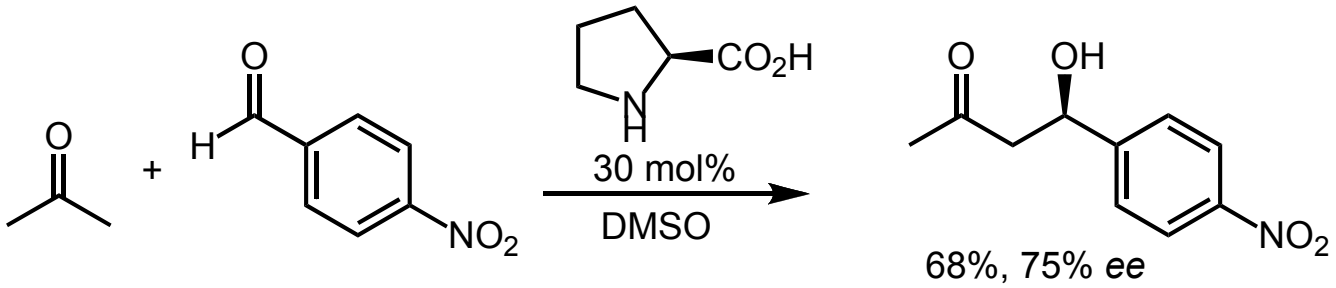
Asymmetric Enamine Catalysis

The First Conceptualization of Asymmetric Enamine Catalysis:



List, B.; Lerner, R. A.; Barbas III, C. F. *J. Am. Chem. Soc.* **2000**, *122*, 2395-2396.

This concept has been successfully applied to :

Asymmetric Aldol Reactions
Asymmetric Michael Reactions
Asymmetric Mannich Reactions
Asymmetric α-Functionalization of Carbonyl Compounds
Asymmetric γ-Functionalization of Carbonyl Compounds

Mukherjee, S.; Yang, J. W.; Hoffmann, S.; List, B.; *Chem. Rev*. **2007**, *107*, 5471-5569.

Despite the great advancements already made with regard to catalyst amounts (e.g., <1% loadings have already been occasionally realized!), very high turnover numbers might be considered yet another challenge.

--- Benjamin List

Enamine Catalysis with Low Catalyst Loadings – High Efficiency via Kinetic Studies

Wiesner, M.; Upert, G.; Angelici, G.; Wennemers, H. *J. Am. Chem. Soc.* **XXXX**, *xxx*, 000

Hong Ren

10-31-09

Today's Focus

How Did They Carry Out the Kinetic Study?

How Did the Results Guide Them to Further Decrease the Catalyst Loading?

Today's Focus

How Did They Carry Out the Kinetic Study?

The Tool + The Model + Understanding of Chemical Kinetics

How Did the Results Guide Them to Further Decrease the Catalyst Loading?

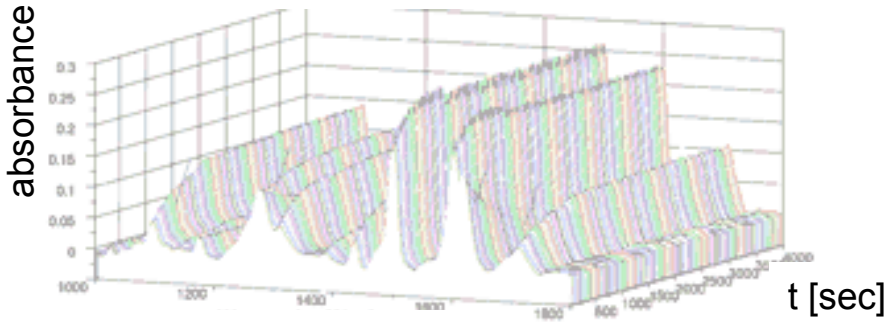
The Tools for the Kinetic Study

in-situ FTIR

Single Reactor

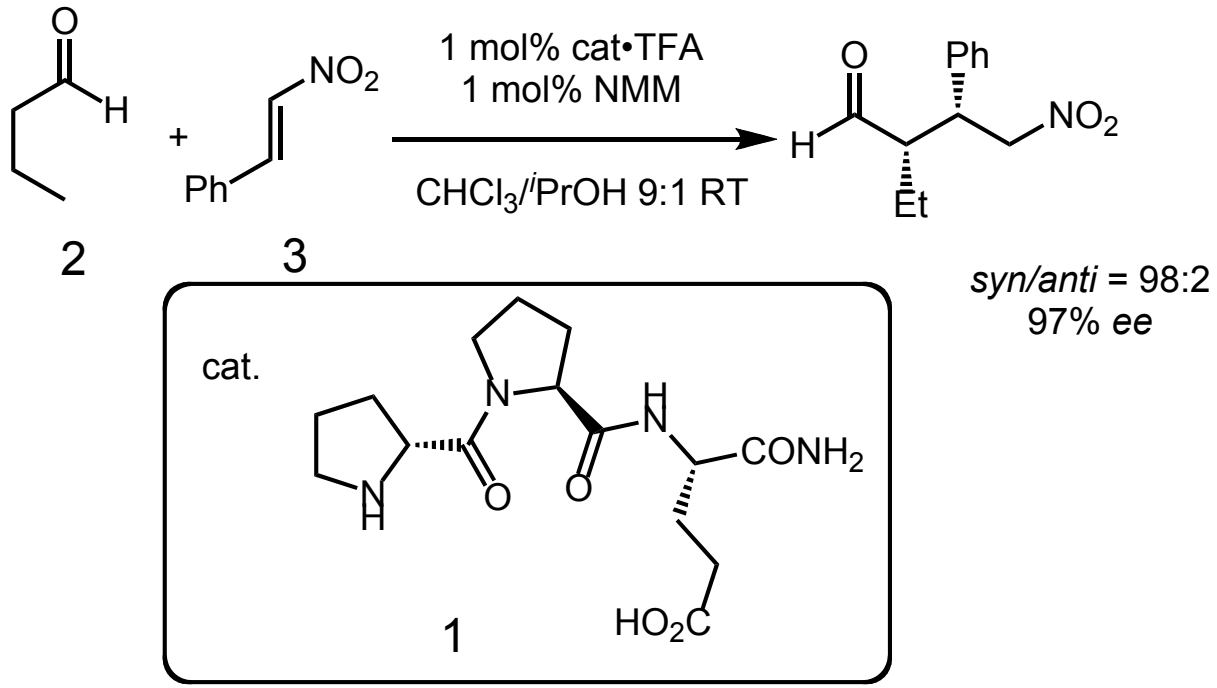
MultiMaxIR™

- Real time, *in situ, quantitative analysis*
- Easy to upgrade
- Wide temperature and pressure range
- Fully automated with integrated analysis
- Wide range of vessel sizes
- Wide wave number range



https://admin.emea.acrobat.com/_a55714086/p55719895/

The Model for the Kinetic Study



No side products formed

No catalyst deactivation takes place

No additives are necessary

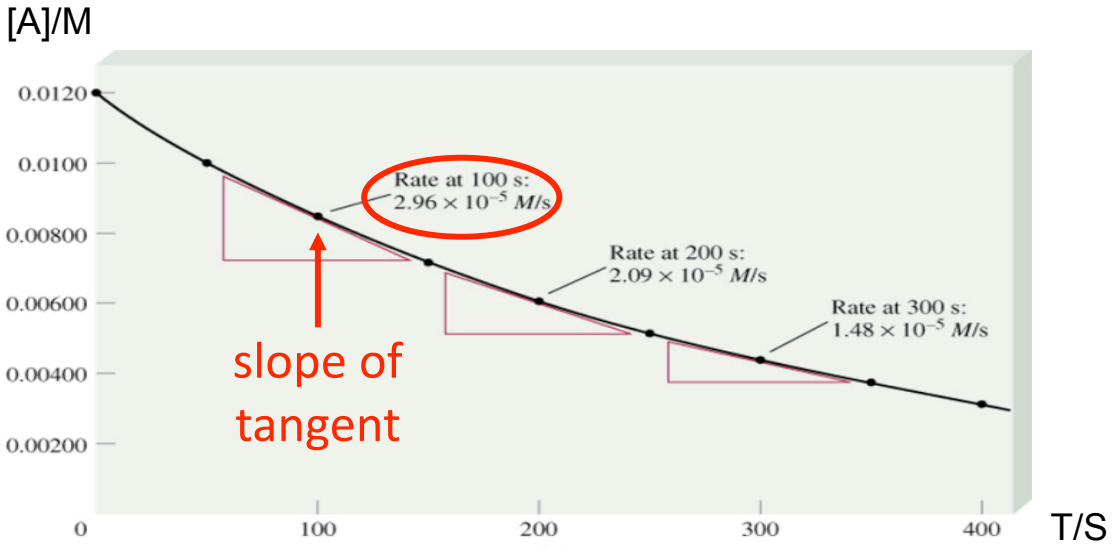
Wiesner, M.; Revell, J. D.; Tonazzi, S.; Wennemers, H.; *J. Am. Chem. Soc*. **2008**, *130*, 5610-5611.

Chemical Kinetics

Kinetics – how fast does a reaction proceed?

Reaction rate is the change in the concentration of a reactant or a product with time (*M*/s).

A ⟶ B



$$\textbf{Average Rate} = -\frac{\Delta[A]}{\Delta t}$$

Δ[A] = change in concentration of A over time period Δt

Instantaneous rate = rate for specific instance in time

(a) Birk, J. P. *J. Chem. Educ. 1976, 53, 704–707.*

(b) (b) Casado, J.; Lo´ pez- Quintela, M. A.; Lorenzo-Barral, F. M. J. Chem. Educ. 1986, 63, 450. 632

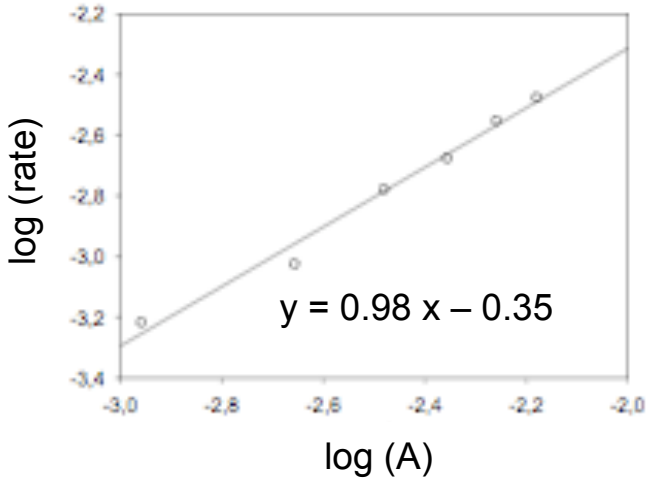
Rate Law

The ***rate law*** expresses the relationship of the rate of a reaction to the rate constant and the concentrations of the reactants raised to some powers.

$$aA + bB \longrightarrow cC + dD$$

$$\text{Rate} = k\,[A]^a[B]^b$$

reaction is ***a*th order** in A
reaction is ***b*th order** in B
reaction is **(a +b)th order overall**



$$\log(\text{rate}) = \log k + a \log[A] + b \log[B]$$

$$\log(\text{rate}_0) = \log k + a \log[A_0] + b \log[B]$$

$$y = a\,x + b$$

a = slope = 0.98

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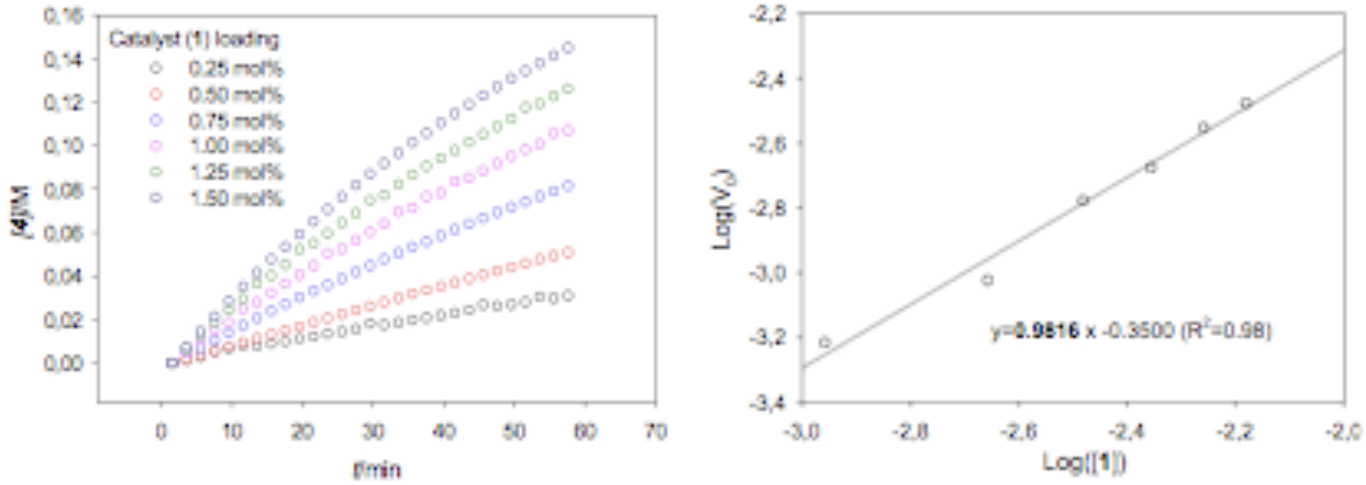
Reaction Order on Catalyst

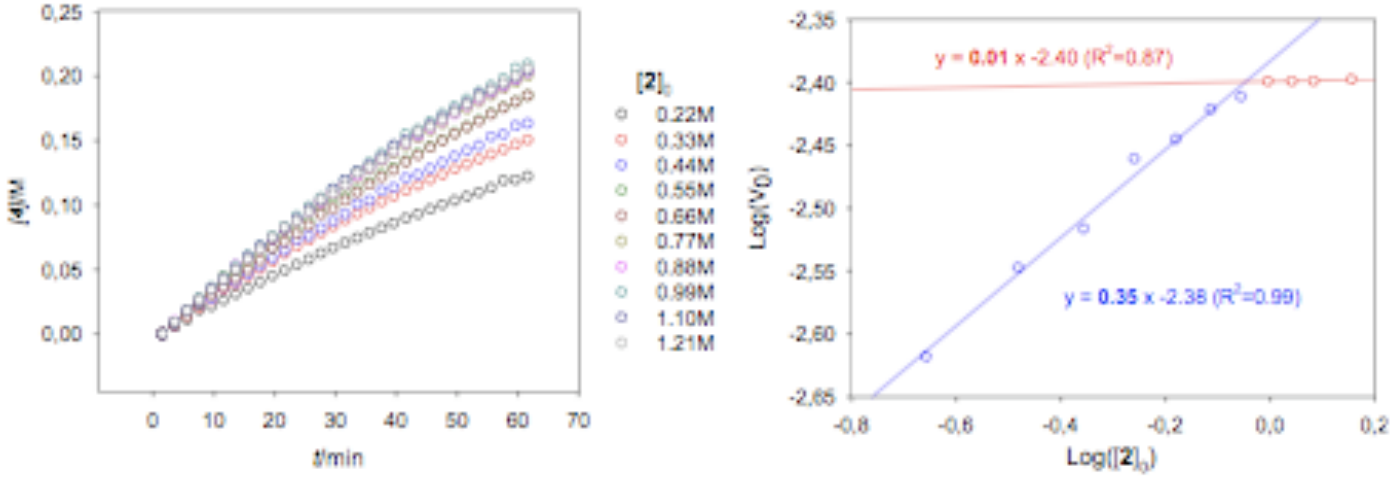
Reaction progress was monitored by the N-O stretching vibration.



Product formation [4] vs. time at different catalyst loading (0.25 – 1.50 mol% = 1.1 – 6.6 mM) and log/log plot of initial rate vs. catalyst concentration [1]

A first order dependence of the reaction on catalyst

Reaction Order on n-Butanal



Product formation [4] vs. time at different initial n-butanal concentrations $[2]_0$ (0.22 – 1.21 M) and log/log plot of initial rate vs. $[2]_0$.

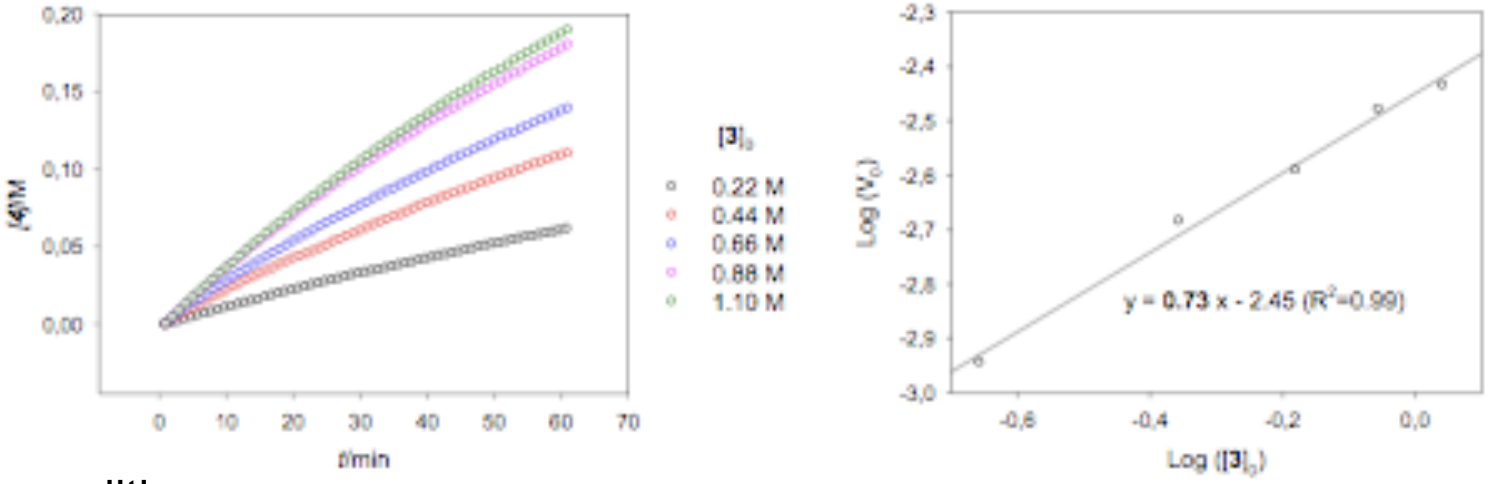
0. 3 order at lower concentration, zero order at higher concentration

Enamine Formation was not rate determining step.
Attempts to detect the enamine were not successful.

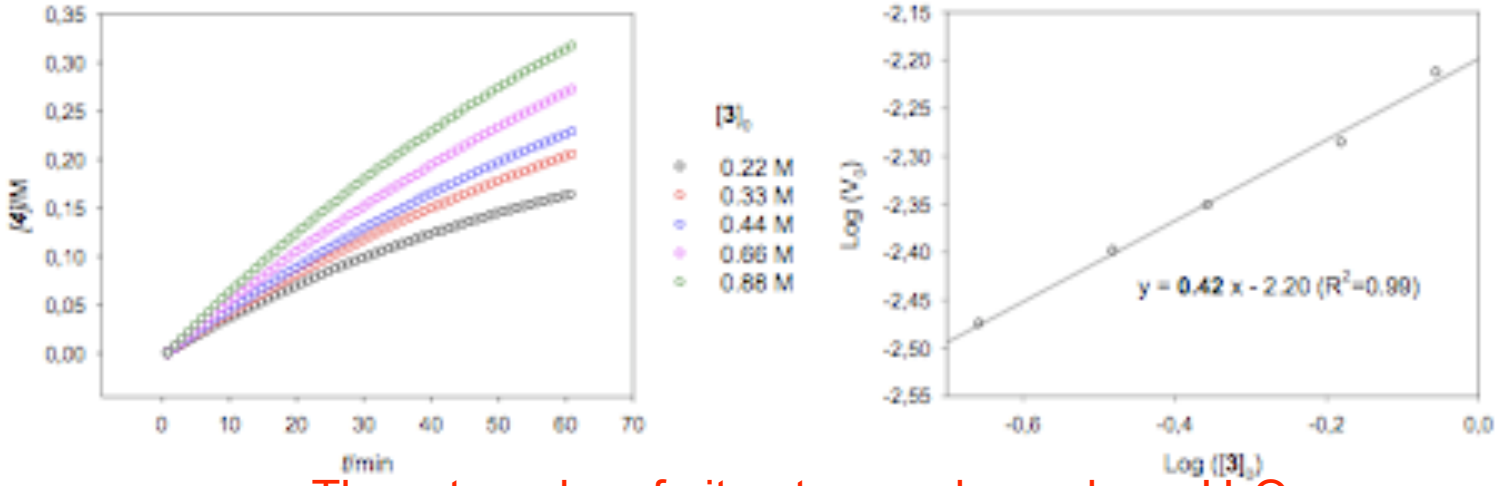
Wiesner, M.; Upert, G.; Angelici, G.; Wennemers, H. *J. Am. Chem. Soc.* **XXXX**, *xxx*, 000

Reaction Order on Nitrostyrene

Wet conditions: (10 mol% H_2O)



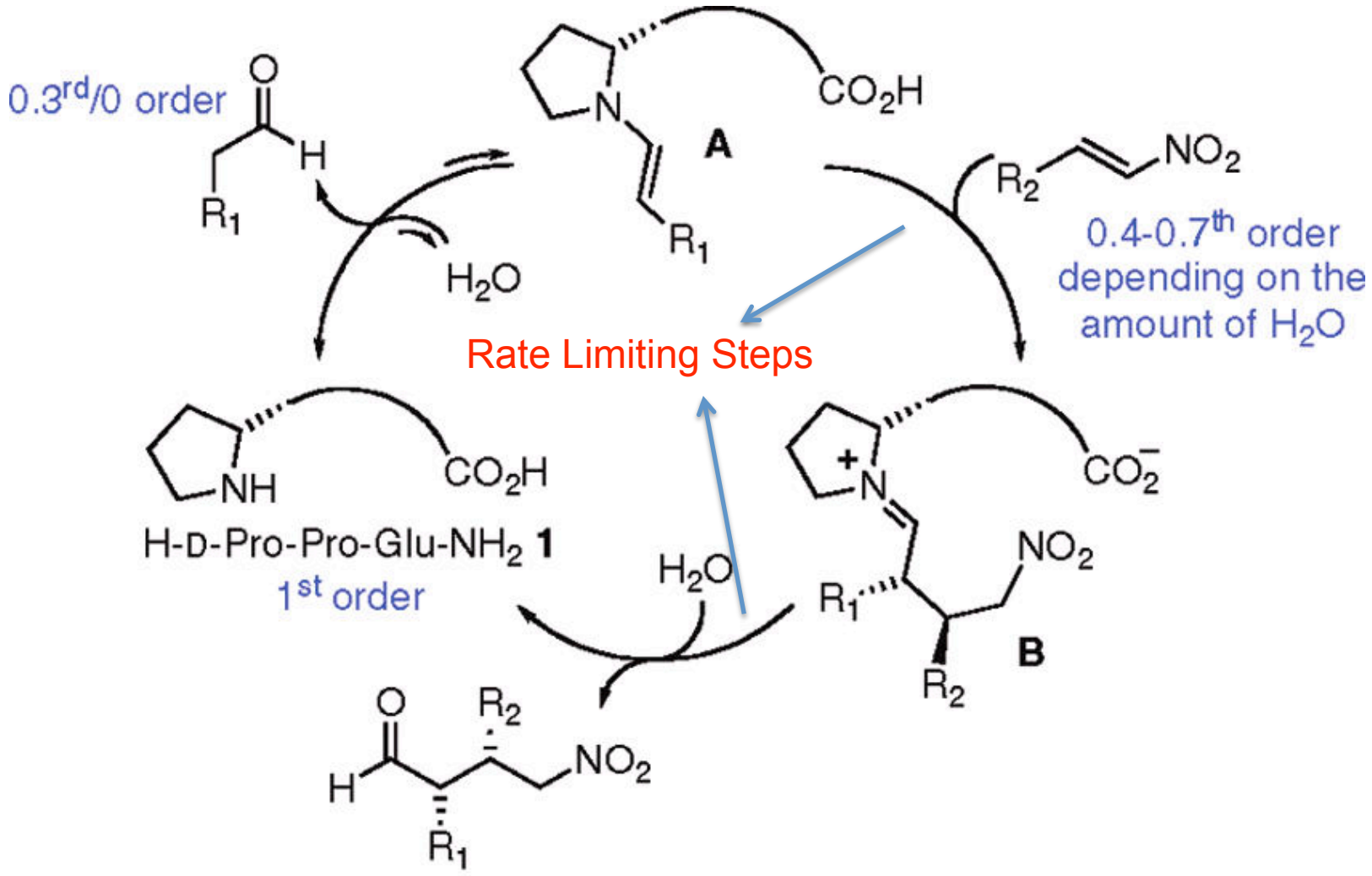
Dry conditions:



The rate order of nitrostyrene depends on H_2O.
It was observed that the addition of the H_2O slowed down the reaction.

Wiesner, M.; Upert, G.; Angelici, G.; Wennemers, H. *J. Am. Chem. Soc.* **XXXX**, *xxx*, 000

Summary of the Kinetic Study

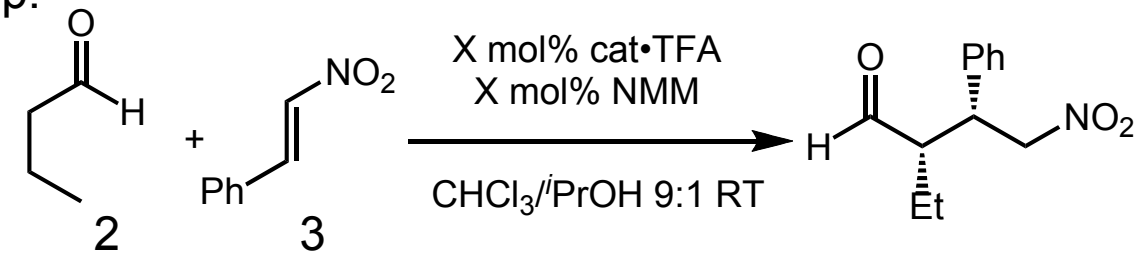


Wiesner, M.; Upert, G.; Angelici, G.; Wennemers, H. *J. Am. Chem. Soc.* **XXXX**, *xxx*, 000

How to Further Decrease the Catalyst Loading

Reduction of the H_2O ------ Because H_2O slows down the reaction.

Increase the eqivalent of nitrostyrene ------ Because it is involved in the rate limiting step.



entry	mol %	ratio 2:3	cond	time (h)	conv (%)	syn/ anti	ee (%)
1	1	1.5:1	std	16	quant	98:2	97
2	1	1:1.5	std	7	>95	98:2	97
3	1	1:1.5	dry	3	>95	97:3	97
4	1	1:1.2	dry	5	>95	95:5	97
5	0.1	1:1.5	dry	48	~90	94:6	97

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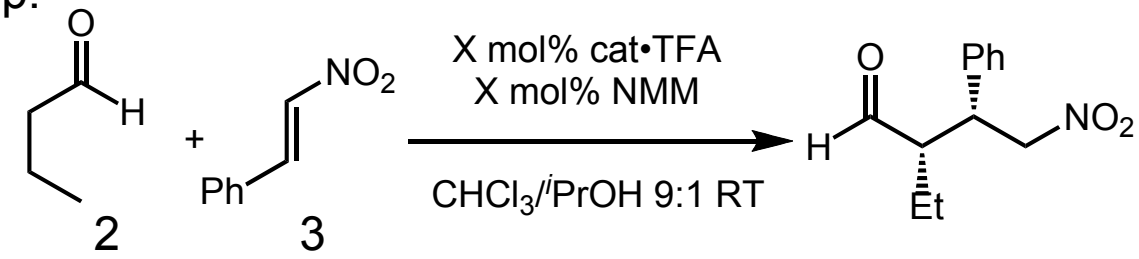

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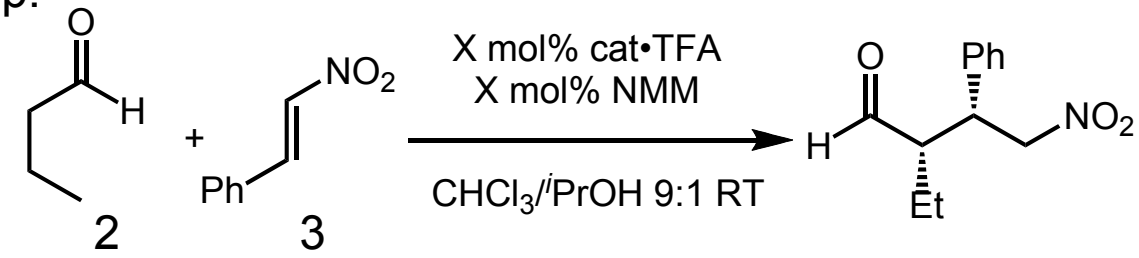

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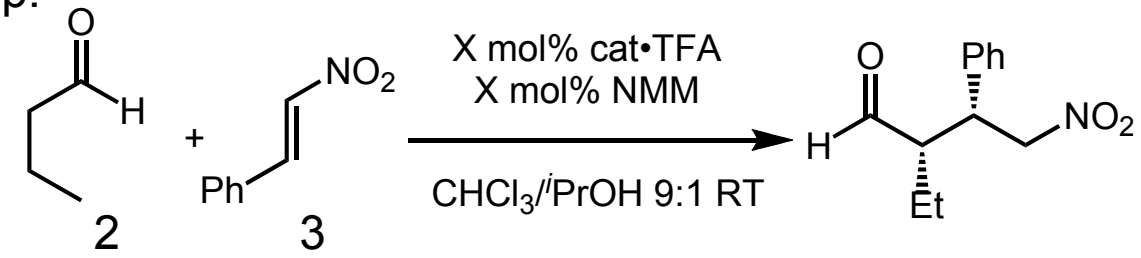

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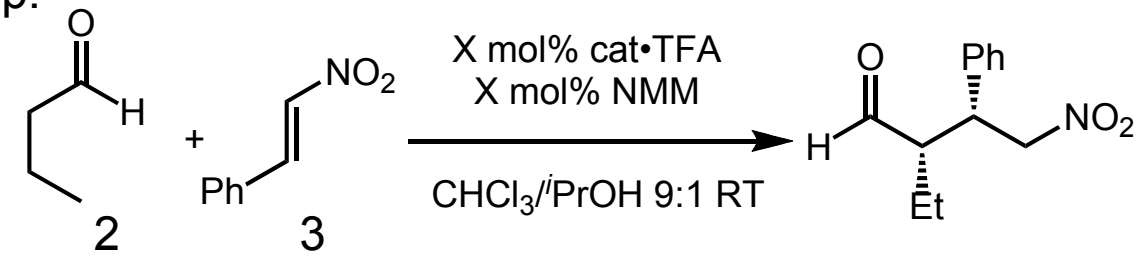

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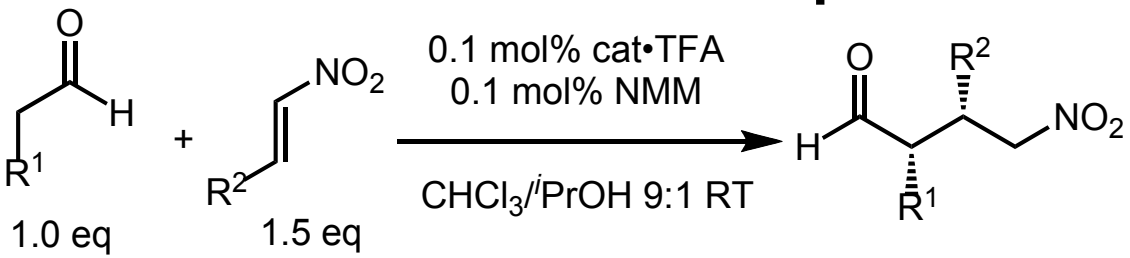
Substrate Scope



entry	R^1	R^2	mol %	yield (%)	syn/anti	ee (%)
1	Et	Ph	0.1	87	94:6	97
2	Me	Ph	0.2	92	95:5	96
3	*n*Pr	Ph	0.1	98	95:5	96
4	Bn	Ph	0.1	87	94:6	98
5	*i*Pr	Ph	0.4	93	95:5	94
6	Et	C_6H_3-2,4-Cl_2	0.1	95	95:5	96
7	Et	C_6H_4-2-CF_3	0.1	96	97:3	97
8	Bn	C_6H_4-2-CF_3	0.1	92	98:2	99
9	Et	C_6H_4-4-OMe	0.4	96	93:7	95
10	Et	$CH_2CH(CH_3)_2$	0.2	92	91:9	98

A Chemist does not always need to work on sophisticated chemistry to realize his dream.