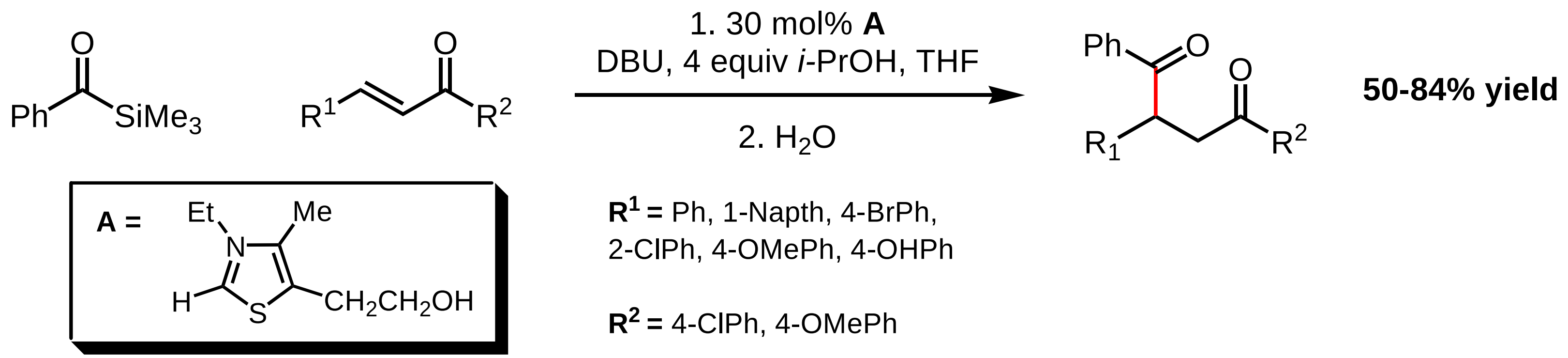
The Stetter Reaction - Generation of 1,4-dicarbonyls



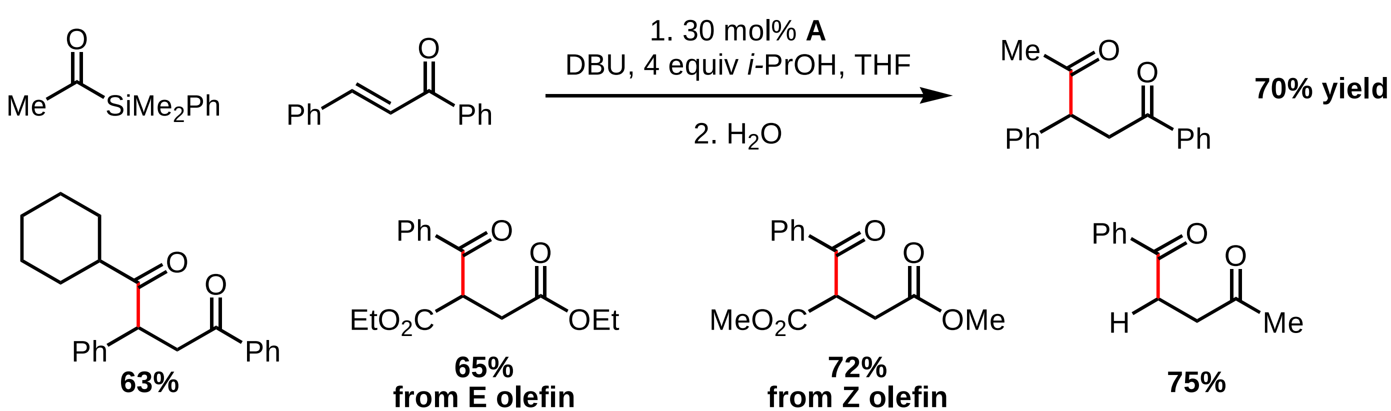
Limited to aromatic aldehydes and Benzoin products are also observed

Stetter *ACIEE* **1976**, *15*, 639

Thiazolium Catalyzed Sila-Stetter



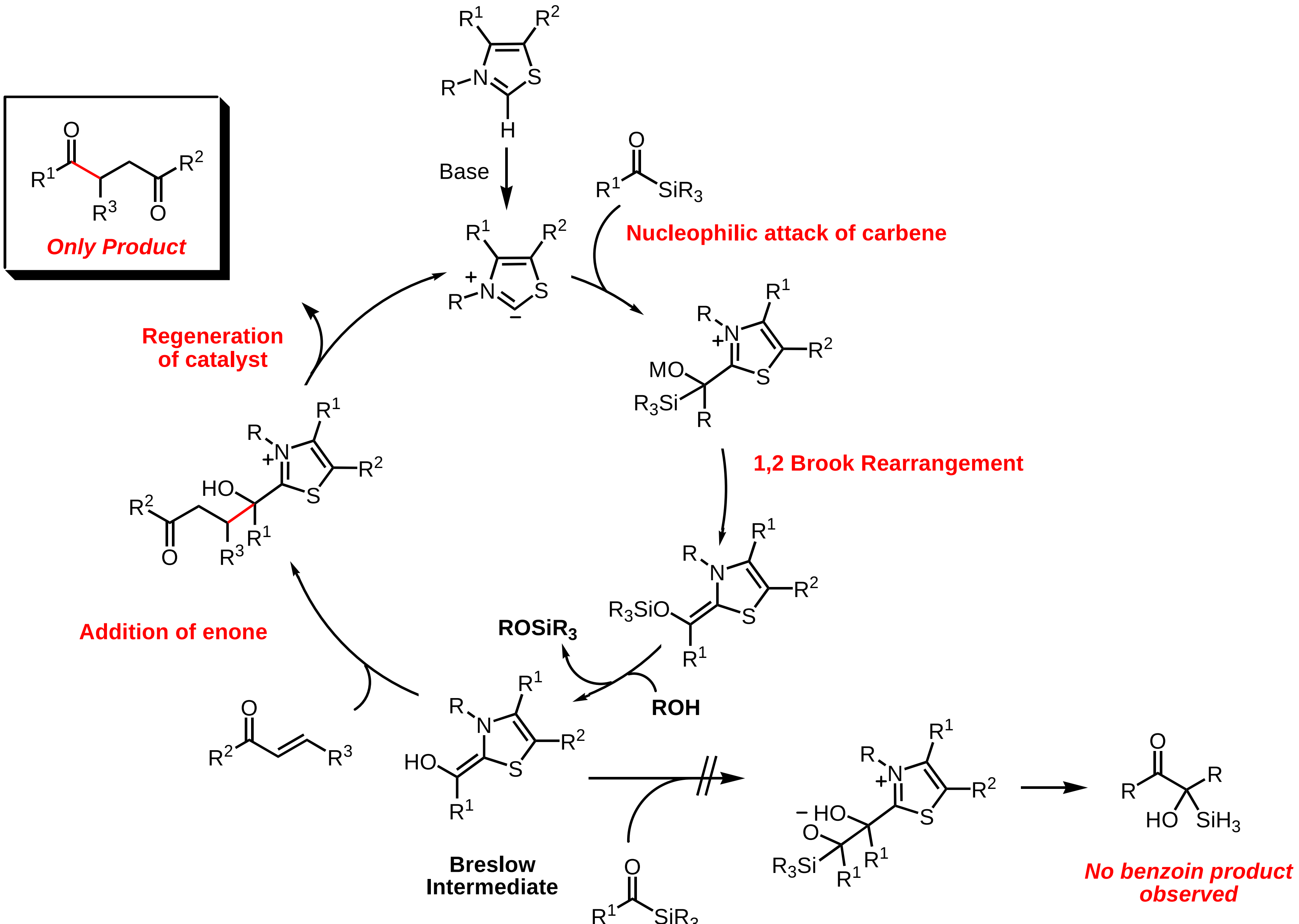
With $SiMe_2Ph$ group, enolizable alkyl acyl silanes also work!



Must use 4-chlorobenzoyltrimethylsilane for nonbisaryl α,β-unsaturated ketones

Scheidt *JACS* **2004**, *126*, 2314

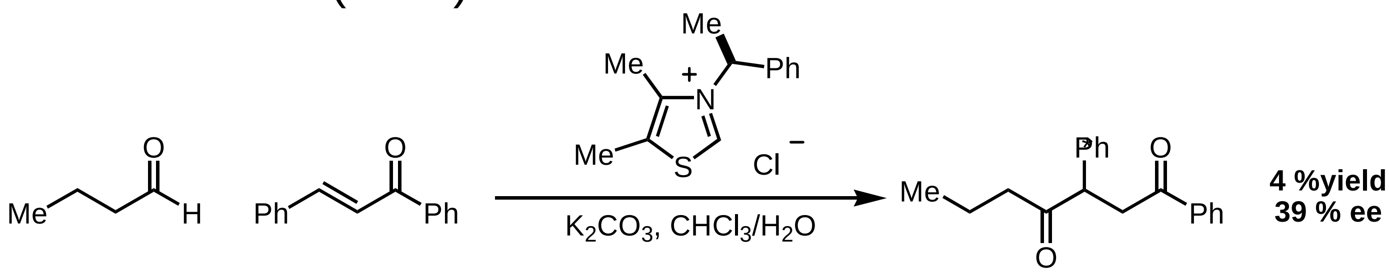
Thiazolium Catalyzed Sila-Stetter



Scheidt *JACS* **2004**, *126*, 2314

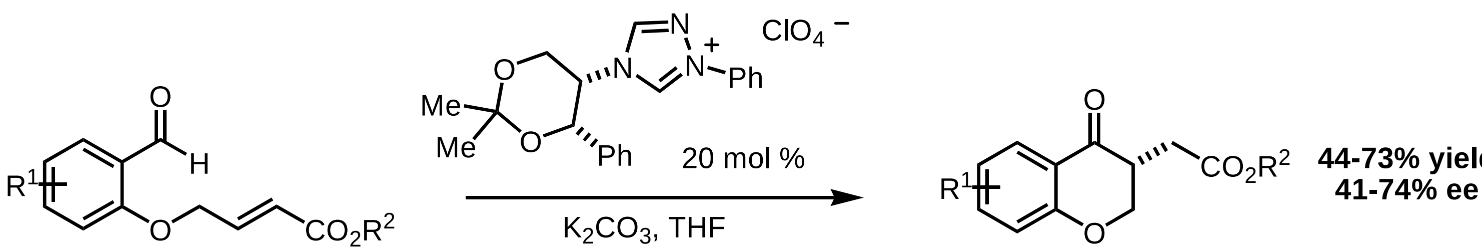
Initial Attempts at Asymmetric Stetter Reactions

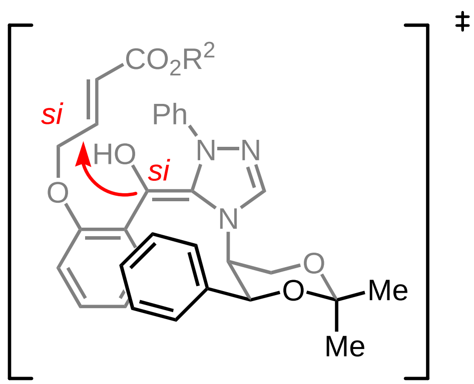
Intermolecular Stetter (1990)



Various triazolium salts also resulted in low yields.

Intramolecular Stetter (1996)

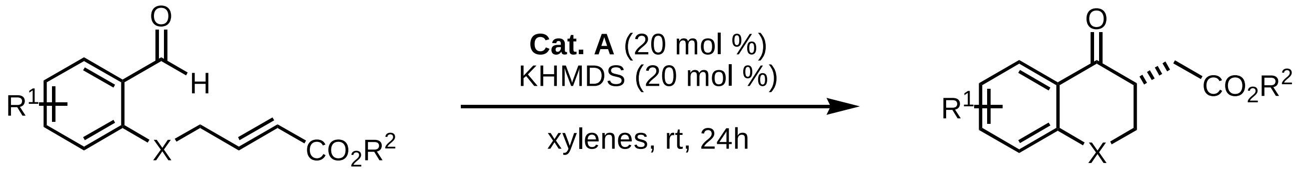




- ***Phenyl group shields one face of the olefin***
- ***Attack of less hindered face leads to an R configuration***

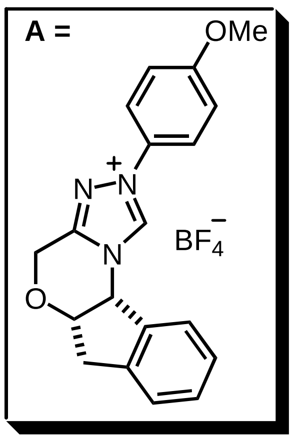
(a) For a review see Enders *Acc. Chem Res.* **2004**, *37*, 534 (b) **Enders** *Helv Chim. Acta.* **1996**, *79*, 1899

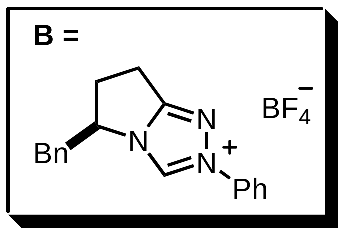
Recent Advancements in Asymmetric Stetter

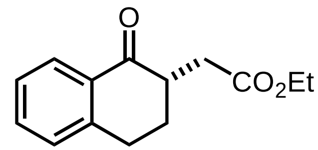


63-95 % yield
82-97 % ee

X = O, S, NMe



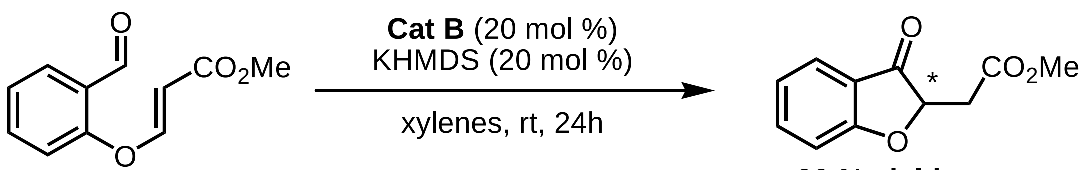




Cat A: 94% yield and 35% ee
Cat B: 92% yield and 90% ee

- ***Electron rich carbene (OMe substituted Cat. A) facilitates addition to electron deficient Michael acceptor.***
- ***Under these conditions, newly generated stereocenters do not racemize.***

An exception



90 % yield
<5 % ee

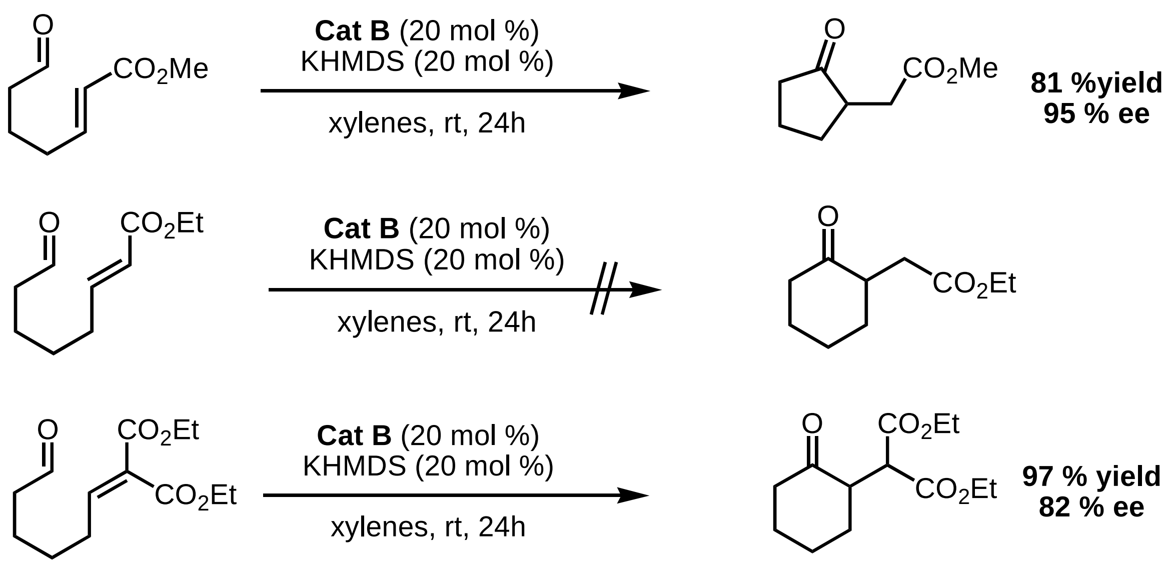
80% ee at 10% conversion

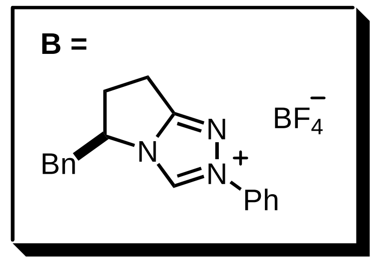
Rapid erosion overtime

Rovis *JACS* **2002**, *124*, 10298

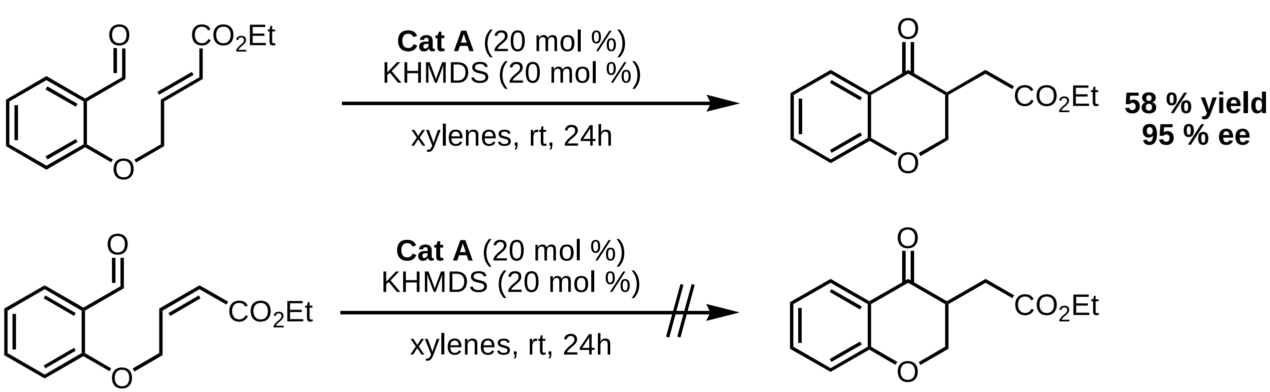
Limitations with the Michael Acceptor

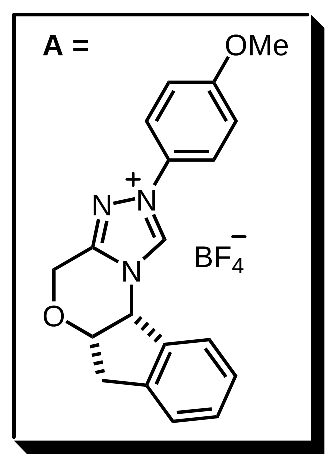
6 membered carbocycles do NOT react unless highly activated





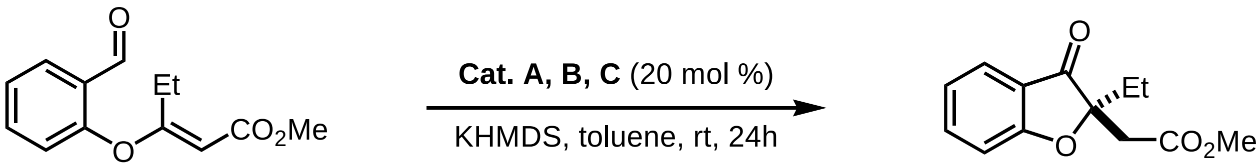
Starting material recovered for Z-alkenes



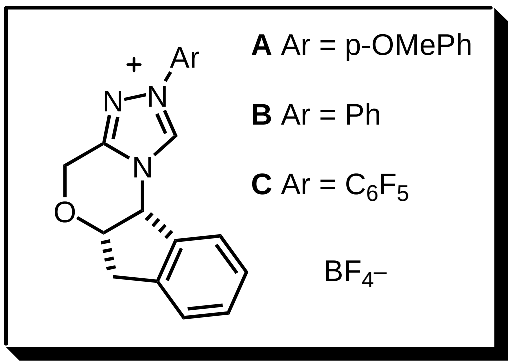


(a) **Rovis** *JACS* **2002**, *124*, 10298. (b) **Rovis** *Synlett* ***2003**,* 1934. (c) **Rovis** *JACS* **2005**, *127*, 6284.

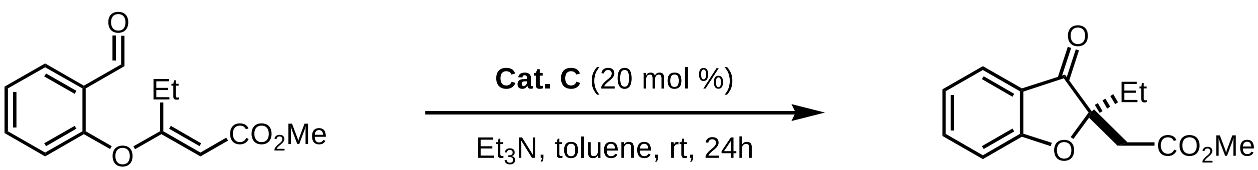
Quaternary Stereocenters via Asymmetric Stetter



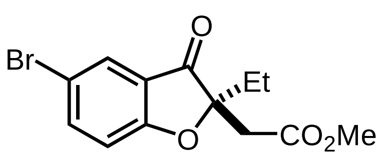
Cat. A: 45% yield 99% *ee*
Cat. B: 80% yield 99% *ee*
Cat. C: 85% yield 99% *ee*



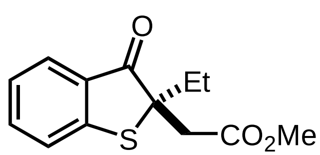
- ***Better yields result from more electron deficient carbenes.***
- ***Implies subtle changes in the mechansim for β-disubstituted Michael acceptors***



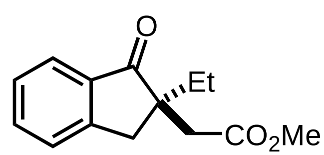
96% yield
97% *ee*



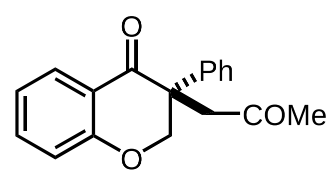
92% yield
89% *ee*



95% yield
92% *ee*



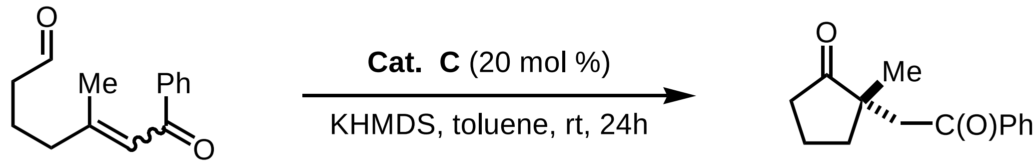
95% yield
99% *ee*



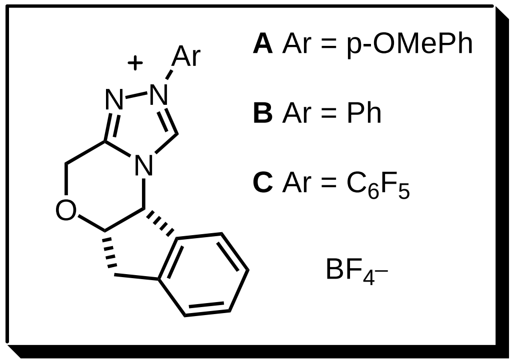
55% yield
99% *ee*

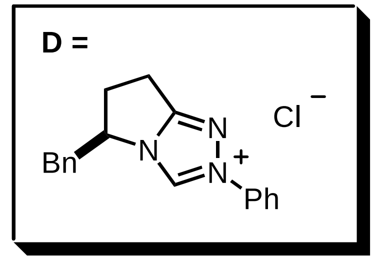
Rovis *JACS* **2004**, *126*, 8876

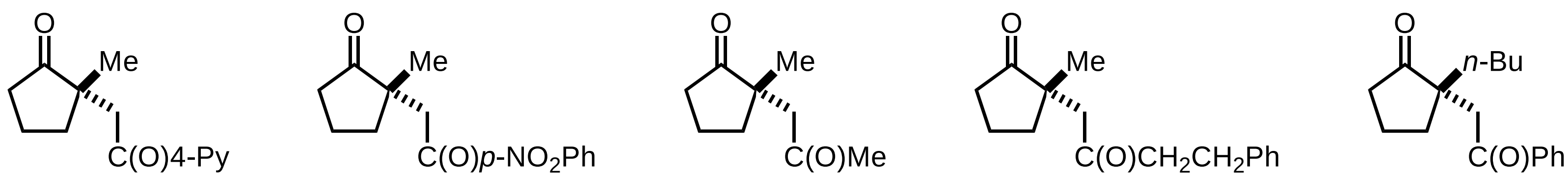
Quaternary Stereocenters from Aliphatics



E-isomer 85% yield 96% *ee*
Z-isomer 50% yield 56% *ee*

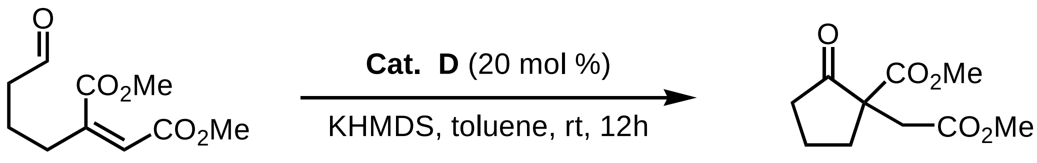






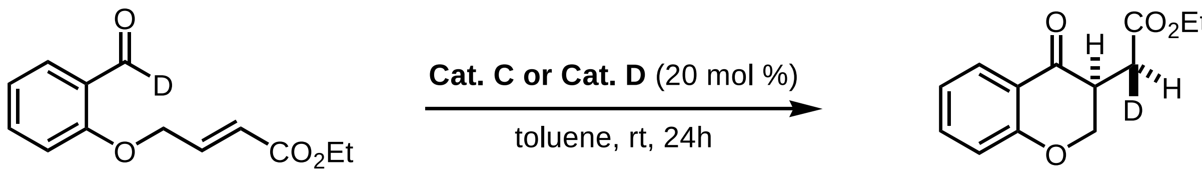
85% yield 96% *ee*	90% yields 84% ee	81% yields 95% ee	63% yields 99% ee	71% yields 98% ee

All carbon tethers with ester Michael acceptors required further activation to react.

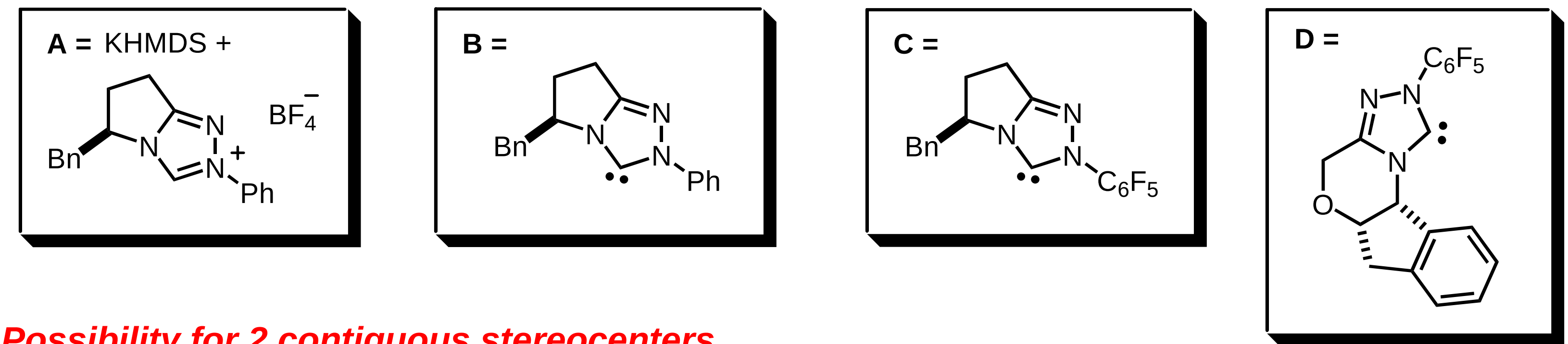


86% yields
90% *ee*

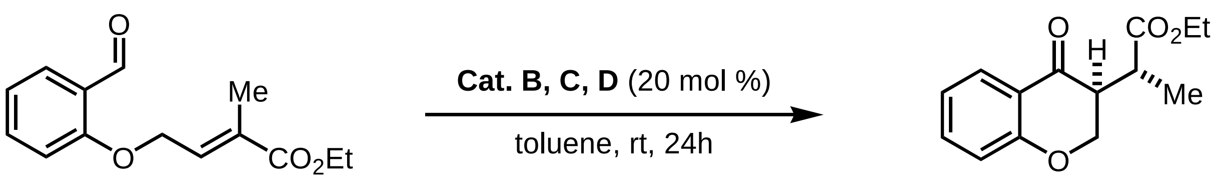
Formation of Contiguous Stereocenters



Cat A: 3:1 dr
Cat B: 9:1 dr

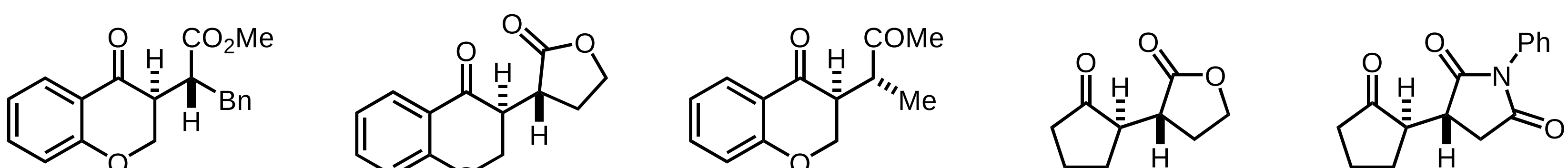


Possibility for 2 contiguous stereocenters



Cat. B: 88% yield 95% *ee* 15:1 dr
Cat. C: 94% yield 95% *ee* 30:1 dr
Cat. D: 80% yield -99% *ee* 150:1 dr

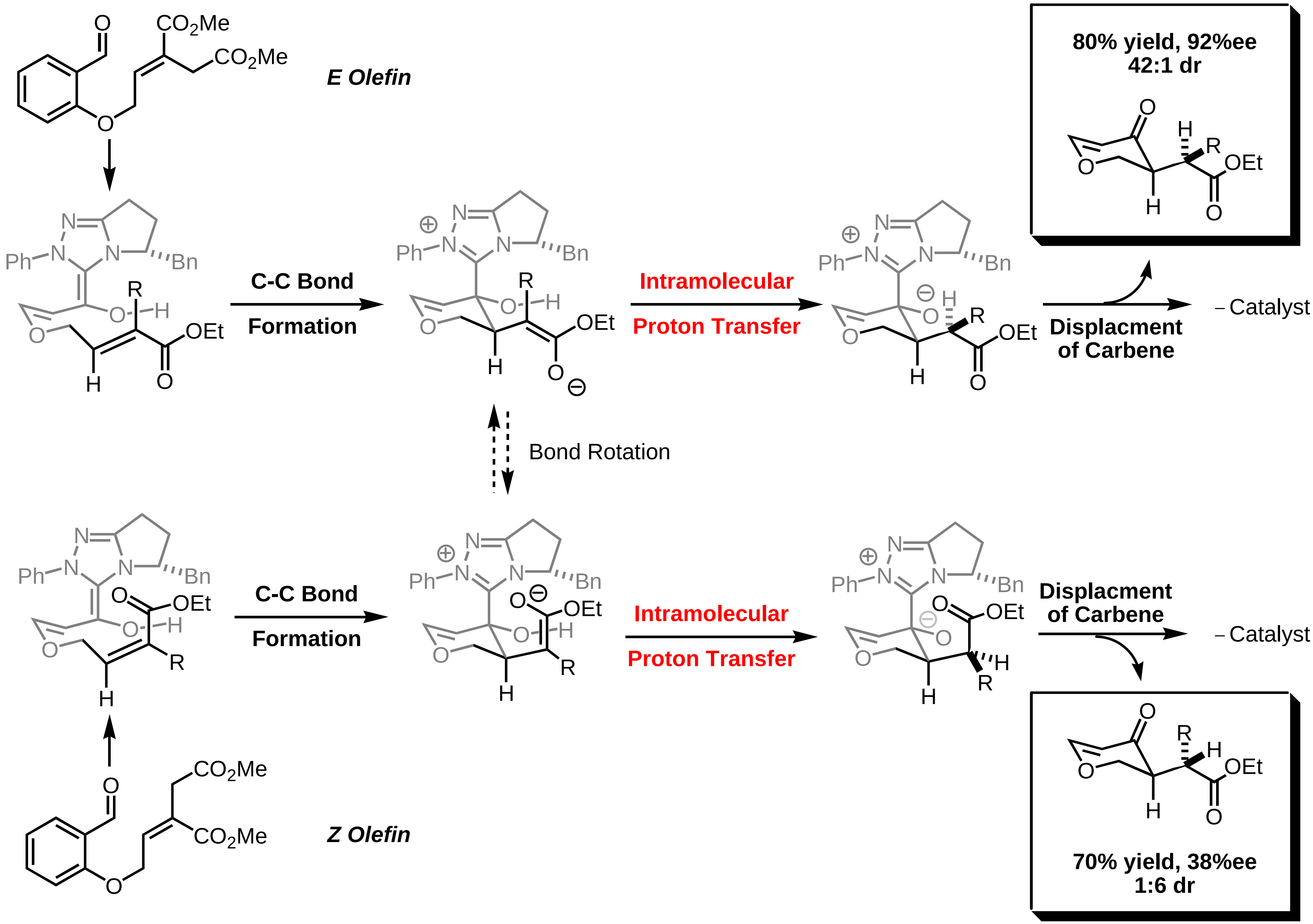
Minimal epimerization of products under reaction conditions



80%yield	**95%yield**	**85%yield**	**94% yield**	**80%yield**
84%*ee* 20:1	**95%*ee* 10:1**	**55%*ee* 10:1**	**99%*ee* 50:1**	**88%*ee* 15:1**

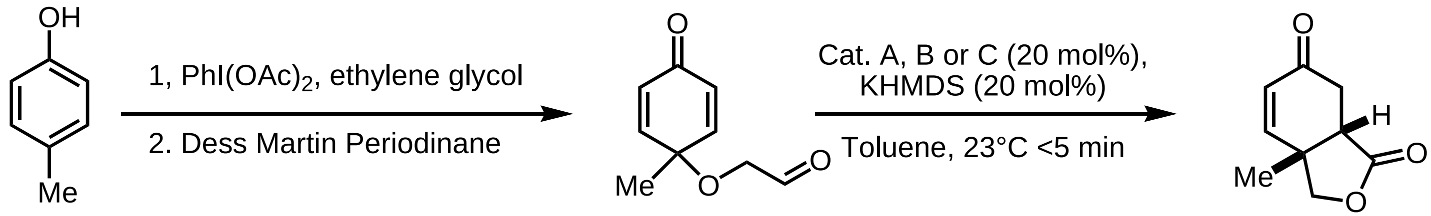
Rovis *JACS* **2005**, *127*, 6284.

Stereochemical Model for Diastereoselectivity

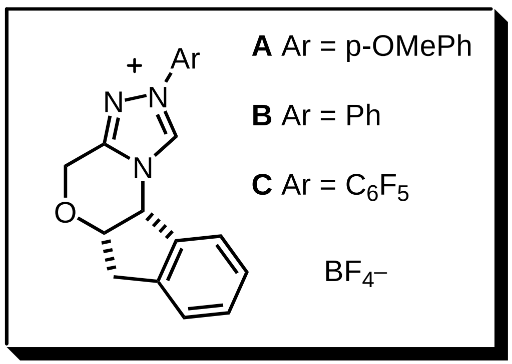


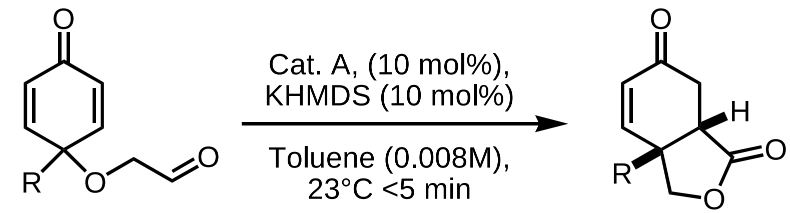
Rovis *JACS* **2005**, *127*, 6284.

Desymmetrization via an Intramolecular Stetter



Cat. A: 90% yield 88% *ee*
Cat. B: 75% yield 80% *ee*
Cat. C: 92% yield 31% *ee*

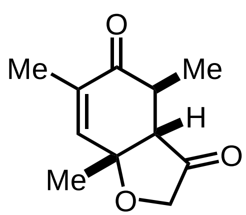




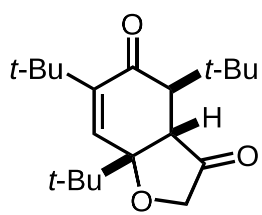
R = Me, Et, *i*-Pr, *t*-Bu, Ph, 4-BrPh, CH_2OAc, CH_2CH_2OMe, $CH_2CH_2CO_2Me$

78-94%
82-94% ee
>95:5 dr

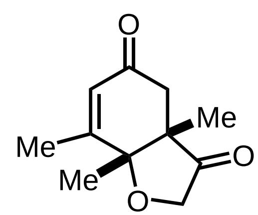
Up to three contiguous stereocenters and quaternary stereocenters can be formed!



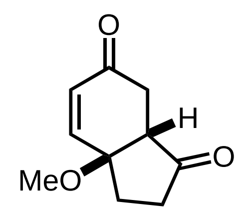
86%yield
>99% ee
single diastereomer



Reaction time: 2 h
62%yield
>99% ee
single diastereomer



64%yield
>99% ee
>95:5 dr

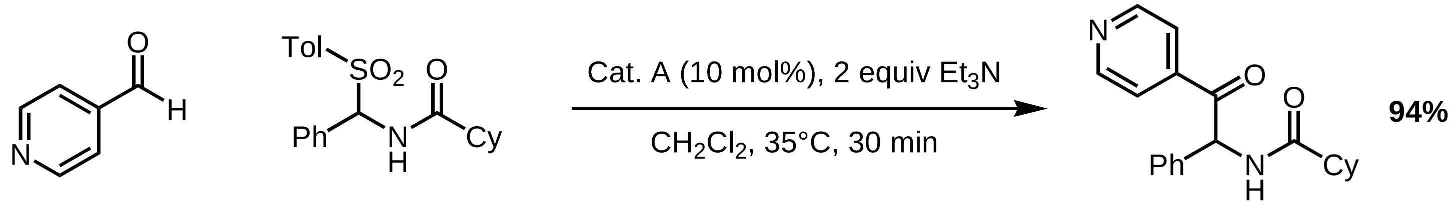


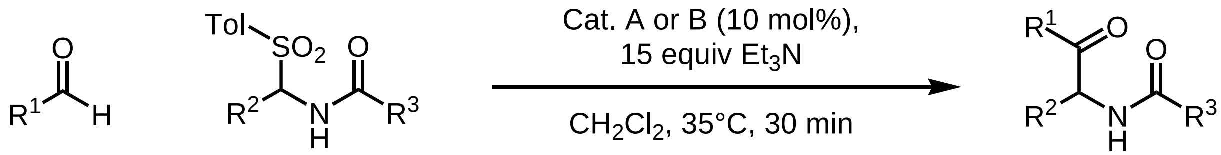
60%yield
>90% ee
>95:5 dr

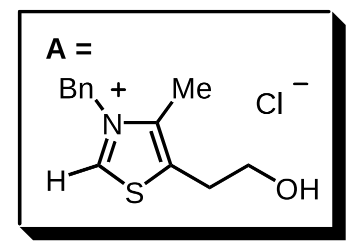
Carbocycles may also be formed using the free carbene of Catalyst A

Rovis *JACS* **2006**, *128*, 2552

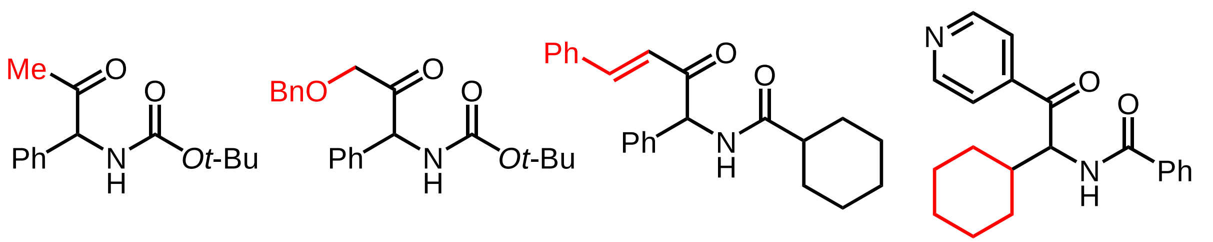
Cross Couplings with Aldehydes and Acyl Imines

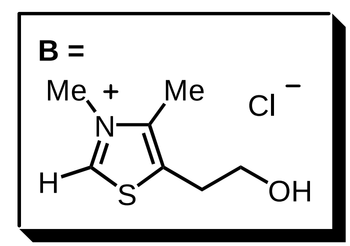




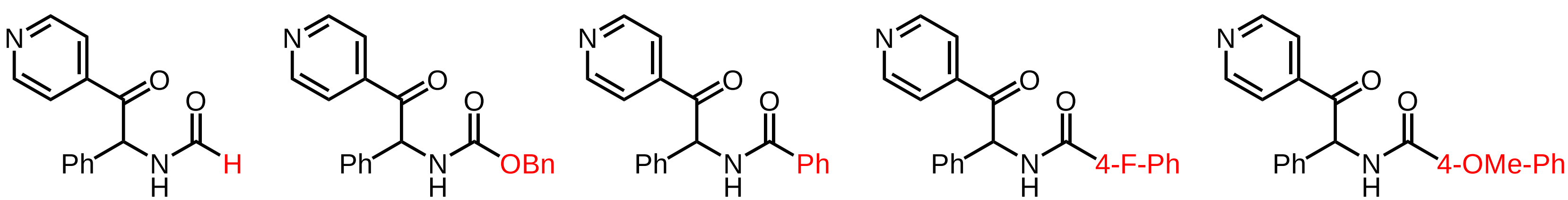


Aromatic, aliphatic and unsaturated substrates viable





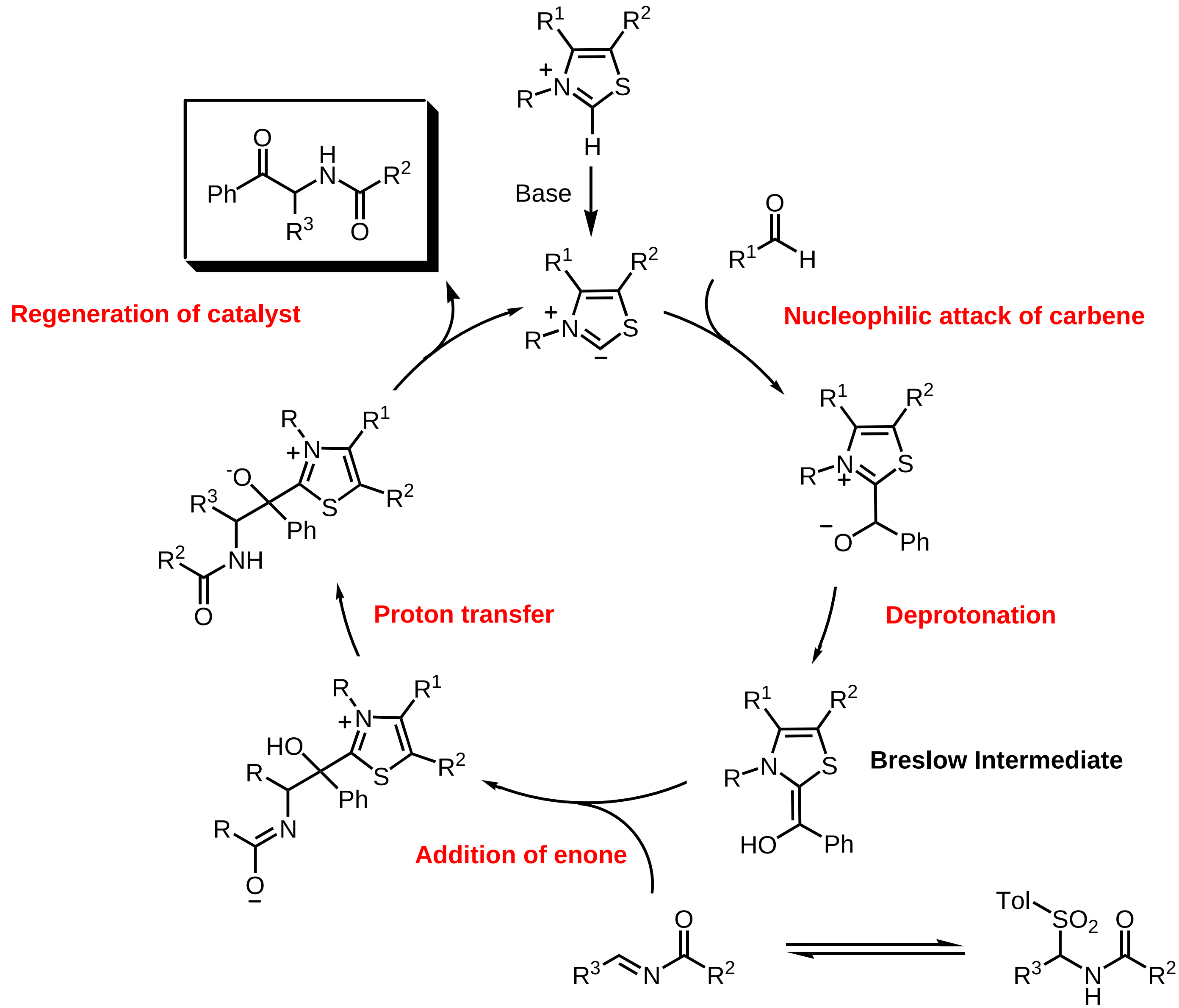
62% **75%** **80%** **< 10%**



86% **96%** **88%** **90%** **97%**

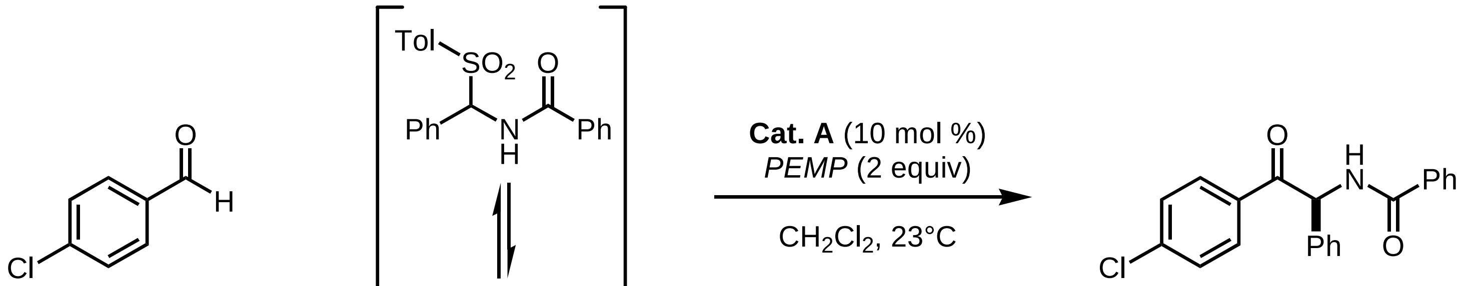
Murry, Frantz et al. *JACS* **2001**, *123*, 9696

Mechanism of Aldehyde-Imine Cross Coupling

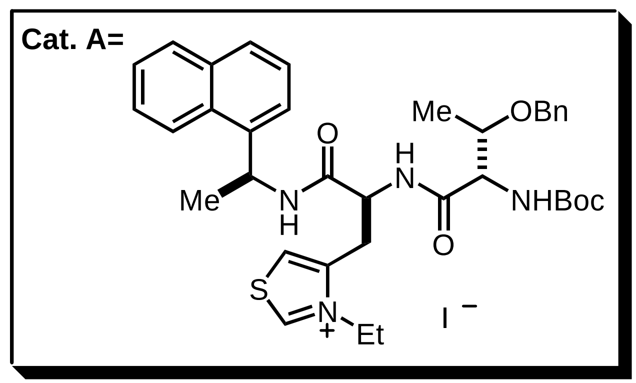


Murry, Frantz et al. *JACS* **2001**, *123*, 9696

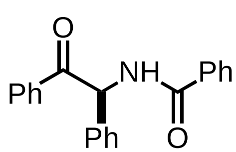
Enantioselective Aldehyde-Imine Cross Couplings



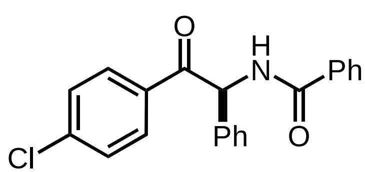
86% *ee*



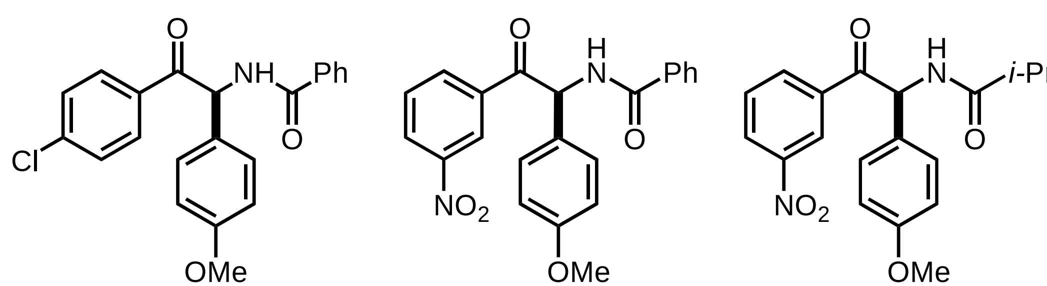
- ***Reaction conditions lead to enolization and degredation of product.***
- ***Use of pentamethylpiperidine (PEMP) slowed rate of racemization.***



2h 15% yield
83%*ee*



1h 57% yield 81%*ee*
2h 100% yield 76%*ee*

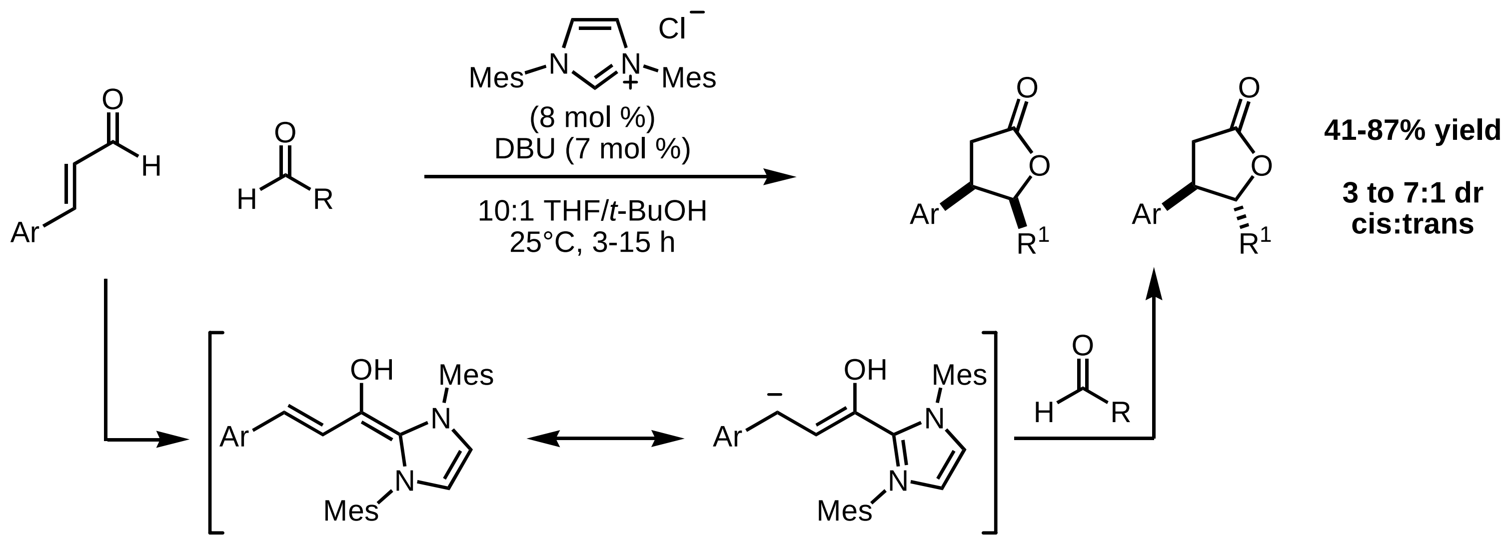


2h 91% yield 85%*ee*

15 min 77% yield 82%*ee*

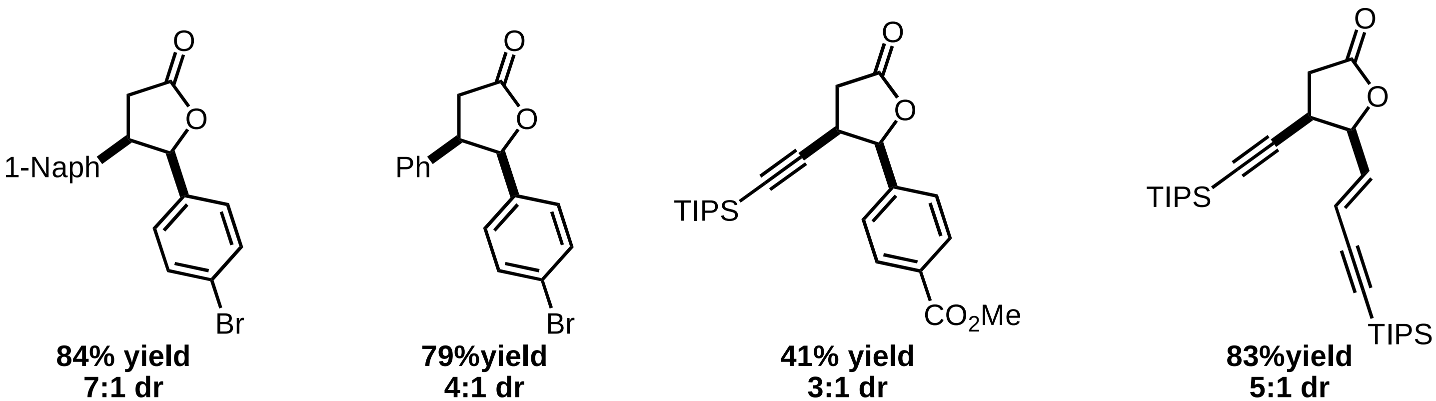
15 min 63% yield79%*ee*

Formation of γ-Butyrolactones from Homoenolates



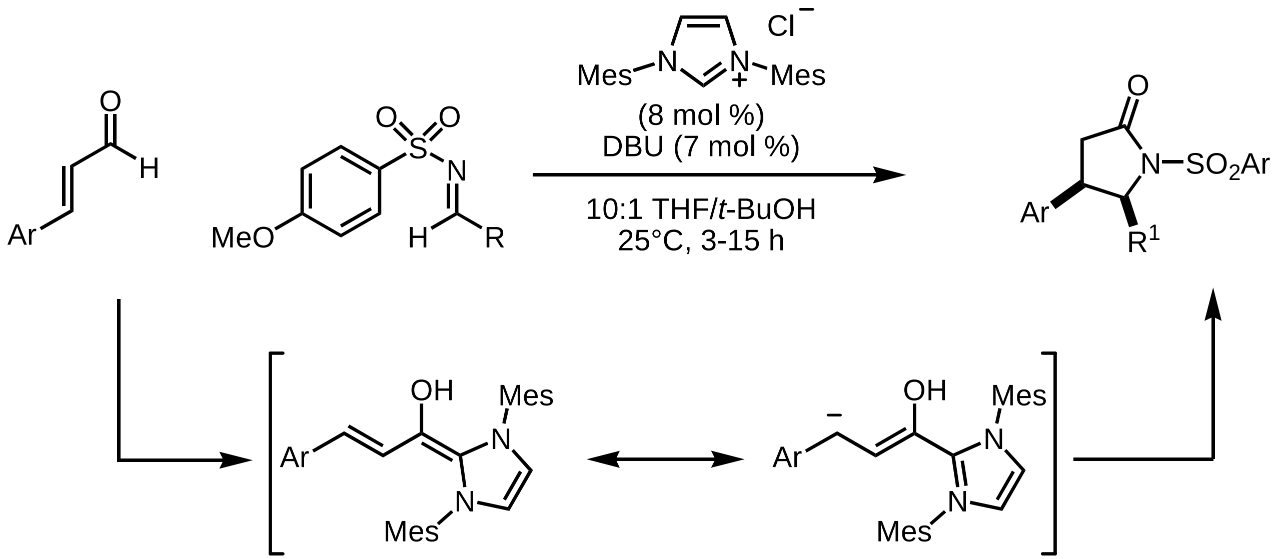
Mesityl groups influences the formation of the homoenolate by

- slowing reactions at the acyl position
- directing reactivity to the β-positon, and
- forestalls protonation of the homoenolate



(a) **Bode** *JACS* **2004**, *126*, 14370 (b) **Glorius** *ACIEE* **2004**, *43*, 6205

γ–Lactams via Nucleophilic Catalysis

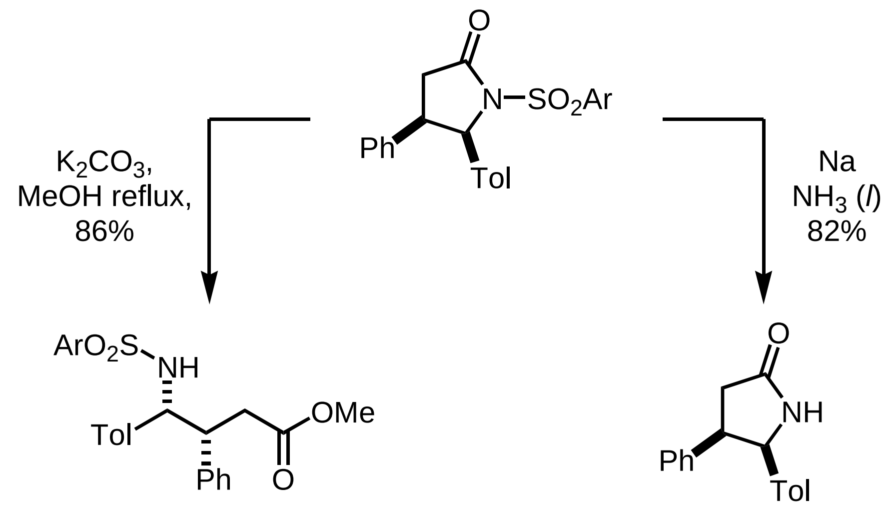


41-87% yield

3 to 7:1 dr
cis:trans

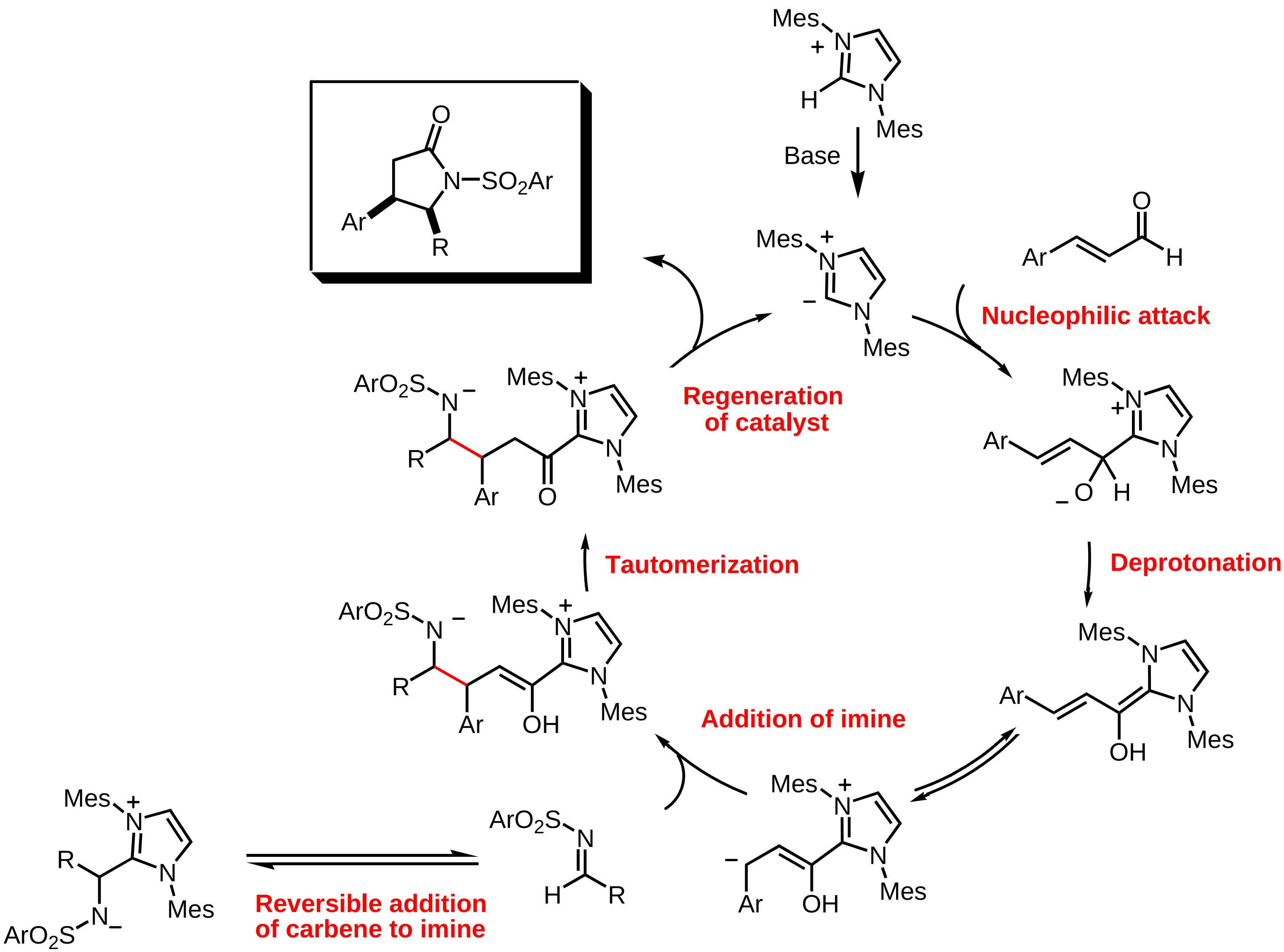
- ***N-alkyl and N-aryl imines were unreactive***
- ***More reactive imines, such as N-tosyl, reacted irreversibly with the carbene catalyst.***
- ***Carbene catalyst reacts preferentially but reversibly with N-4-methoxybenzensulfonyl imines***
- ***Electron poor aldehydes were better nucleophiles***
- ***Electron rich imines were better electrophiles***

Transformations of γ-Lactams



Bode *Org. Lett.* **2005**, *7*, 3131

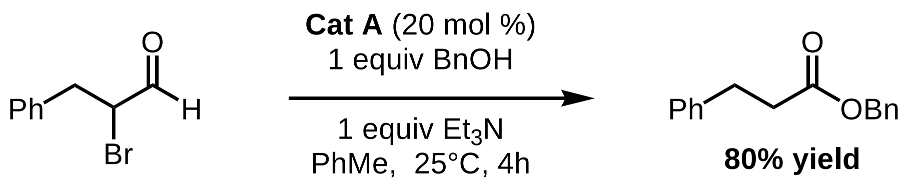
Mechanism of N-Sulfonylimine-Enal Annulation

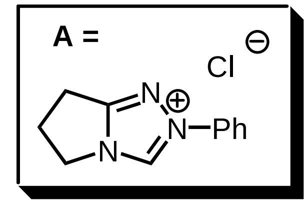


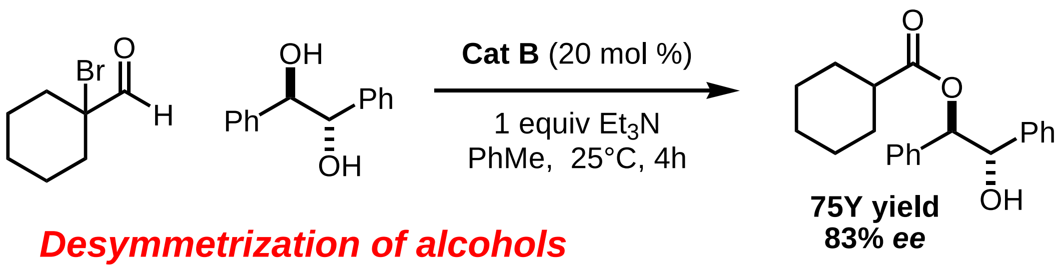
(a) **Bode** *JACS* **2004**, *126*, 14370. (b) **Bode** *Org. Lett.* **2005**, *7*, 3131, (c) **Glorius** *ACIEE* **2004**, *43*, 6205

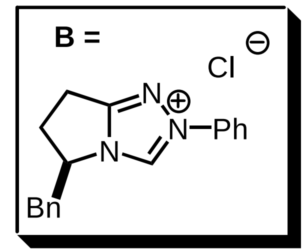
Other uses of N-Heterocyclic Carbenes

Internal Redox Reactions - Rovis *JACS* **2004** *126*, 9518



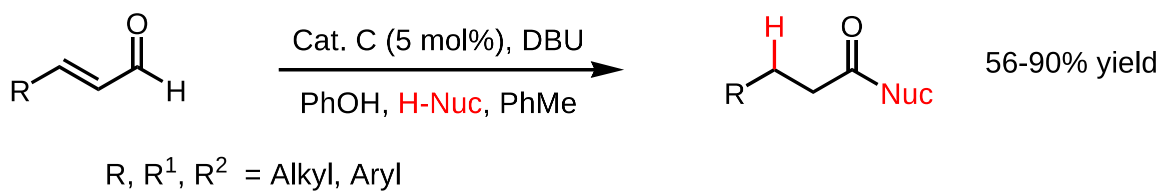


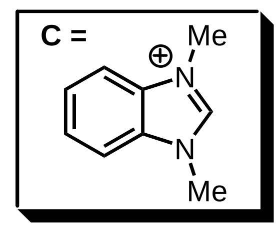


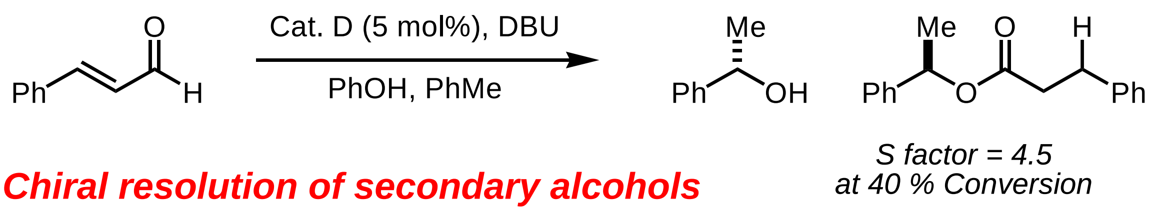


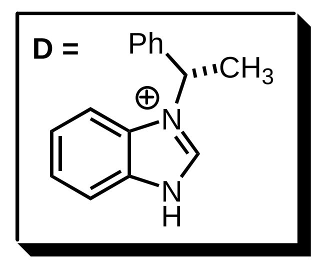
Desymmetrization of alcohols

Conversion of α,β Unsaturated Aldehydes in to Saturated Esters - Scheidt *Org. Lett.* **2005,** *7,* 905





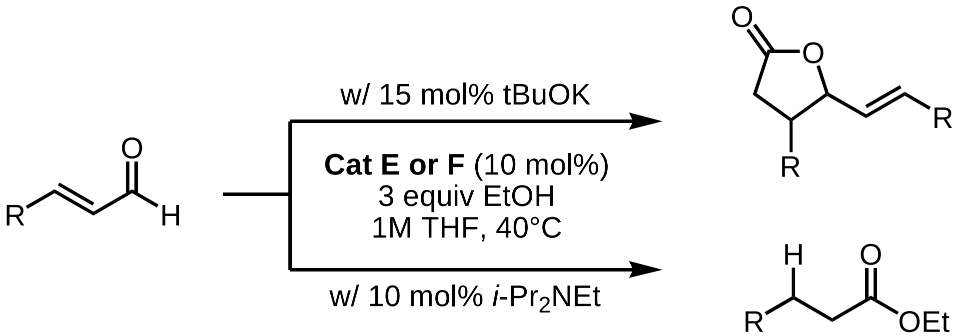


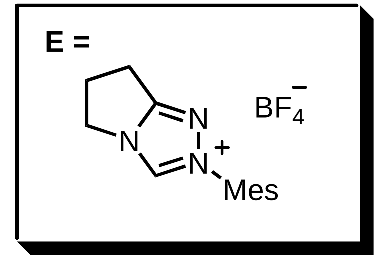


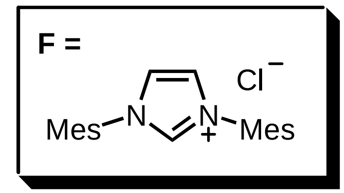
Chiral resolution of secondary alcohols

Other uses of N-Heterocyclic Carbenes

Activated Carboylxates from Enals - Bode *Org. Lett.* **2005,** *7,* 3873







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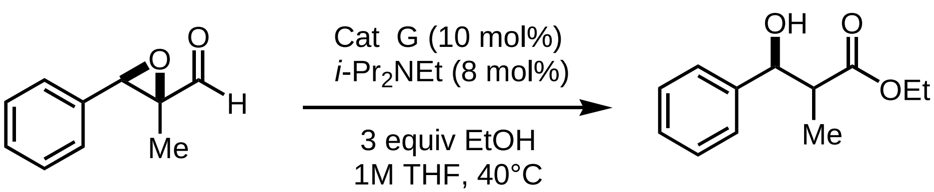

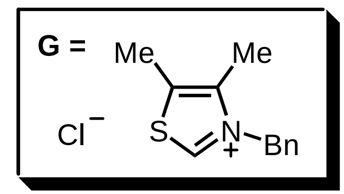

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