Catalytic Asymmetric Esterification of Ketenes

Schaefer, C.; Fu, G. C, *Angew. Chem. Int. Ed.* **2005**, *44*, 4606-8.

Wiskur, S. L.; Fu, G. C. *JACS*, **2005**, *127*, 6176-7.

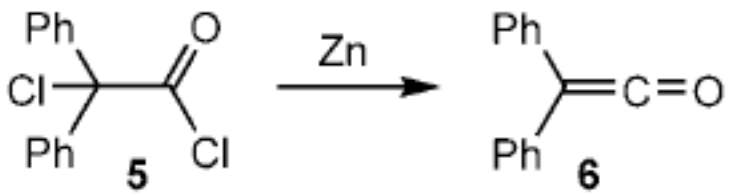
Hodous, B. L.; Ruble, J. C.; Fu, G. C. *JACS*, **1999**, *121*, 2637-8.

Tidwell, T. T. *Angew. Chem. Int. Ed.* **2005**, *44*, ASAP

Yiqian Lian

Oct-13-2005

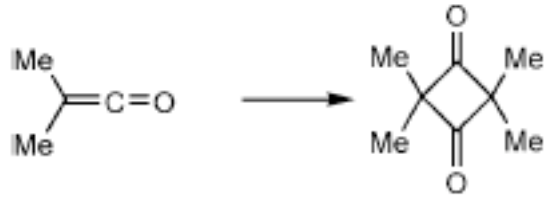
The Discovery of Ketene

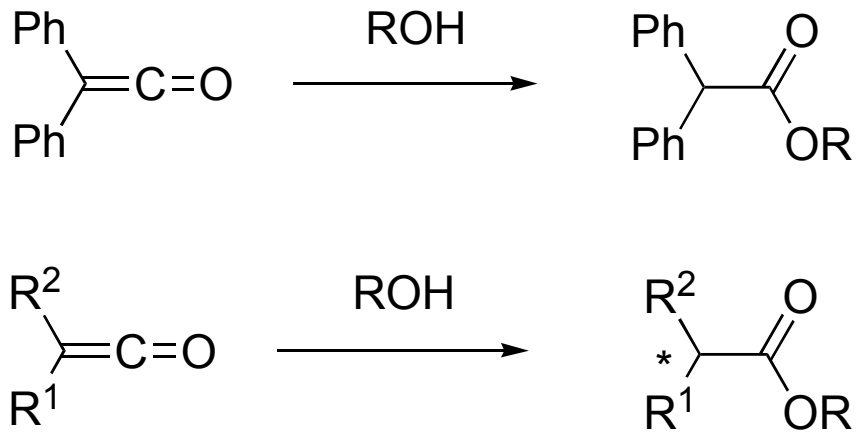


Staudinger, H. *Ber, Dtsch. Chem. Ges*. **1905**, *38*, 1735.

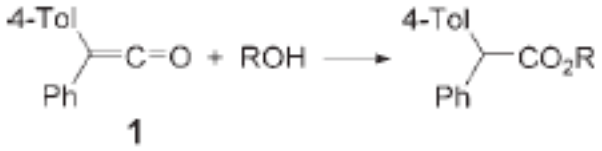
Figure 2. Hermann Staudinger (1881–1965).

Some Reactions with Ketenes

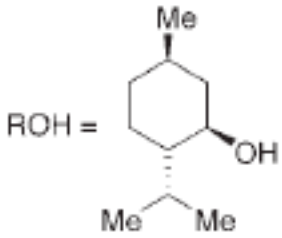




Asymmetric Reaction ?

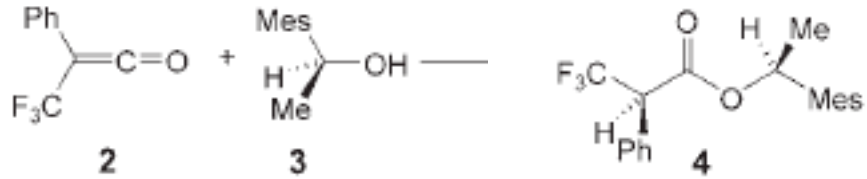


1



(–)-menthol

Weiss, R. *Monatsh. Chem*. **1919**, *40*, 391.



2 **3** **4**

53% *de*

Anders, E.; Ruch, E.; Ugi, I. *Angew. Chem. Int. Ed*. **1973**, *12*, 25.

First Example of Catalytic Asymmetric Reaction

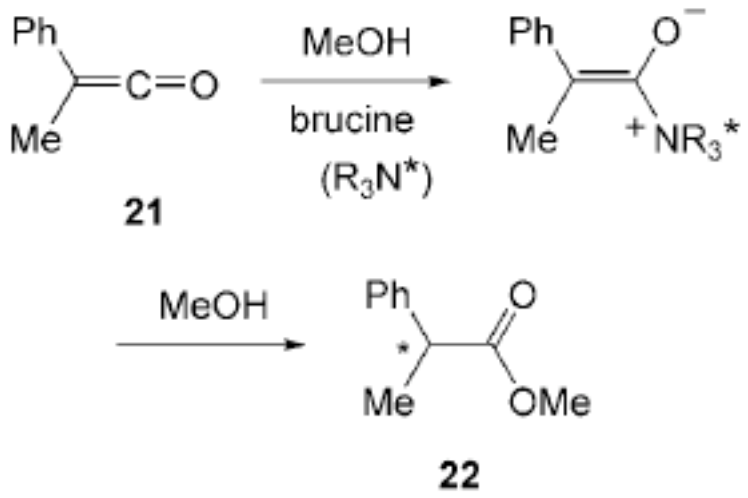
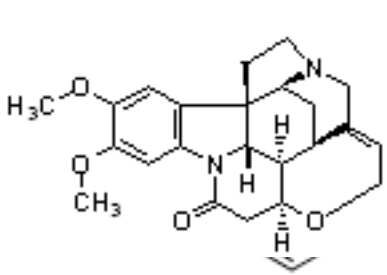
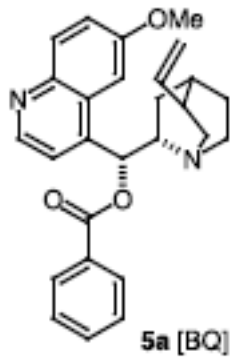


Figure 7. Horst Pracejus (1927–1987).

The selectivity was temperature dependent:

- ♦ 25% ee (S) at -110 °C ⇒ 10%ee (R) at 80 °C;
- ♦ 76% ee (S) at -110 °C using benzoylquinine;

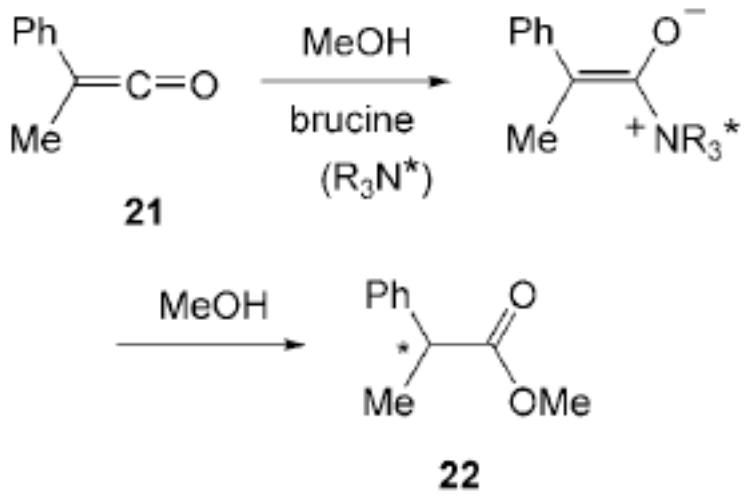




5a [BQ]

Pracejus, H. *Justus Liebigs Ann. Chem.* **1960**, *634*, 9.

First Example of Catalytic Asymmetric Reaction



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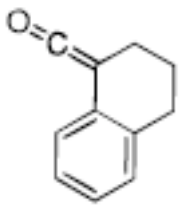
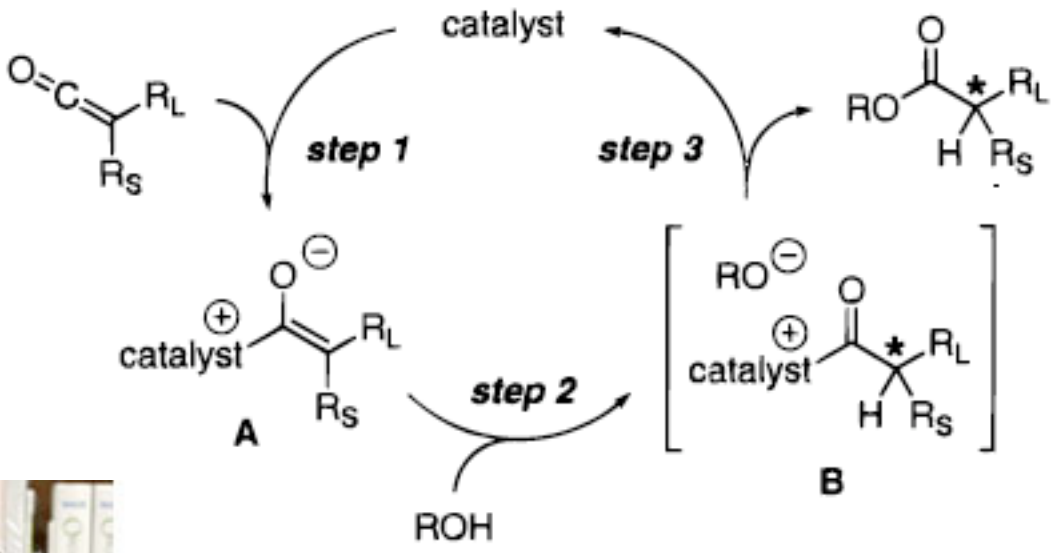
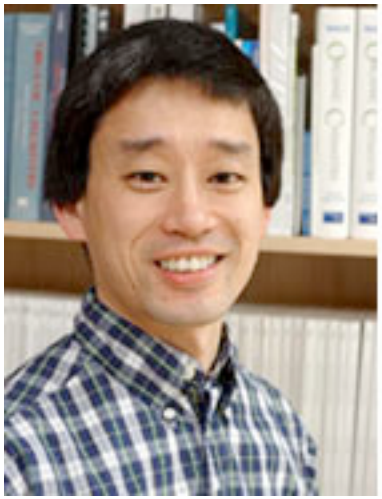


Pracejus, H. *Justus Liebigs Ann. Chem.* **1960**, *634*, 9.

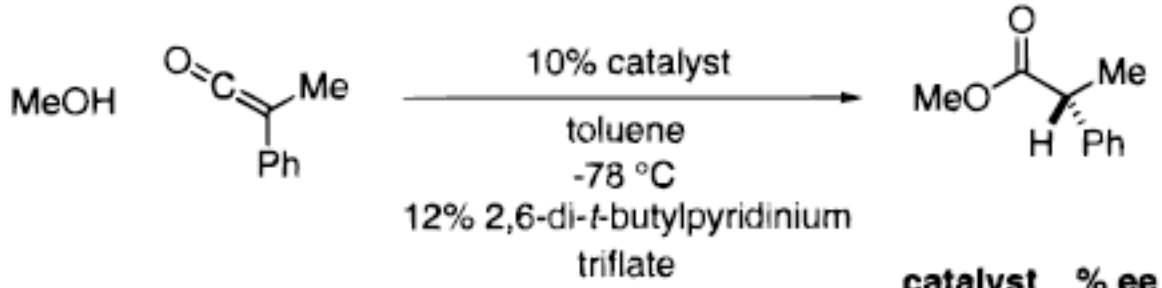
Fu's Strategy





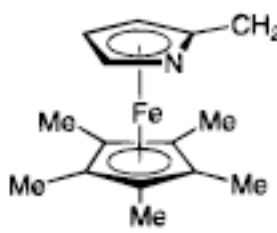
Hodous, B. L.; Ruble, J. C.; Fu, G. C. *JACS*, **1999**, *121*, 2637-8.

Screening and Optimization



catalyst	% ee
(+)-**2a**	27
(+)-**2b**	28
(+)-**2c**	77
(+)-**2d**	68
(+)-**1a**	<5
(+)-**1b**	<5

R = Me: (-)-**1a**
Ph: (-)-**1b**



R^1 = Me: (+)-**2a**
TES: (+)-**2b**
TBS: (+)-**2c**
TBDPS: (+)-**2d**

- 64% ee with 0.5% cat.
- Without triflate, 56% ee using **2C**.

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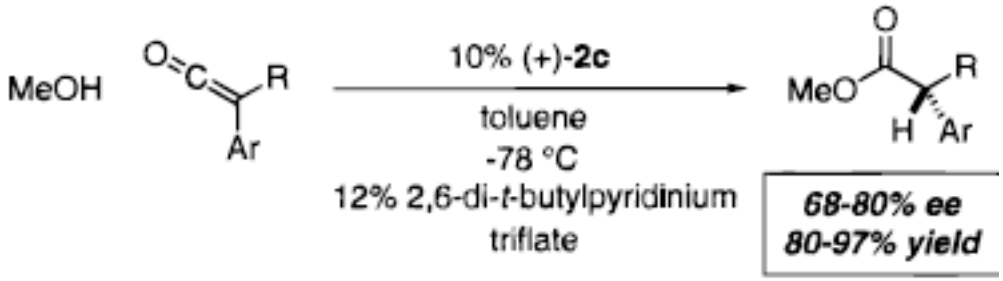
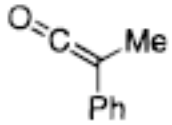
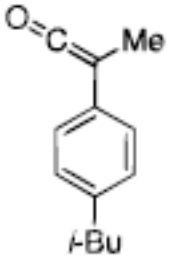
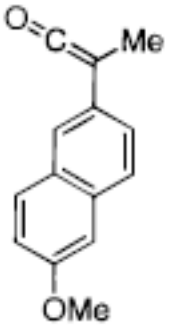
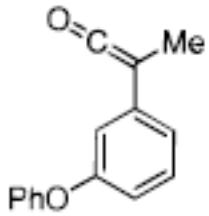
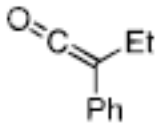
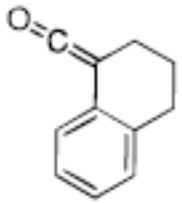
Enantioselective Addition of Methanol to Ketenes

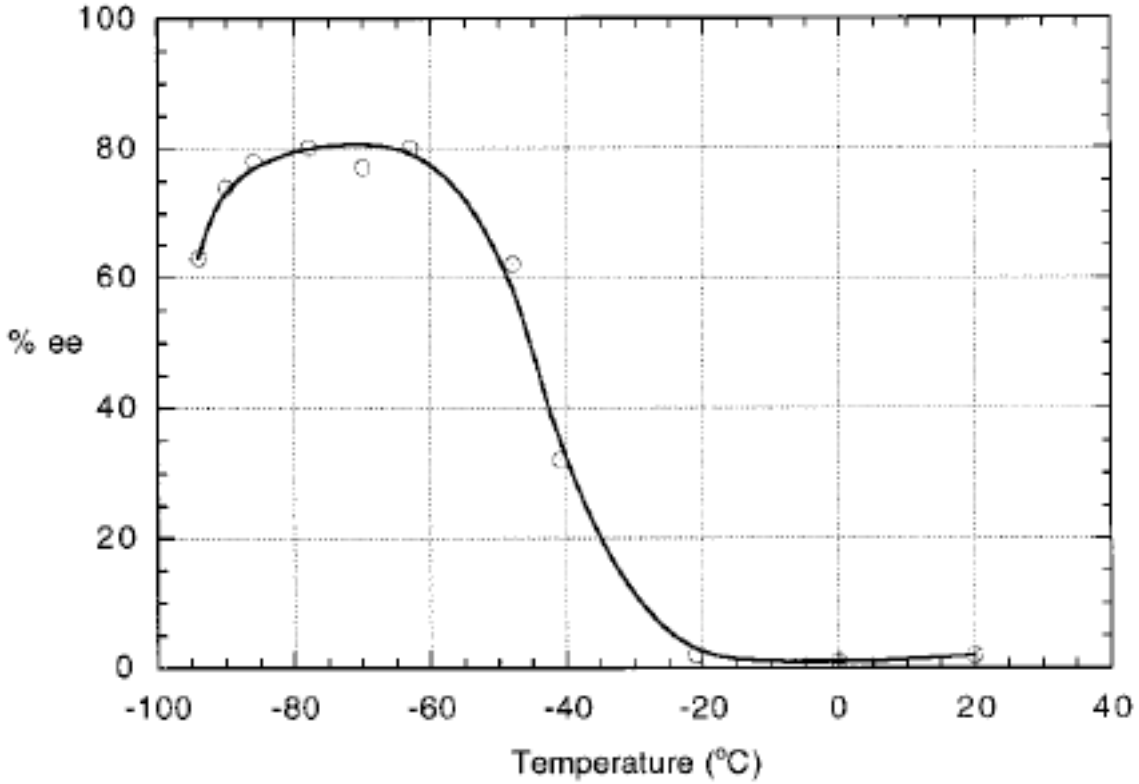


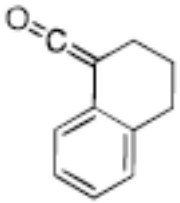
Entry	Substrate	% ee	% Yield
1		77	87
2		77	88
3		75	80

Entry	Substrate	% ee	% Yield
4		74	96
5		68	92
6		80	97

Hodous, B. L.; Ruble, J. C.; Fu, G. C. *JACS*, **1999**, *121*, 2637-8.

Temperature Study





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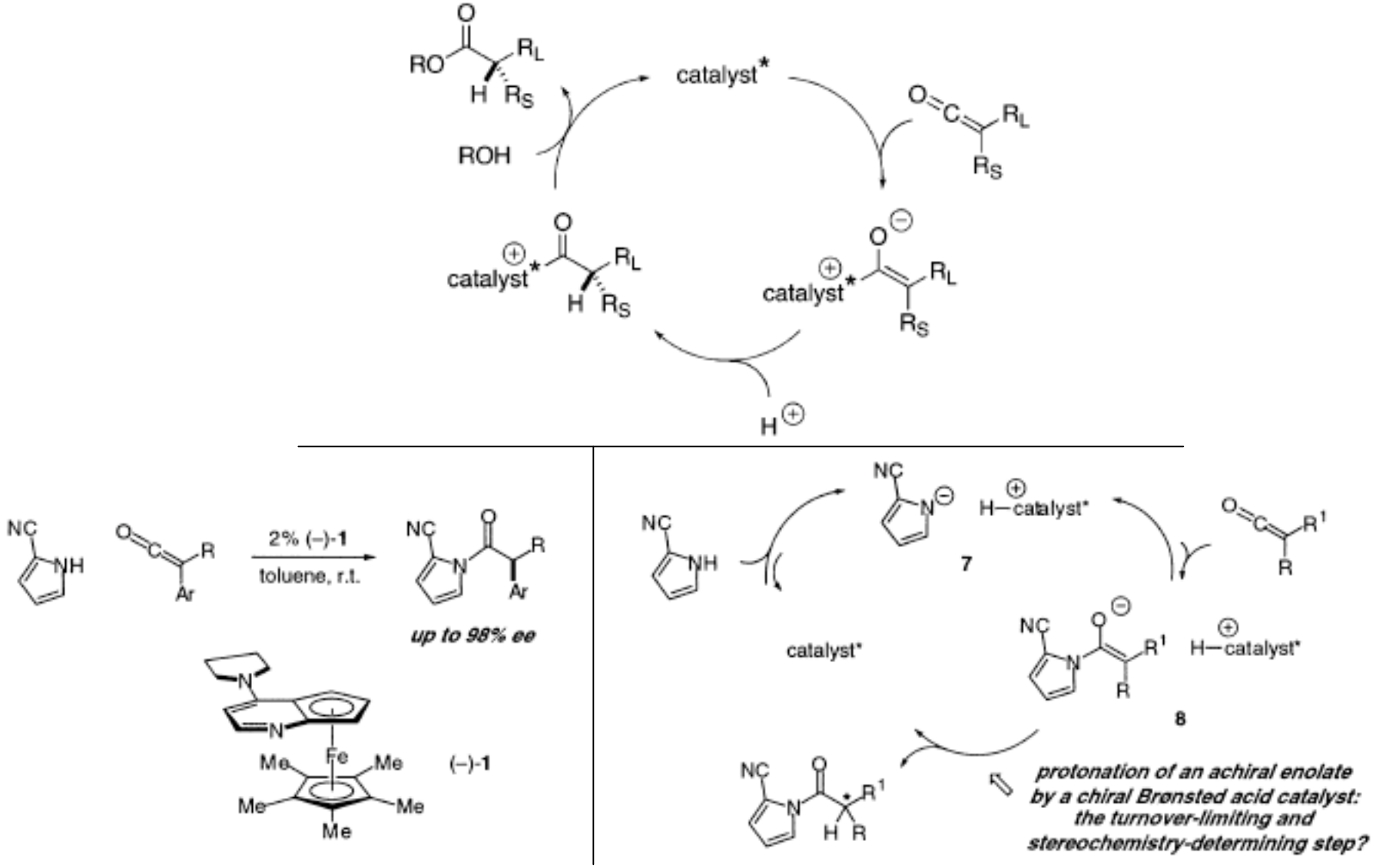
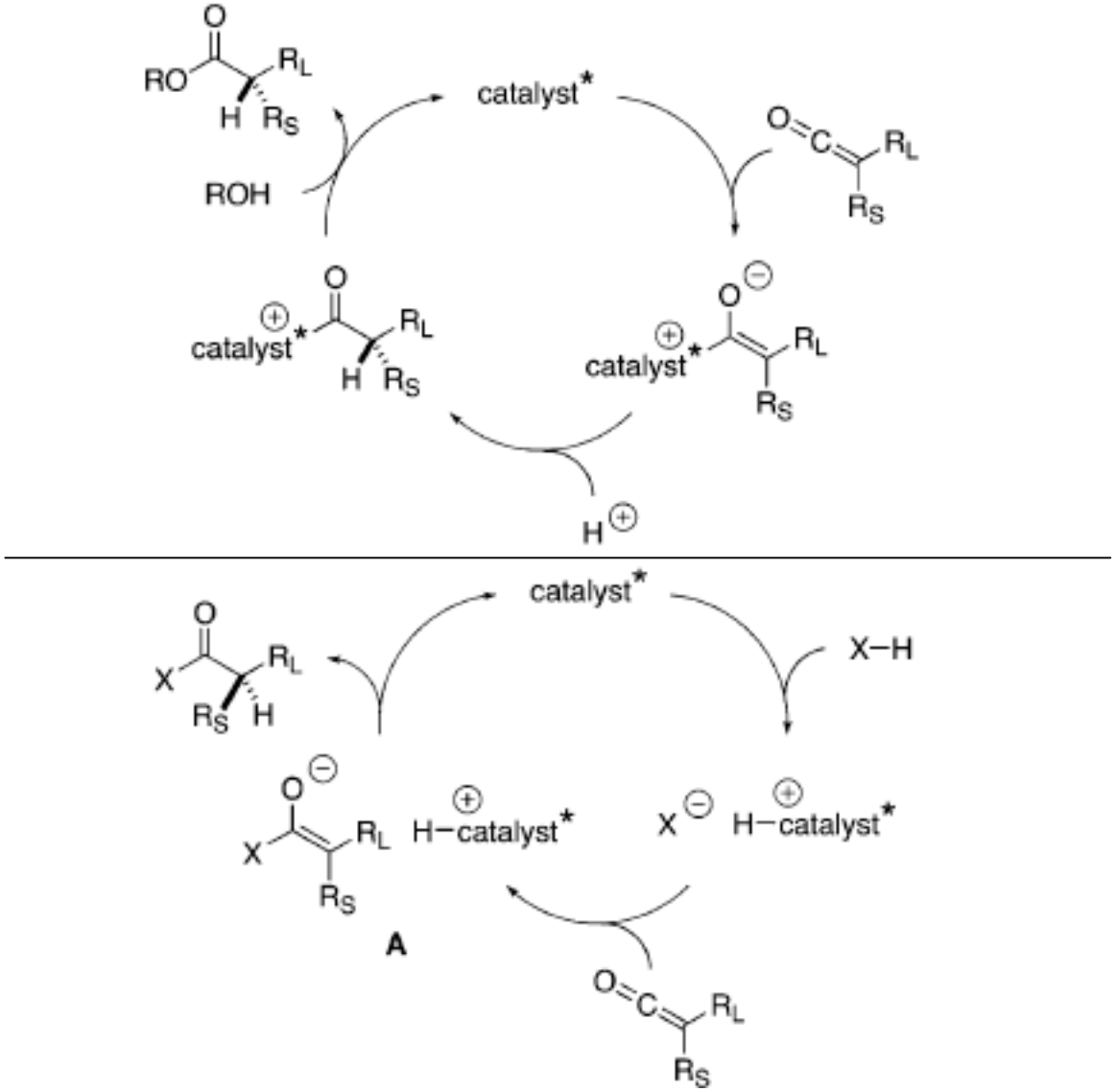
About the Proposed Mechanism



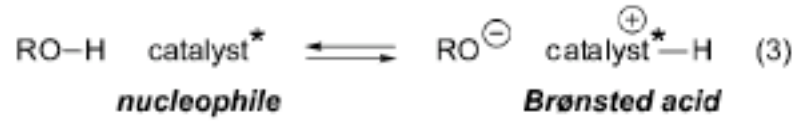
Hongous, B. L.; Fu, G. C. *JACS*, **2002**, *124*, 10006-7.

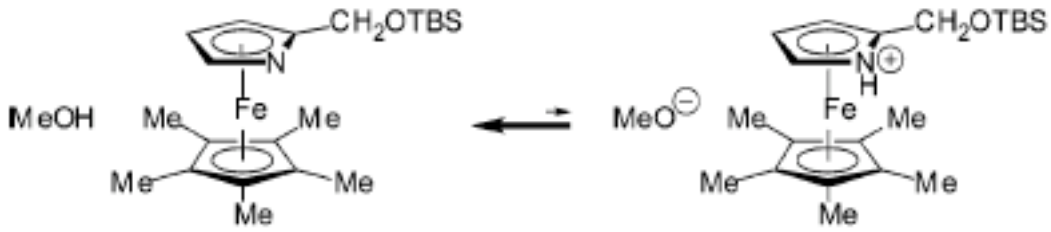
More Thoughts on the Mechanism

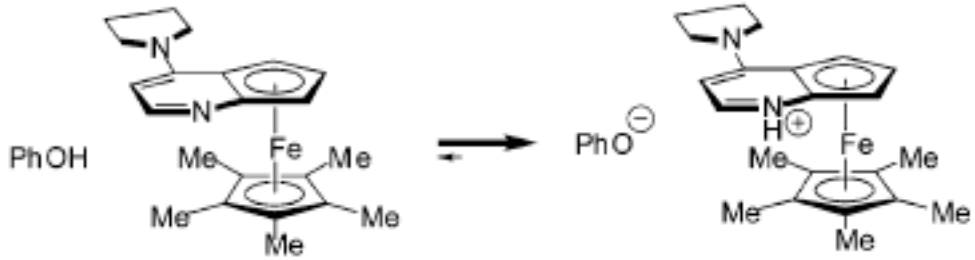


Wiskur, S. L.; Fu, G. C. *JACS*, **2005**, *127*, 6176-7.

Nucleophilic Catalysis vs. Brønsted Acid Catalysis







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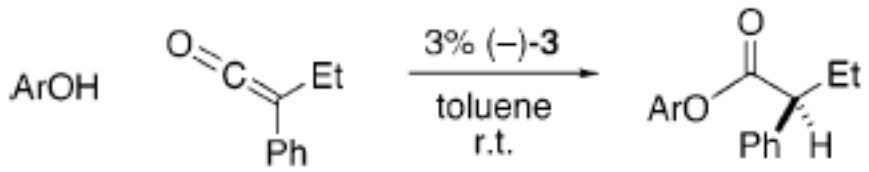
Screening of Phenols

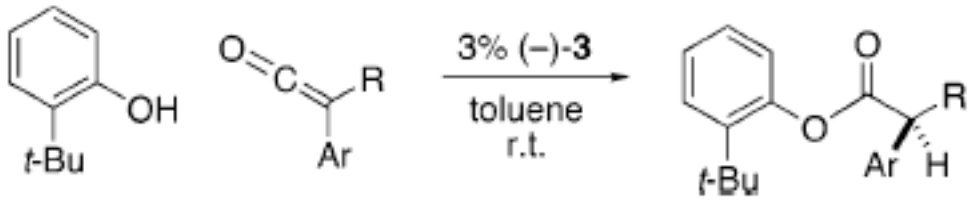


entry	ArOH	ee (%)
1	PhOH	47
2	4-(trifluoromethyl)phenol	35
3	4-methoxyphenol	72
4	2-methoxyphenol	80
5	2-methylphenol	81
6	2-isopropylphenol	80
7	2-phenylphenol	88
8	2-*tert*-butylphenol	91

3

Wiskur, S. L.; Fu, G. C. *JACS*, **2005**, *127*, 6176-7.

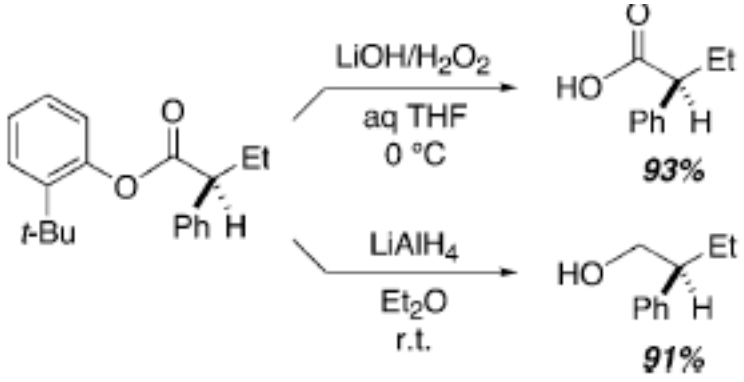
Catalytic Enantioselective Synthesis of Esters from Ketenes



entry	Ar	R	ee (%)	isolated yield (%)
1	Ph	Me	79	87
2	Ph	Et	91	89
3	Ph	*i*-Bu	84	79
4	Ph	cyclopentyl	87	88
5	Ph	*i*-Pr	91	66
6	*o*-tol	Et	92	84
7	*o*-anisyl	Me	94	78
8	*p*-Cl	*i*-Pr	89	97
9	3-thienyl	*i*-Pr	79	94

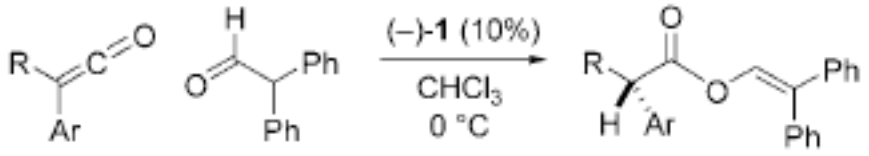
Ar: ortho-substituted

R: >ethyl

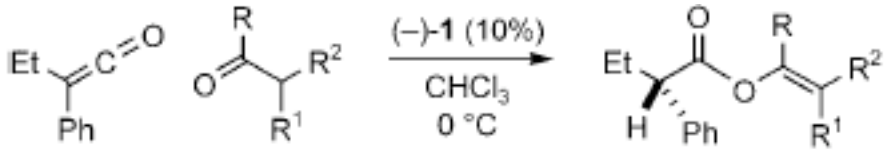


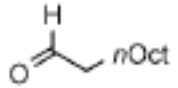
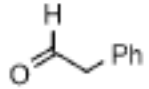
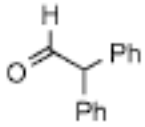
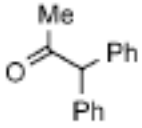
Wiskur, S. L.; Fu, G. C. *JACS*, **2005**, *127*, 6176

Ketenes with Aldehydes to Generate Enol Ethers



(–)-1



Entry	Carbonyl compound	*ee* [%]	Yield [%][b]
1		–	0
2		92	55
3		91	84
4		–	0

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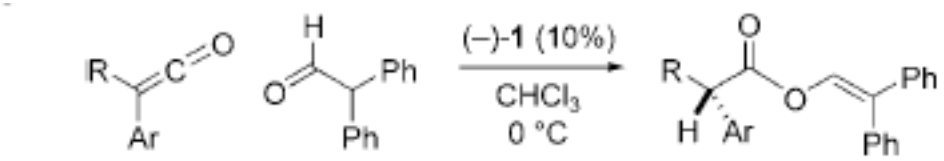
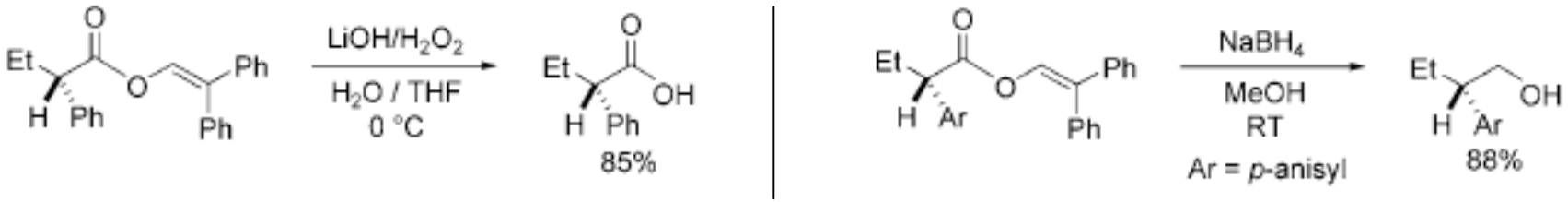
Ketenes with Aldehydes to Generate Enol Ethers



Entry	Ar	R	*ee* [%]	Yield [%][b]
1	Ph	Me	78	74
2	Ph	Et	91	84
3	Ph	*i*Bu	77	81
4	Ph	*i*Pr	98	95
5	Ph	cyclopentyl	97	99
6	Ph	*t*Bu	88	96
7	*o*-tolyl	Et	98	99
8	*o*-anisyl	Me	97	95
9	*p*-anisyl	Et	92	89
10	4-chlorophenyl	Et	88	96



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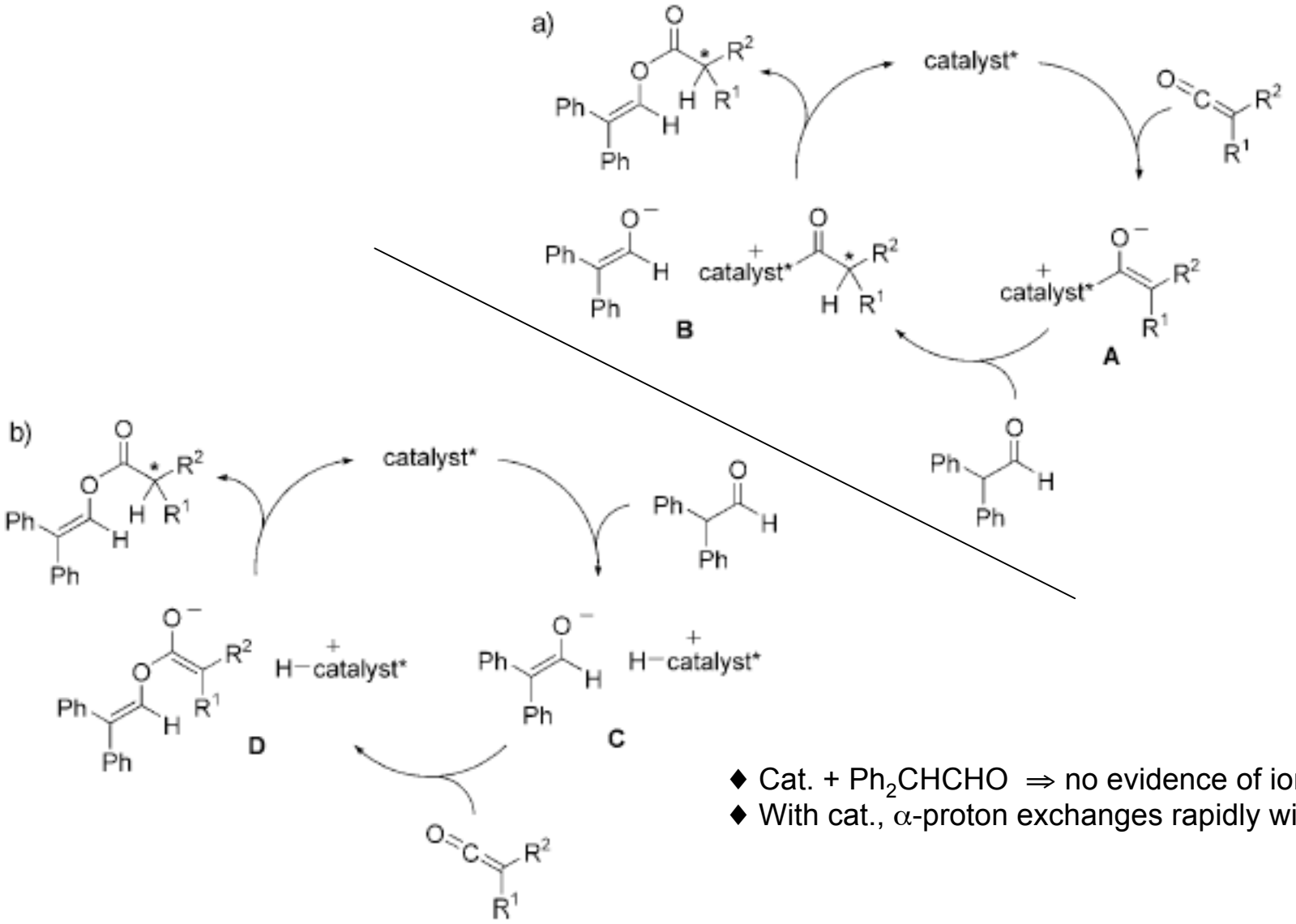
What is the Mechanism?



- Cat. + Ph_2CHCHO $\Rightarrow$ no evidence of ion pair;
- With cat., α-proton exchanges rapidly with D_2O.

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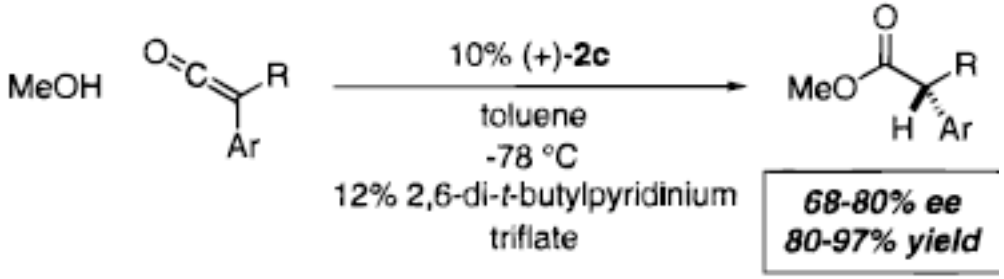
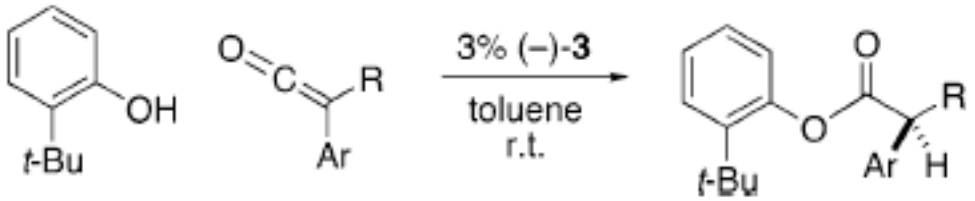
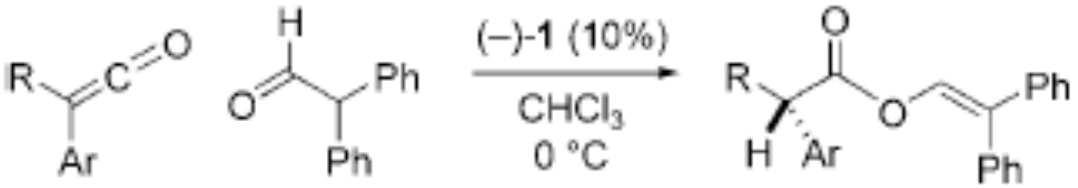
Summary



68-80% ee
80-97% yield



79-94% ee
66-97% yield



77-98% ee
66-99% yield