Enantioselective Synthesis of Quaternary Stereocenters via a Catalytic Asymmetric Stetter Reaction

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Current Literature
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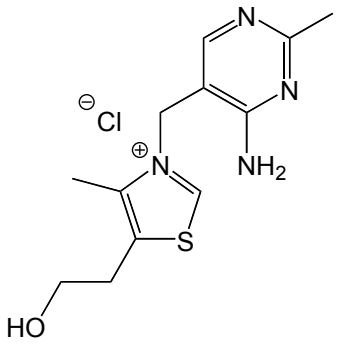
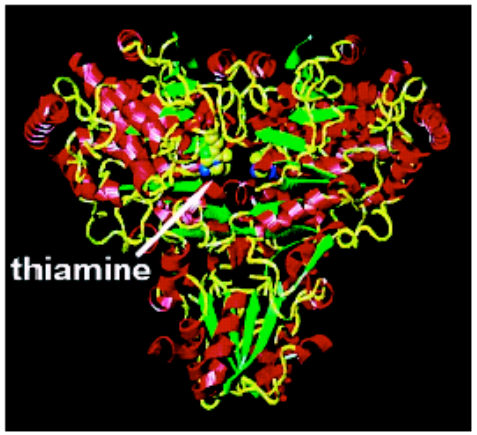
Topics of presentation:
- Carbene catalysts
- Stetter reaction and uses
- Methods of quaternary center formation
- Current paper and data

Nucleophilic Carbenes as Catalysts

In nature:

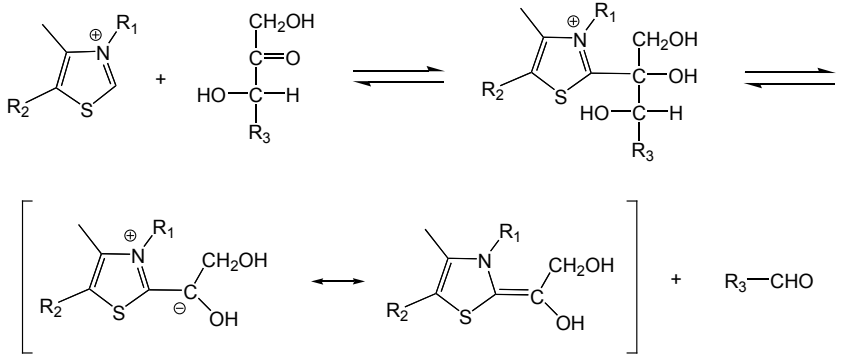


Thiamine (Vitamin B_1), a coenzyme

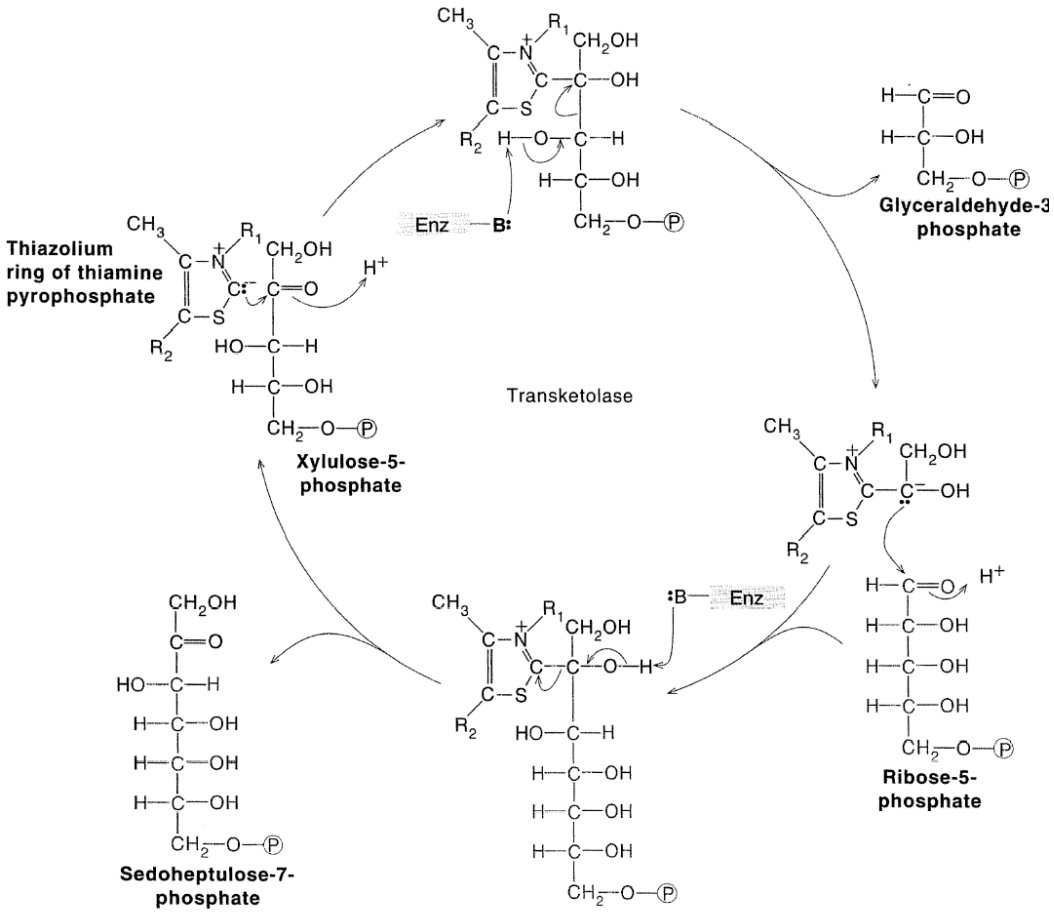


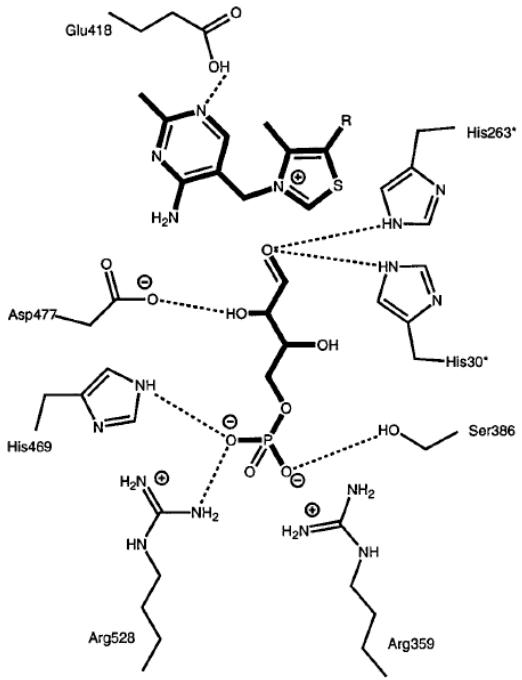
Structure of transketolase enzyme with bound coenzyme at center
(Enders, D., et al. *Acc. Chem. Res.* **2004**, ASAP)

- Enzyme catalyzes the rearrangement of ketosugars to aldosugars in carbohydrate synthesis (Schneider, et al. *J. Bio. Chem.* **1997**, *272,* 1864-1869)
  - *i.e., converts xylulose-5-P to glyceraldehyde-3-P*



Catalytic Cycle of Transketolase Enzyme



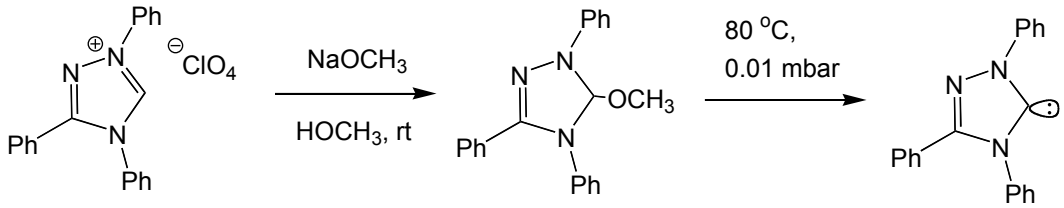


Interactions of erythrose-4-p with transketolase (Schneider, et al.)

Nucleophilic Carbenes as Catalysts

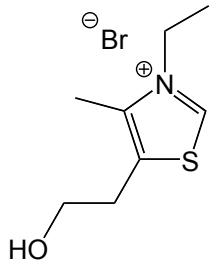
For synthetic purposes:

- Thiamine catalyzed the Benzoin condensation (1943, Ukai, et al.)
- Chiral thiazolium salt used for asymmetric Benzoin condensation (1966, Sheehan, et al.)
- First stable carbene isolated in 1991 (Arduengo, et al.)
- First carbene commercially available in 1995 (Enders, et al.)



Crystalline solid - Air and moisture stable up to 150 °C

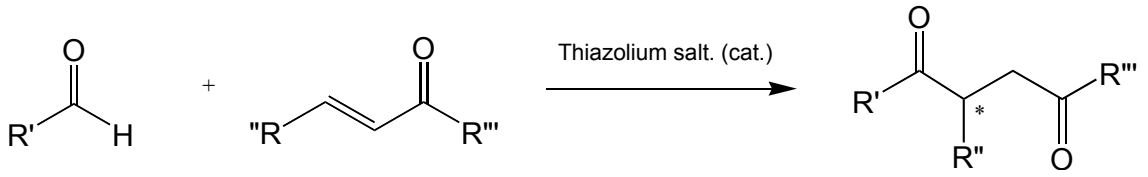
1,3,4-Triphenyl-4,5-dihydro-1H-triazol-5-ylidene
(http://www.eburon-organics.com)



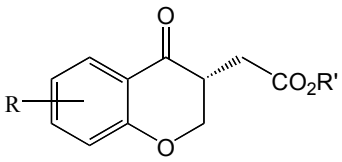
3-Ethyl-5-(2-hydroxyethyl)-4-methylthiazolium bromide
(Chem Pacific, Inc.: 100 mg for $200; Aldrich; etc.)

The Stetter Reaction

-Discovered in the 1970's (*Angew. Chem. Int. Ed. Engl.* **1976**, *15*, 639-648)
- used concept of nucleophilic thiazolium catalyst to acylate Michael acceptors with aldehydes

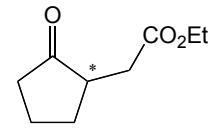


First asymmetric intramolecular Stetter (Enders, et al. 1996)

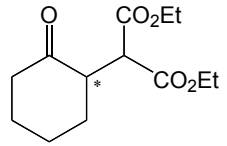


ees = 41-74%

Asymmetric intramolecular Stetter with aliphatic substrates (Rovis, et al. 2003)

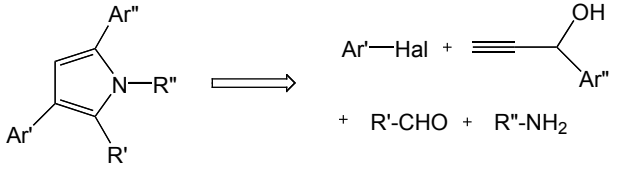


ee = 95%

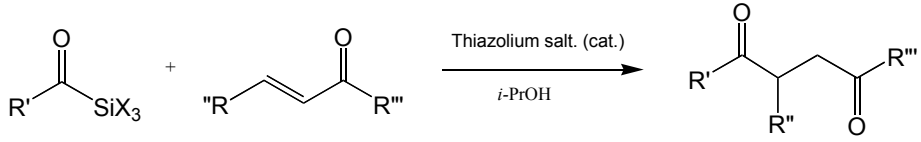


ee = 82%

One-pot pyrrole synthesis via a Coupling-Isomerization-Stetter-Paal-Korr sequence (Muller, et al. 2001)

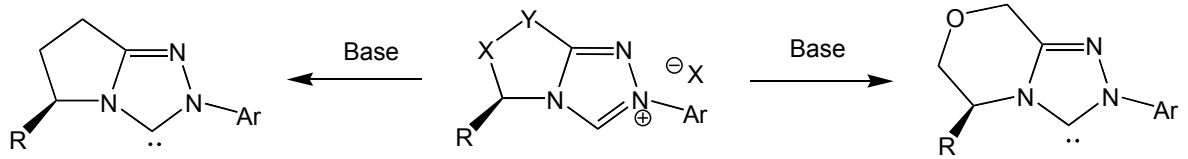


Thiazolium cat. Sila-Stetter (Scheidt, et al. 2004)



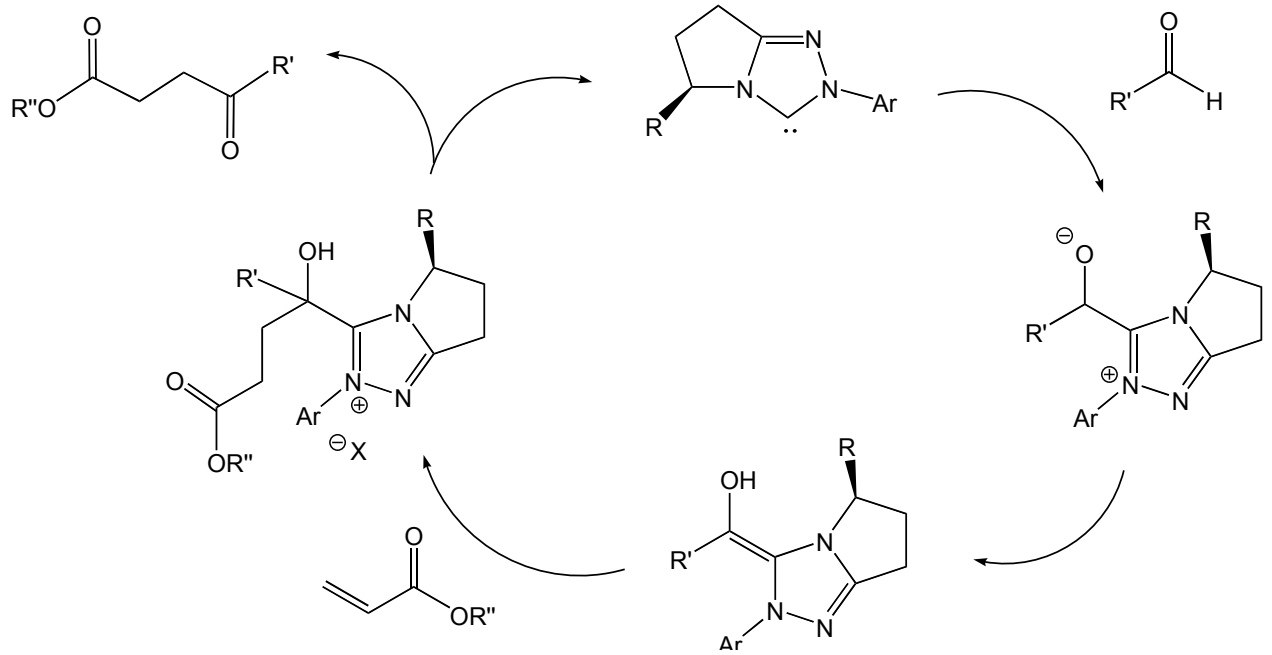
Generic Catalyst and Mechanism of the Stetter Reaction

Catalyst



Triazolium salt
(Air- and water-stable solid)

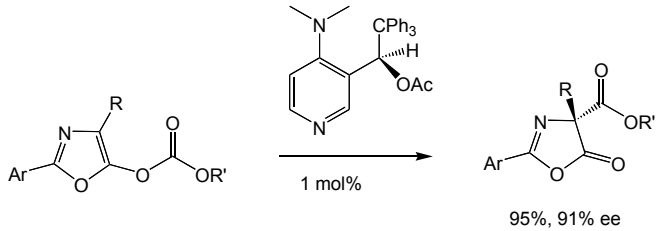
Mechanism



Methods of Synthesizing Quaternary Stereocenters

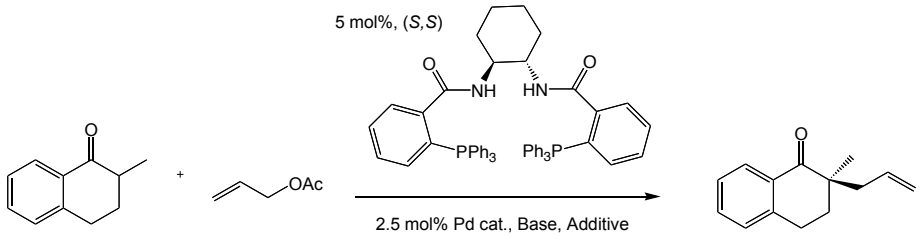
- Intramolecular Heck cyclizations

- Rearrangement of enol carbonates
  - via chiral DMAP catalysts (Vedejs, et al.)



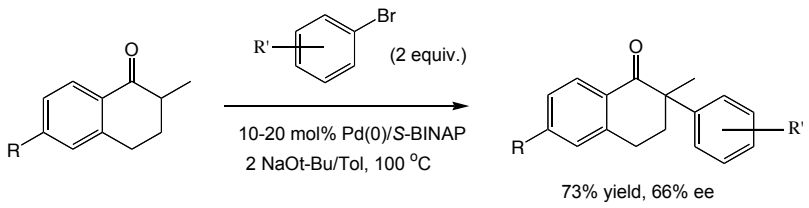
95%, 91% ee

- Transition metal-mediated asymmetric allylations (Trost, et al.)



i.e., 99% yield and 86% ee

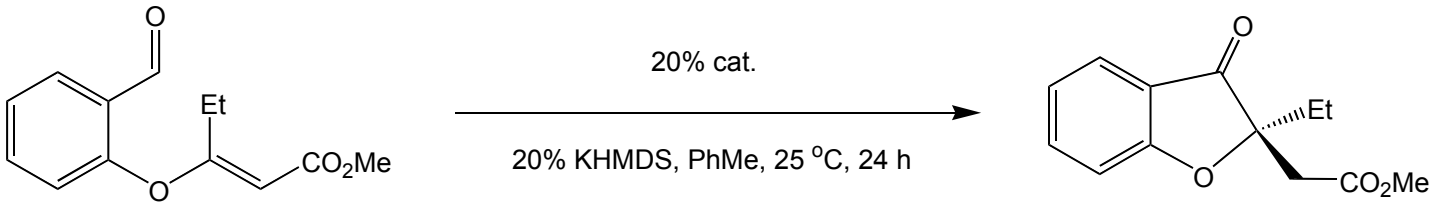
- Asymmetric arylation of ketone enolates (Buchwald, et al.)

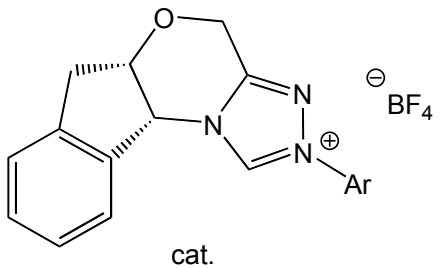


73% yield, 66% ee

Evaluation of Chiral Catalysts for Generating Quaternary Stereocenters

- Trost, et al. used Stetter reaction to form quaternary centers, but system required 3 equiv. of achiral thiazolium salt (*JACS* **1979**, *101*, 1284-1285)
- Here, Rovis, et al. succeed in engendering quaternary centers via an asymmetric triazolium catalyst

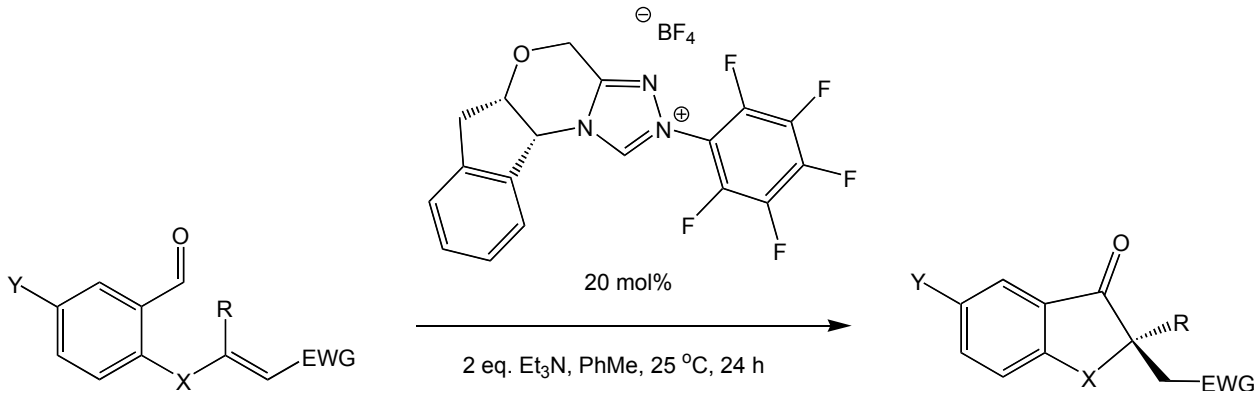




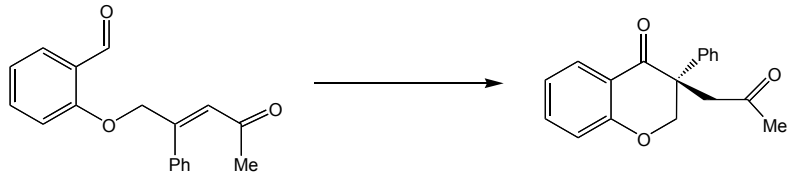
cat.

Ar	cat.	yield (%)	ee(%)
p-OMePh	**A**	45	99
Ph	**B**	80	99
C_6F_5	**C**	85	99

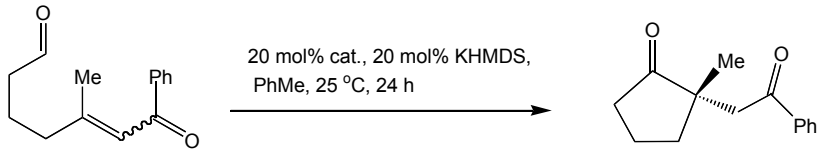
Evaluation of Aromatic Aldehydes with Pentafluorophenyl Catalyst



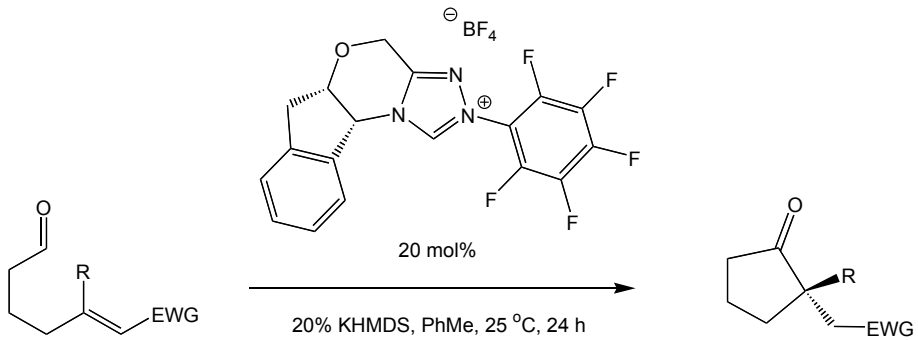
Entry	X	Y	R	EWG	Yield(%)	ee(%)
1	O	H	Et	CO_2Me	96	97
2	O	Br	Et	CO_2Me	92	89
3	S	H	Et	CO_2Me	95	92
4	CH_2	H	Me	CO_2Et	95	99
5		below			55	99

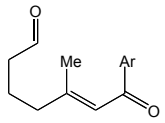
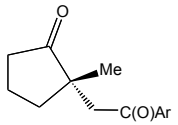
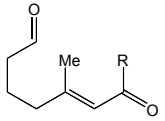
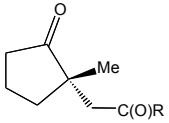
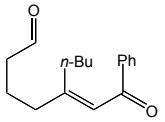
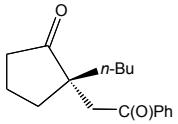


Evaluation of Aliphatic Aldehydes with Pentafluorophenyl Catalyst



E-isomer: 85% yield, 96% ee
Z-isomer: 50% yield, 56% ee



Substrate		Product	Yield (%)	ee(%)
	Ar = 4-Py = *p*-NO_2Ph		85 90	96 84
	R = Me = $(CH_2)_2$Ph		81 63	95 99
			71	98

Future Work

- Elucidate factors responsible for improved catalytic performance
- Expand reactivity of carbene catalyst