Structure, Mechanism and Reactivity of Hantzsch Esters

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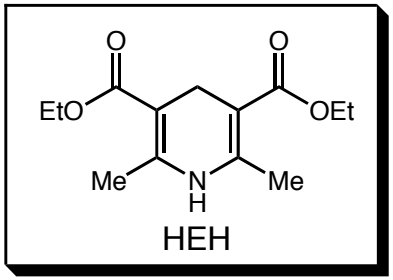
MacMillan Lab
Group Meeting
08/25/04

Lead References:

Lavilla, R. *J. Chem. Soc., Perkin Trans*., 2002, **1**, 1141.
Stout, D. M. and Meyers, A. I. *Chem. Rev*., 1982, **82**, 223.
Kuthan, J. and Kurfürst, A. *Ind. Eng. Chem. Prod. Res. Dev*.,1982, **21**, 191.
Eisner, U. and Kuthan, J. *Chem. Rev*., 1972, **1**, 1.

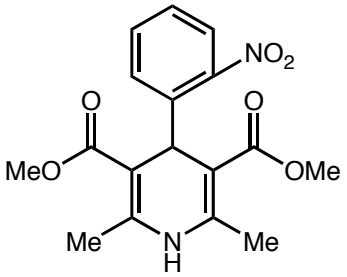
A little background on the Hantzsch ester



HEH

- First discovered in 1882 by Arthur Hantzsch

- Derivatives exhibit important pharmacological properties such as antihypertensive, antibiotic, antiinflammatory, and antifungal activity



nefipidine

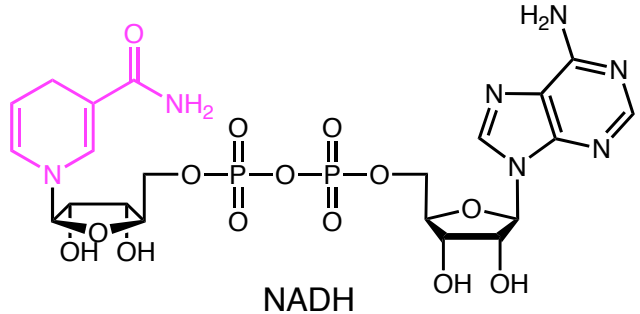
- Calcium antagonist vasodilator. Treats high blood pressure and angina.
- Adalat (Bayer 1999) $1 bill.
  Procardia (Pfizer 1998) $822 mill.

- Other dihydropyridine derivatives are used as rocket fuel additives, antioxidants, and photographic materials

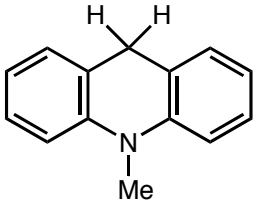
- Closely related to NADH, a ubiquitous biological reductant found in the biosphere

Bioreductants and their inspired organoreductants

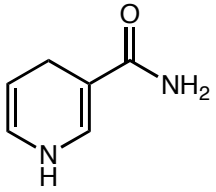
- Reduced nicotinamide adenine dihydropyridine (NADH)



NADH

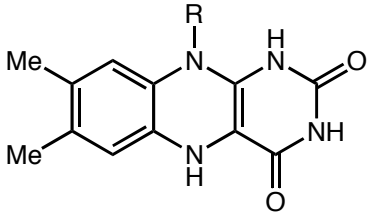


10-methylacridan



nicotinamide

- Reduced flavin adenine mononucleotide (FADH) is the other major reductant found in biology

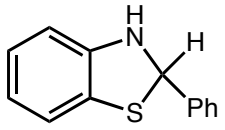


isoalloxazine

R = AMP and D-Ribitol

R. H. Garrett and C. M. Grisham, in *Biochemistry*, Saunders College Publishing 1995, p. 470-474

- A non-biomimetic organoreductant



benzothiazoline

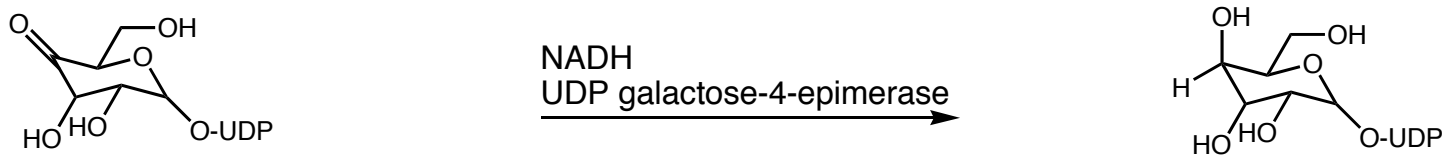
- usually used in conjuction with $AlCl_3$ to reduce enones.

Chikashita, H. *et al. J. Chem. Soc. Perkin Trans. 1* **1987**, 699

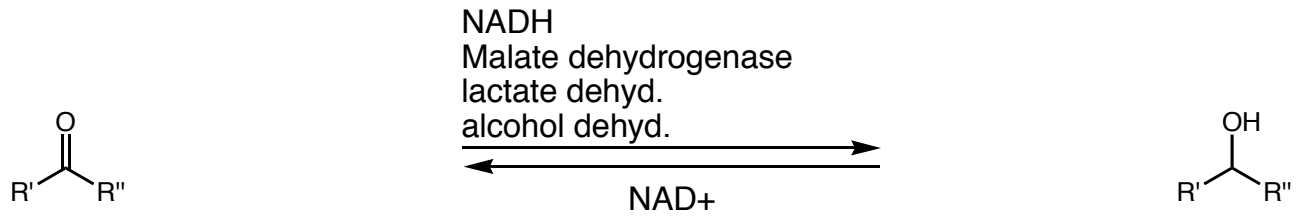
Some interesting enzymatic transformations

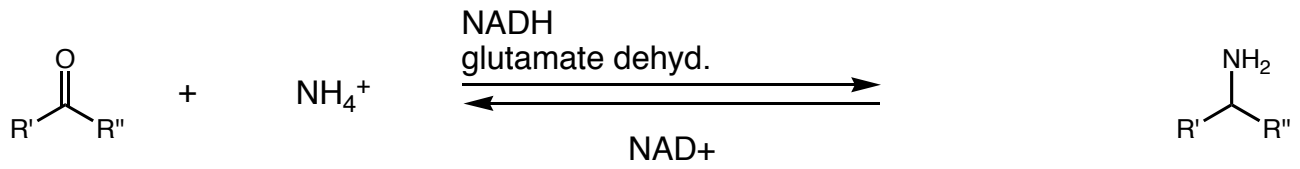
- Enzymes catalyze the following reactions to produce chiral products

- Most NADH biochemical transformations are reversible redox reactions



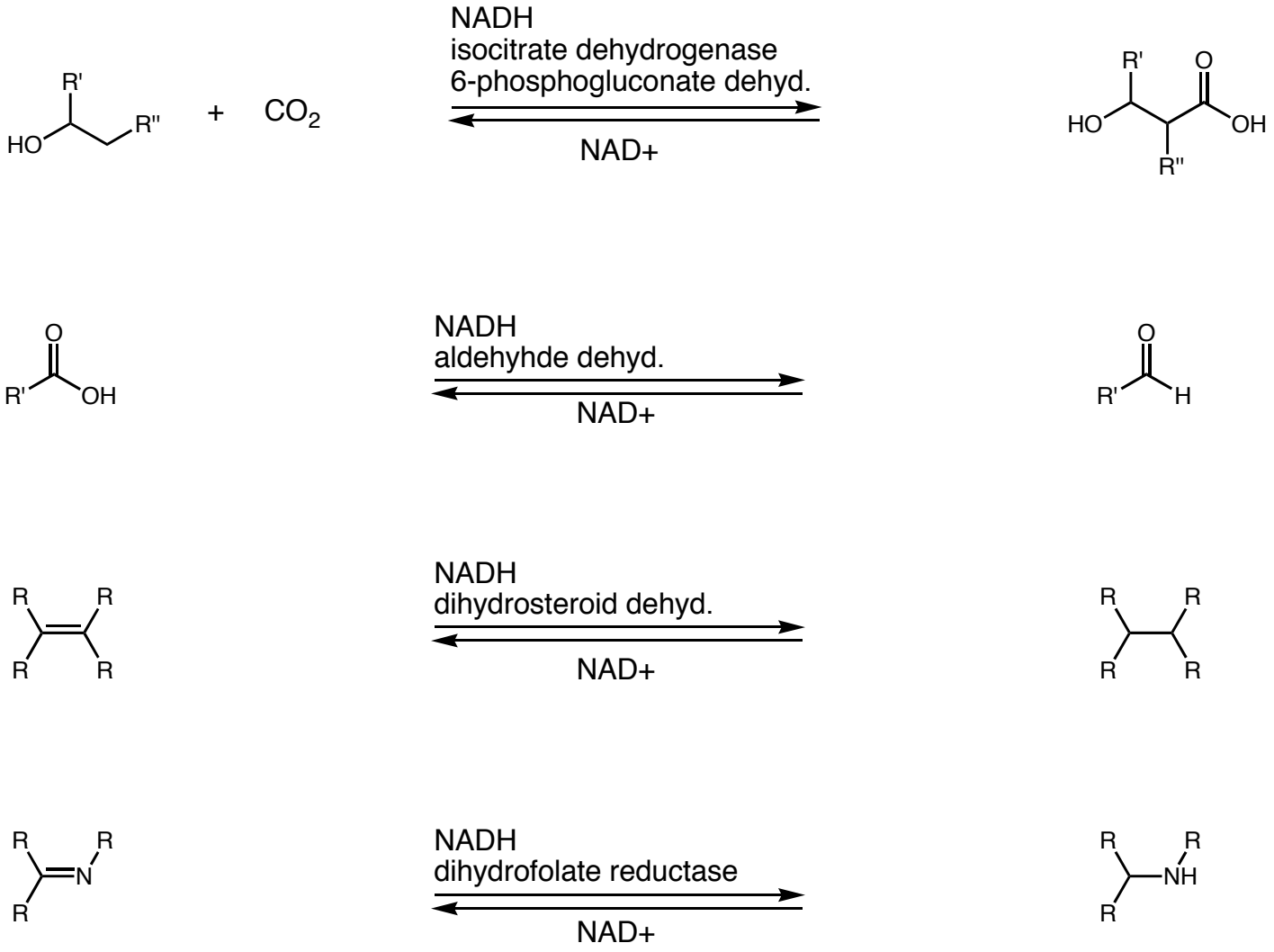
- Biosynthesis of UDP-galactose occurs via oxidation/reduction of UDP-glucose.





R. H. Garrett and C. M. Grisham, in *Biochemistry*, Saunders College Publishing 1995, p. 472-473

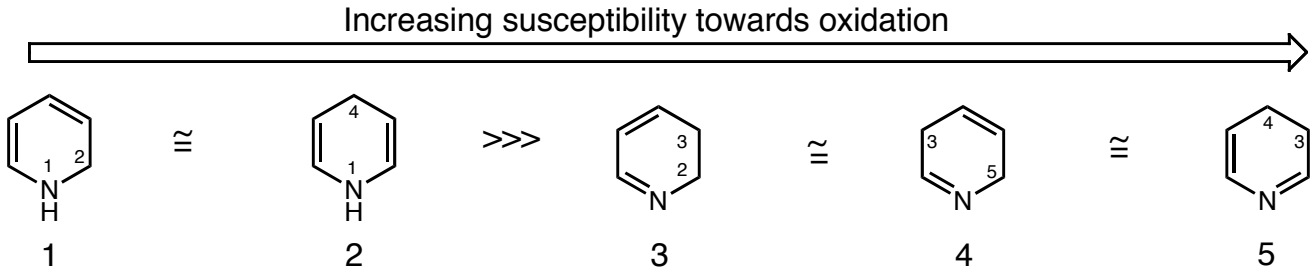
Pertinent enzymatic transformations con't.



R. H. Garrett and C. M. Grisham, in *Biochemistry*, Saunders College Publishing 1995, p. 472-473.

General structure considerations

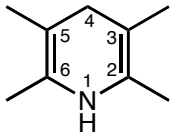
■ Theoretically, 5 isomeric DHP forms can exist



- Structures 1 and 2 are the most common. Presumably, the N lone pair delocalization into the pi system stabilizes the structure. Observe, 5 sp^2 hybridized centers in 1 and 2 versus 4 in 3-5.

■ Substituent effects

- EWG's capable of resonance interaction (COR, CO_2R, CN, NO_2) in the 3,5 positions stabilize 1,4 DHP's by extending conjugation.
- Conversely, electron donating groups (SPh, OPh) in the 3,5 position destabilize the molecule.
- Nitrogen alkyl substitution, though possible to prepare, destabilizes 1,4 DHP's.
- 2,6 alkyl substitution remains largely unexplored.



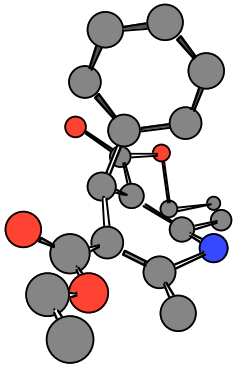
Meyers, A. I. and Stout, D. M. *Chem. Rev.* **1982**, *82*, 223.
Kuthan, J. and Kurfurst, A. *Ind. Eng. Chem. Prod. Res. Dev.* **1982**, *21*, 191.

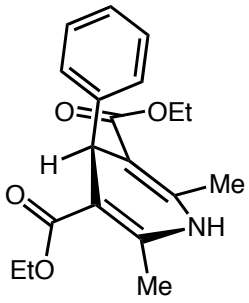
Hantzsch esters adopt two potential conformations

X-ray studies

- 4-unsubstituted Hantzsch esters adopt a planar conformation.
- aryl and pyridyl substituents at the 4-position induce a puckered ("flat boat") configuration.

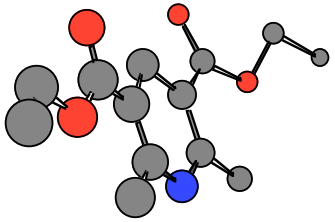
Puckered conformation

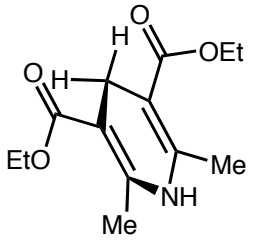




Goldmann, S. *et al. J. Med. Chem*. **1990**, *33*, 1413.
Fossheim, R. *et al. J. Med. Chem*. **1982**, *25*, 126.

Planar Conformation





Leustra, A. *et al. Bull. Soc. Chi. Belg*. **1979**, 133.

Three postulates aim to explain the reduction mechanism of 1,4 dihydropyridines

- The following mechanisms have been proposed:

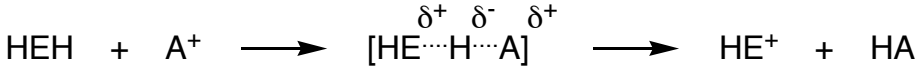
  I. Single step hydride transfer
  II. Two step electron transfer-hydrogen atom abstraction
  III. Three step electron transfer-proton transfer-electron transfer

- Data supporting each process were derived from nicotinamide analogues and Hantzsch ester derivatives

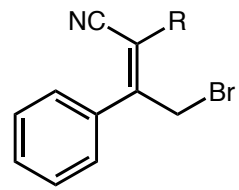
- No unified mechanism has been established

Single-step hydride transfer

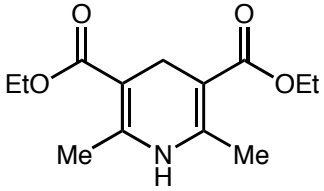
- Occurs in most Hantzsch ester reductions that proceed under thermal conditions
- General scheme



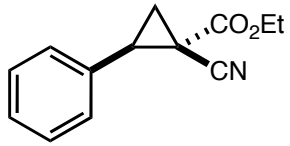
- Experimental results that support this mechanism



R = CN, CO_2Et

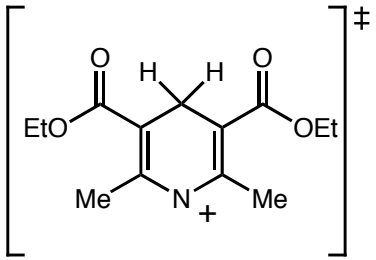


CH_3CN, dry, deaerated
RT, 7h, dark

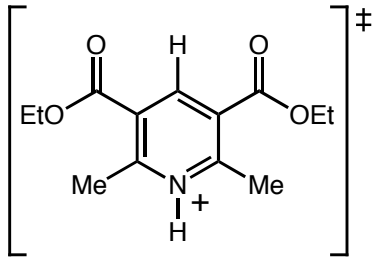


90%, only isomer

- Free energy calculations indicate the single electron transfer mechanism is less likely than hydride transfer by two-fold (for CN +158.17 kJ/mol vs. 87.47 kJ/mol).
- Deuterated C-4 and N Hantzsch analogues were used to determine hydride source via NMR.



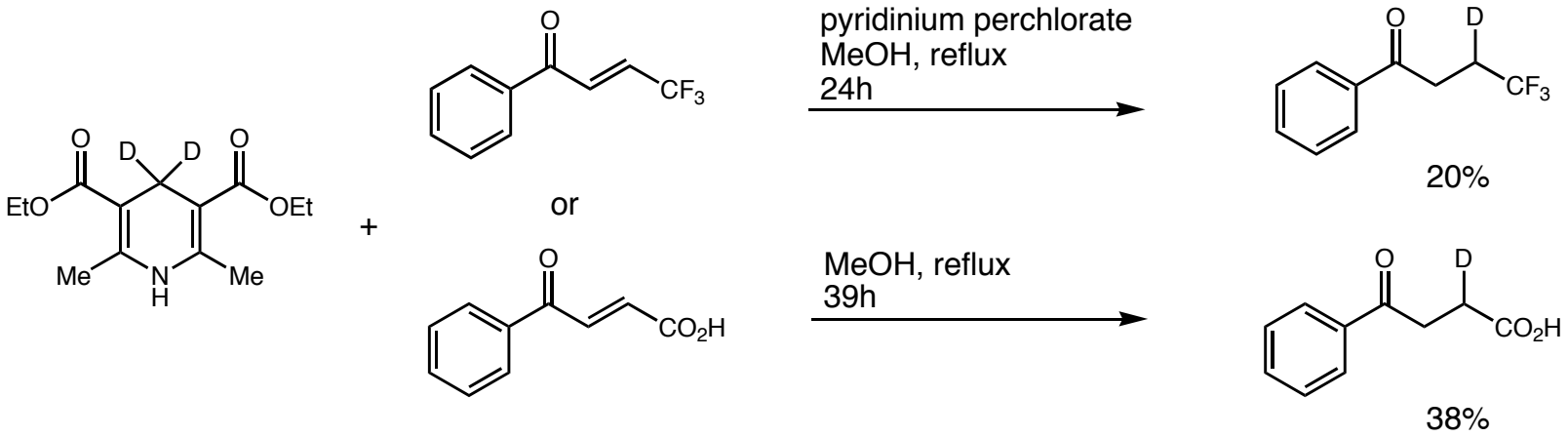
vs.



Zhu, X. *et al. J. Org. Chem.* **1999**, *64*, 8980.

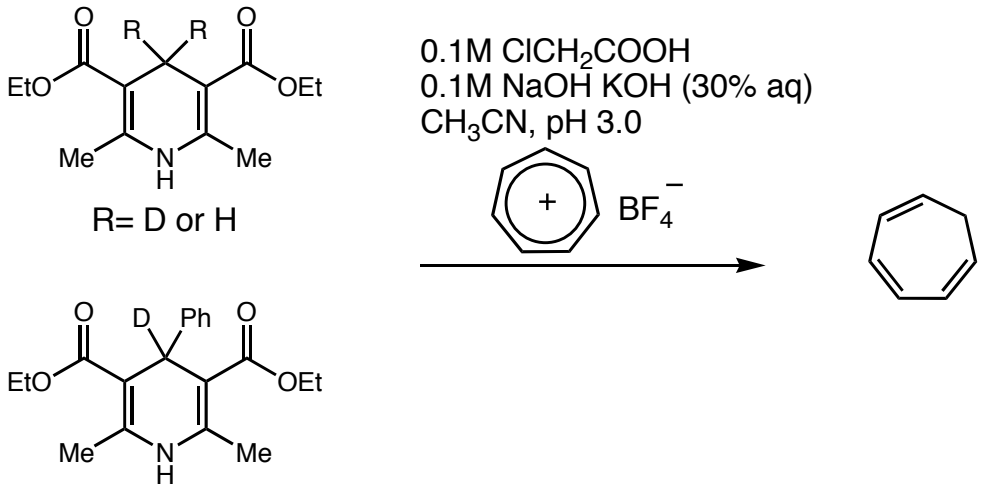
Various studies support single-step hydride transfer

- Deuterated product detected by ^{1}H and ^{19}F NMR. Authors support hydride transfer mechanism



Norcross, B. E., Klinedinst, Jr., P. E., Westheimer, F. H. *J. Amer. Chem. Sci.* **1962**, *84*, 797.

- Kinetic isotope effect and thermodynamics support single step hydride transfer.

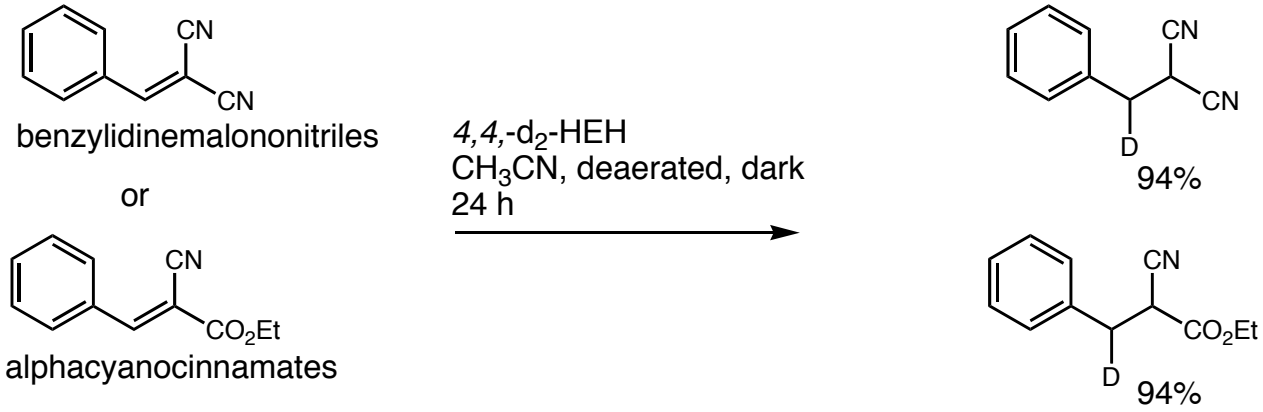


- Deuterium KIE value of 4.16 indicates direct hydride dissociation from C-4 is rate limiting step.
- Presence of the bulky phenyl group decreases reaction rate ~10^4 fold.
- Electrochemical experiments support direct hydride transfer for both cases.

Cheng, J.-P. *et al. Tet Lett.* **2000**, *41*, 257.

Further evidence for a single-step hydride mechanism

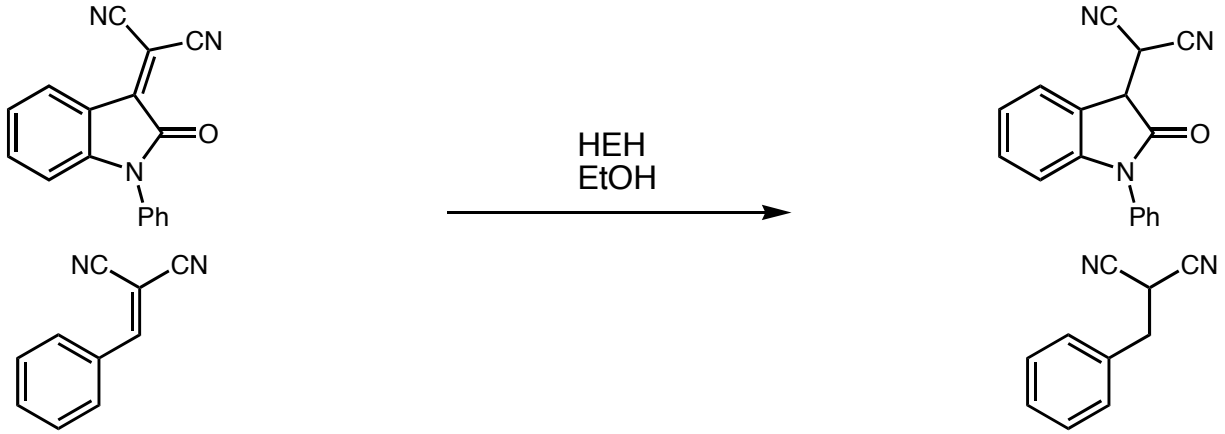
- Thermodynamic and kinetic studies provide an arguement for this process.
- Deuterium regiochemistry determined by ^{1}H NMR and MS.



- A KIE comparison of N-d and C-d,d Hantzsch derivatives gave values <1.4 and >5.2, respectively. Values above 2.0 indicate the C-H bond is being broken in the rate determining step.
- Free energy changes of electron transfer were 167-178 kJ/mol vs hydride 75-90.5 kJ/mol.

Zhu, X. Q. et al. *J. Chem. Soc., Perkin Trans. 2* **2000**, 1857.

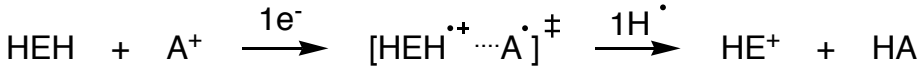
- Molecular electrostatic potential and HOMO/LUMO comparisons support a hydride attack



Garden, S. J. *et al. J. Org. Chem.* **2003**, *68*, 8815.

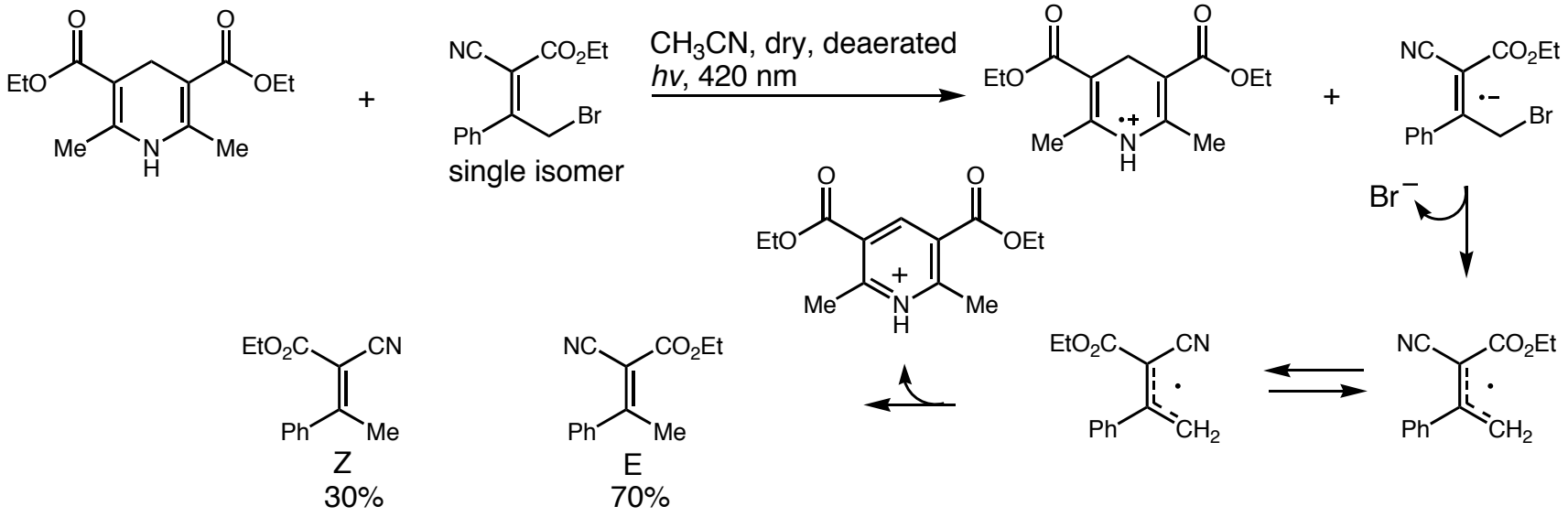
Two step transfer: 1 electron- 1 hydrogen

- General scheme



- Occurs predominantly under photoexcited conditions or with strong oxidants

- Evidence is found in specific cases

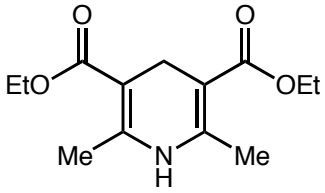


- Only the Z isomer is reacted.
- Deuterium studies indicate a proton is abstracted from C-4.

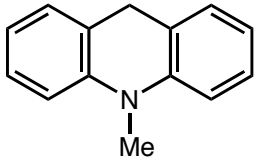
Zhu, X.- Q. *et al. J. Org. Chem.* **1999**, *64*, 8980.

1 Electron, 1-Hydrogen evidence continues. . .

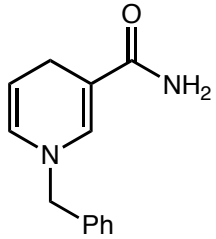
- Three NADH analogues are analyzed kinetically and thermodynamically



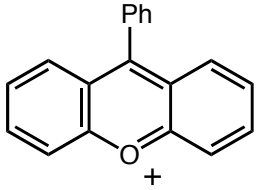
HEH



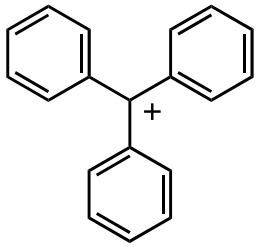
$AcrH_2$



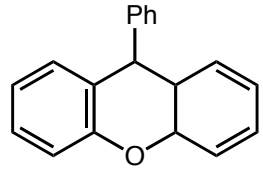
BNAH

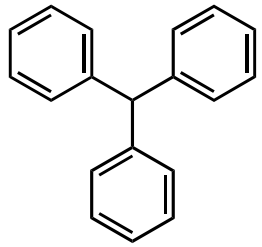


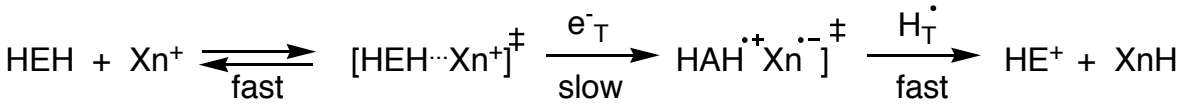
or



30% CH_3CN
70% H_2O (v/v)
KCl





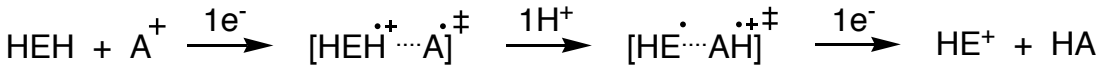


- A slight endothermic electron transfer was followed by a large exothermic proton transfer.
- HEH, despite being a poorer electron donor than BNAH (0.446V, 0.182V, respectively), reacts faster.
- Failure of CF_3COOD to deuterate the intermediate radical anion suggests electron and proton steps may overlap.

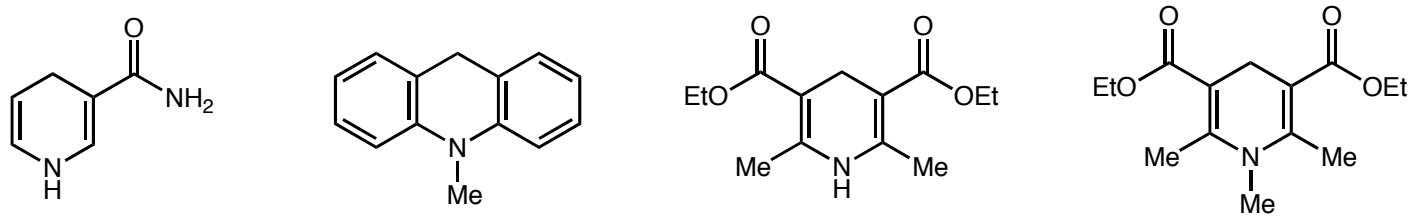
Cheng, J. - P. and Lu, Y. *J. Phys. Org. Chem.* **1997**, *10*, 577.

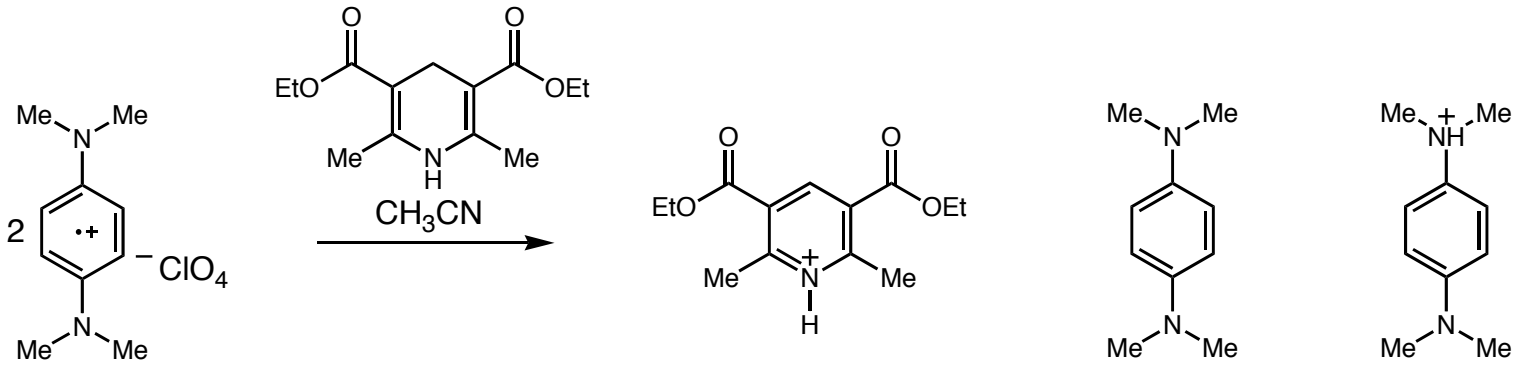
Multi-step transfer: electron-proton-electron (e^- - H^+ - e^-)

- General scheme



- Cheng returns with the same reductants and a different mechanistic postulate.



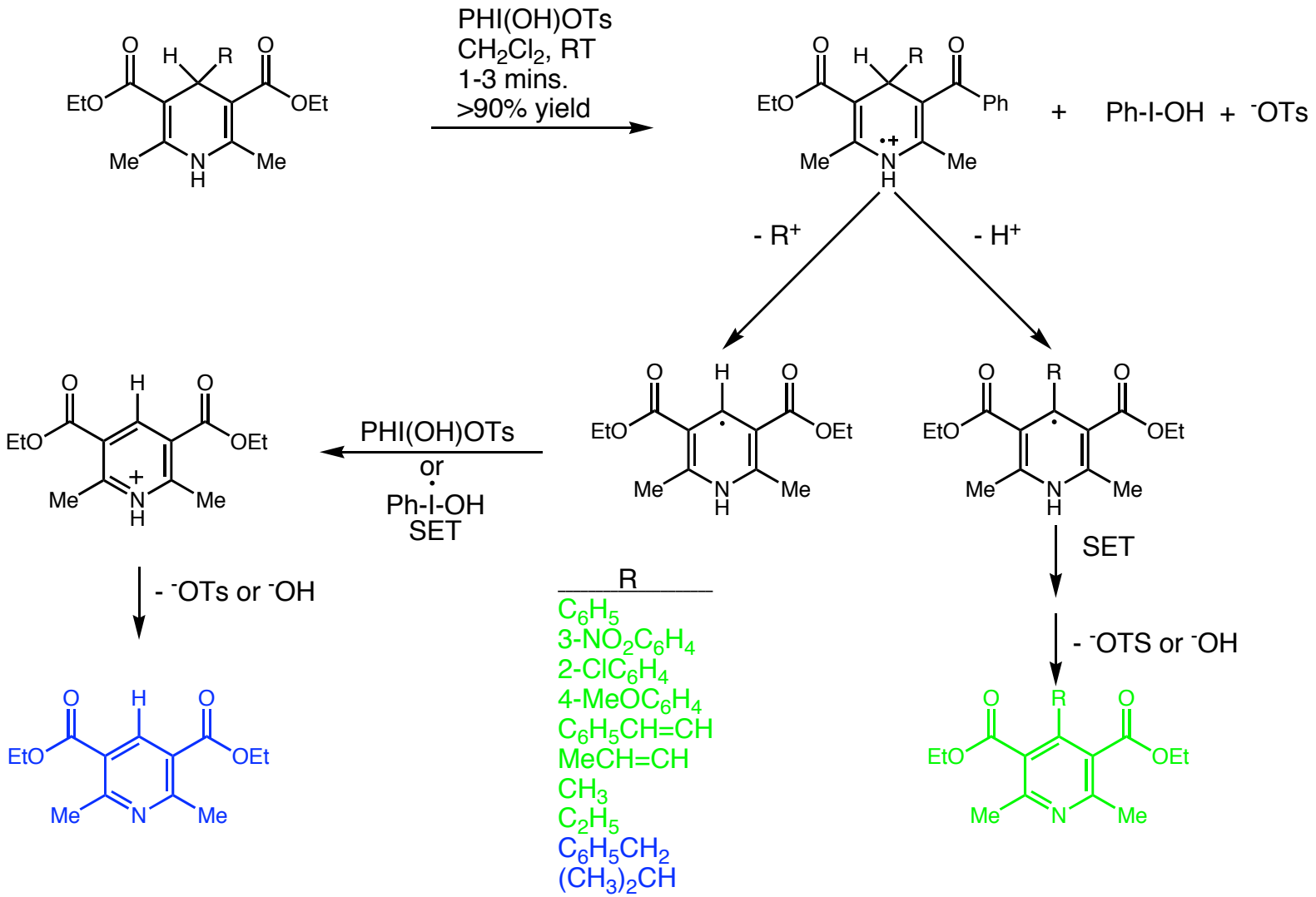


- Uses titration calorimetry and electrochemistry to develop hypotheses.
- In this experiment, HEH can deliver a hydride or undergo the e^- - H^+ e^- mechanism with equal probability.
- N-substituents on nicotinamide derivatives have a large effect. EWG's favor heterolytic bond cleavage, EDG's favor homolytic bond cleavage.

Cheng, J. - P. *et al. Chem. Eur. J.* **2003**, *9*, 871.

An interesting effect of e^- - H^+ - e^- on 4-substituted Hantzsch DHP's

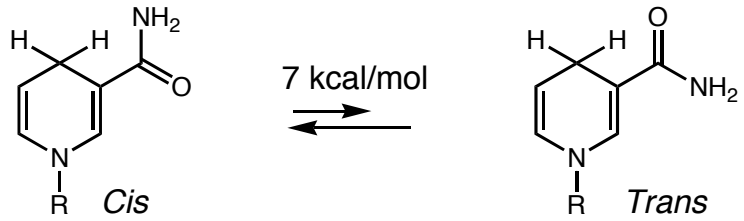
- Creates a potential source of alkyl cations



Lee, K. - H. and Ko, K. - Y. *Bull. Korean Chem. Soc.* **2002**, *23*, 1505.

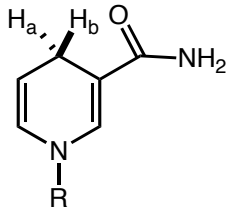
Hantzsch DHP ester groups may play a role sterically and electronically

- Nicotinamide amides can exist in either a *cis* or *trans* geometry

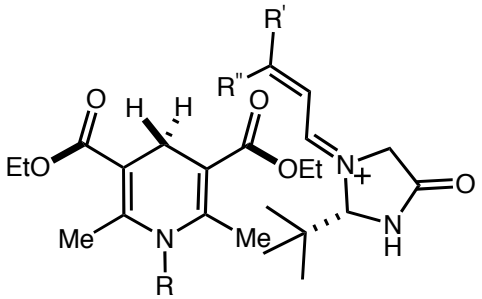


Cis = ground state
Trans = reduction transition state

- The carbonyl is slightly tilted towards the incoming electropositive substrate



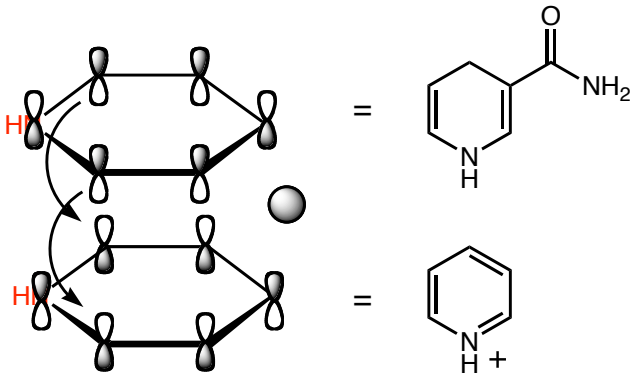
- Electrostatic interaction of both carbonyl groups with electrophile



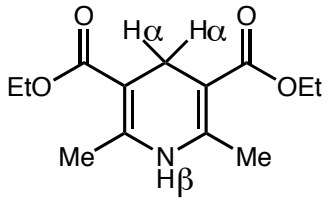
Houk, K. N. *et al. J. Am. Chem. Soc.* **1995**, *117*, 4100.
Cheng, J. - P. and Lu, Y. *J. Phys. Org. Chem.* **1997**, *10*, 577.

Orbital overlap may provide a key for understanding Hantzsch DHP orientation during hydride delivery

- Two interesting concepts arise when analyzing FMO's

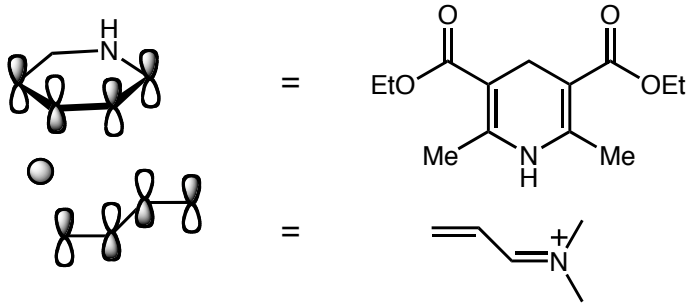


- Houk's nicotinamide models indicate a favorable LUMO donor/LUMO receiver overlap that lowers the activation energy.



- Garden's HOMO coefficient calculations show Hα = 0.2325 and Hβ = -0.001.

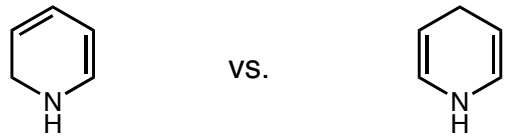
- Based on these data, it may be possible to determine Hantzsch ester/substrate overlap by analyzing LUMO/LUMO coefficients.



Houk, K. N. *et al. J. Am. Chem. Soc.* **1995**, *117*, 4100.
Garden, S. J. *et al. J. Org. Chem.* **2003**, *68*, 8815.

Hantzsch ester preparation

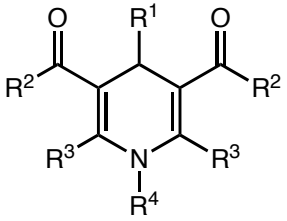
- Many methods provide reasonable routes leading to Hantzsch derivatives
- Cyclocondensation routes are the most efficient and predictable
- Reduction of pyridine derivatives has been used with mixed success



- Main methods of preparation (reactants will be discussed)

1) Warming the reagents in alcohol (usually EtOH).
2) Using hexamethlyenetetramine in place of formaldehyde and ammonia.
3) Utilization of NH_4OAc and primary amine salts with acetic acid or pyridine as solvents

- General trends for varying certain substituents on the Hantzsch DHP

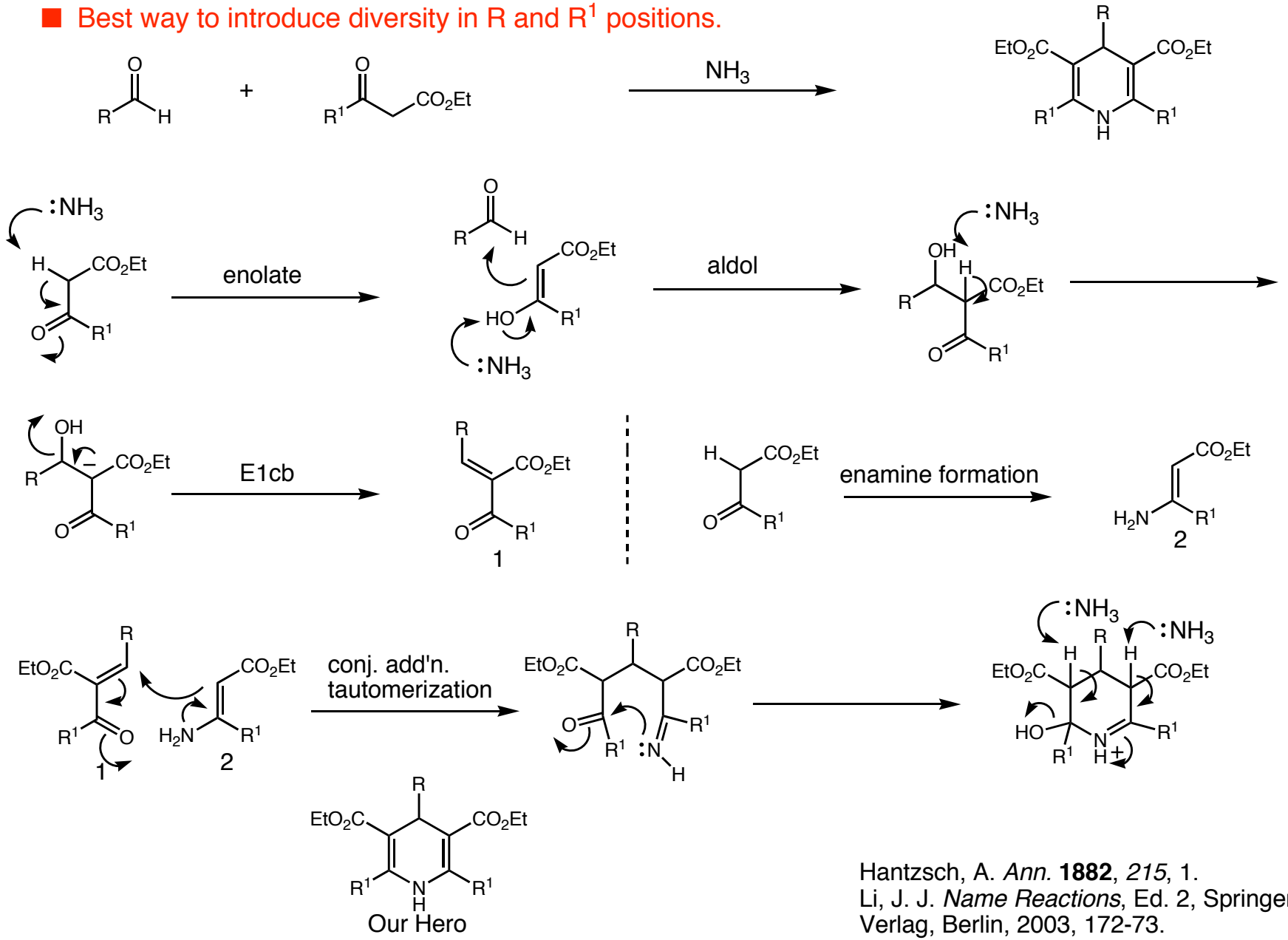


- If R^1 = varied, while R^2 = OR, Me, NH_2, R^3 = Me and R^4 = H, then use method 1.
- If R^1 = varied, while R^2 = Me, NMe_2, OEt, OMe, O-i-Pr, O-n-Bu, R^3 = Me and R^4 = alkyl, aryl, then use method 1.
- If R^2 = varied, while R^1 = R^4 = H and R^3 = Me, then use method 2.
- If R^3 = varied and R^1 = varied, while R^2 = Et and R^4 = H, then use method 3.

Kuthan, J. and Kurfurst, A. *Ind. Eng. Chem. Prod. Res. Dev.* **1982**, *21*, 191.

Namesake Preparation is most efficient

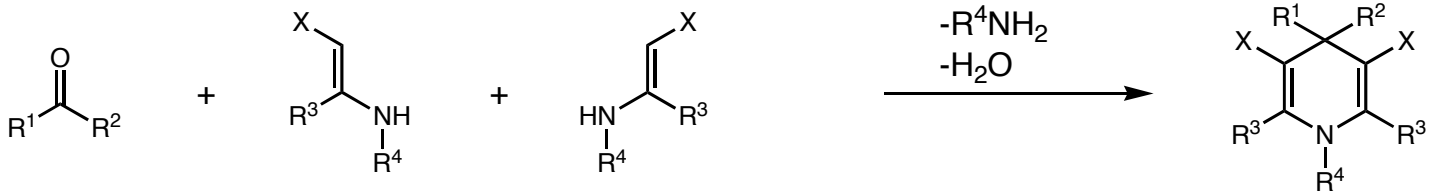
- Best way to introduce diversity in R and R^1 positions.



Hantzsch, A. *Ann.* **1882**, *215*, 1.
Li, J. J. *Name Reactions*, Ed. 2, Springer - Verlag, Berlin, 2003, 172-73.

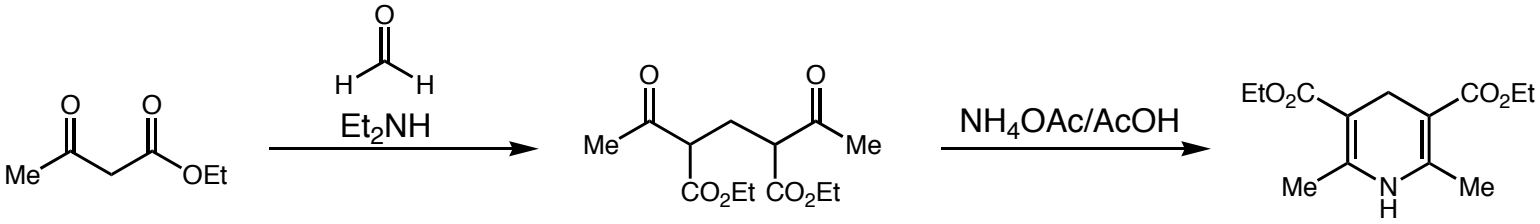
Cyclization/condensation methods lead to a variety of Hantzsch derivatives

- Use of enamino ketones, esters and nitriles (X groups)



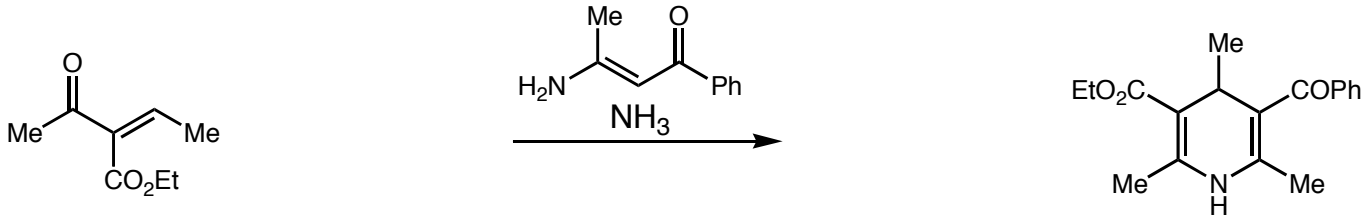
- Great way to introduce nitrile groups to the 3 and 5 positions.

- Use of 1,5 diketones



- The diester intermediate is not isolated.

- Use of α-β unsaturated ketones



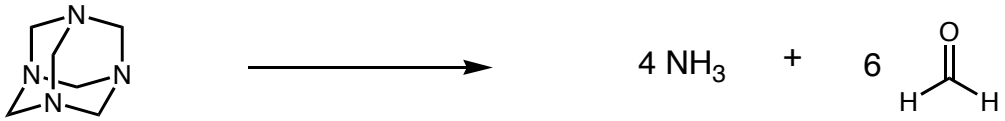
- Can react with enamines or ketones to provide unsymmetrical products.

Kuthan, J. and Kurfurst, A. *Ind. Eng. Chem. Prod. Res. Dev.* **1982**, *21*, 191.
Eisner, U. and Kuthan *J. Chem. Rev*. **1072**, *72*, 1.

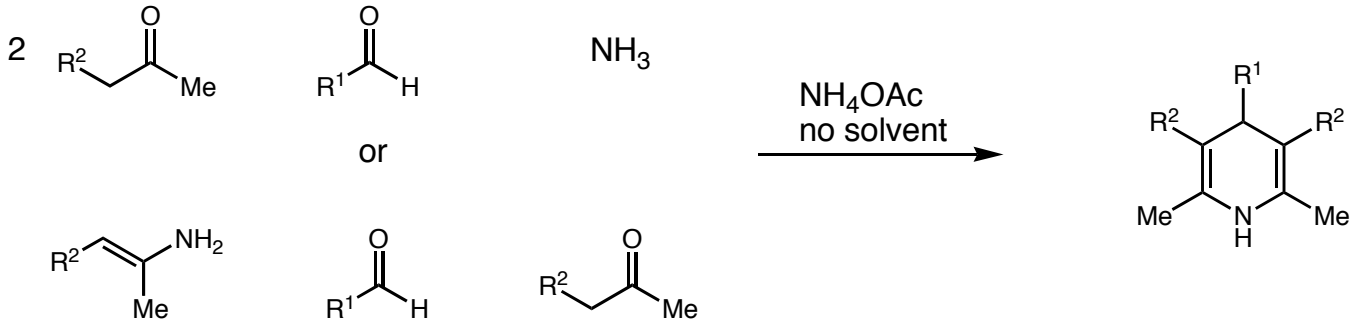
The advent of microwave technology has streamlined the synthesis

- Useful modifications of Hantzcsh's synthesis

  - Hexamethylenetetramine provides a cheap and easily handled source of ammonia and formaldehyde.



  - The advent of microwave technology has reduced reaction time to minutes. Many functional groups can tolerate these conditions.

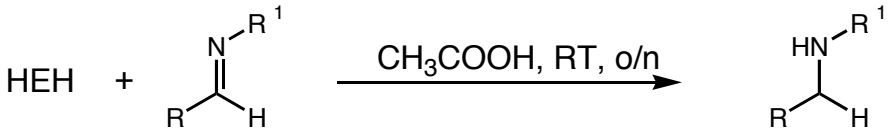


R	R^2
H	CO_2Et
H	CO_2Me
H	CO_2tBu
H	$COCH_3$
H	CN
Me	CO_2Et
Me	CN
iPr	CO_2Et
iPr	CN
Ph	CO_2Et
Ph	CN

Barbry, D. *et al. Molecules* **2002**, *7*, 528.

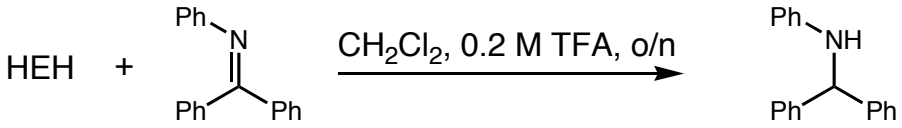
Hantzsch esters reduce imine derivatives

Imine, both preformed and under reductive amination conditions



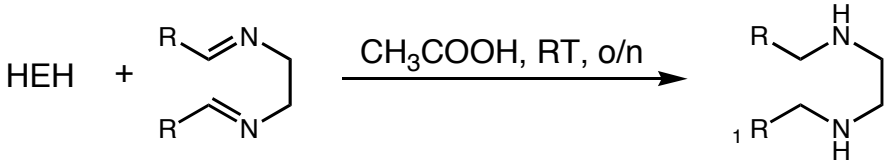
R	R^1	% yield
p-MeOPh	p-MeOPh	90
Ph	2-Naphthyl	89
p-OHPh	o-OMePh	79
Ph	p-OHPh	95
Ph	Ph	66

Ketimine



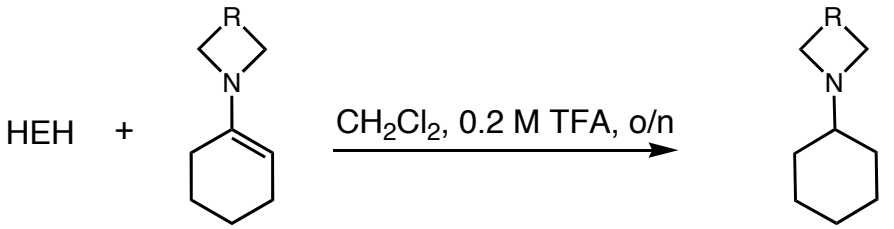
60% yield

Bisarylidene-ethylenediamines



R	% yield
p-ClPh	50
Ph	45

Enamines

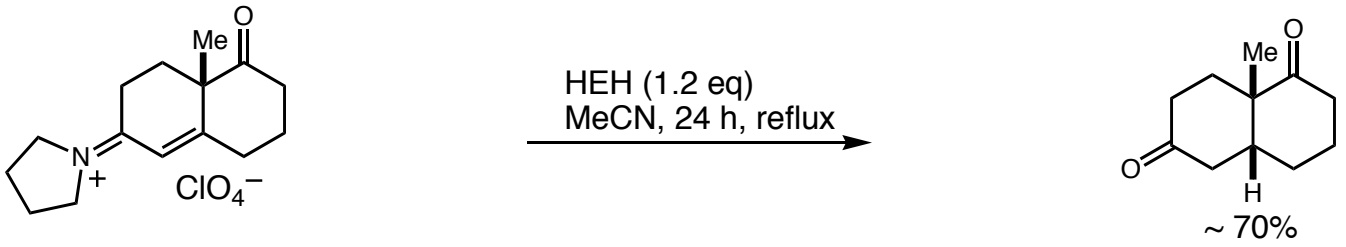


R	% yield
- $(CH_2)_2$ -	55
- $(CH_2)_3$ -	58
- CH_2OCH_2 -	50

Singh, S. *et al. J. Chem. Soc. Perkin Trans. 1*, **1985**, 437.

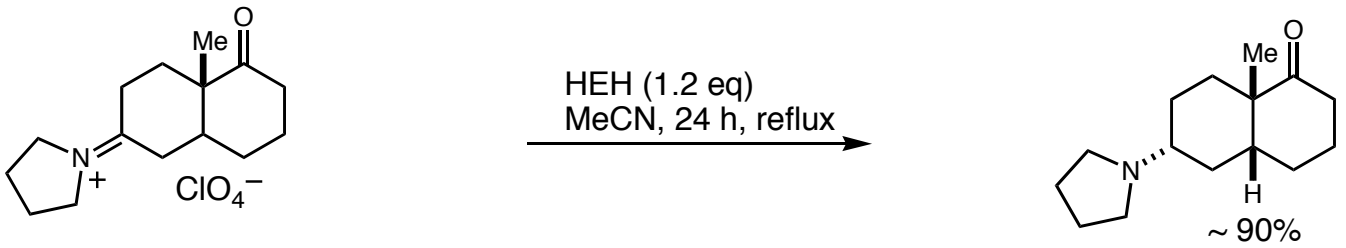
Other imine derivative examples

- Steroid unsaturated iminium gives a single isomer



Pandit, U. K. *et al. J. Chem. Soc. Chem. Comm.* **1974**, 327.

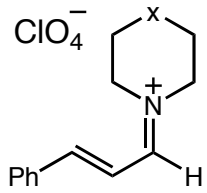
- Steroid iminium gives a single isomer



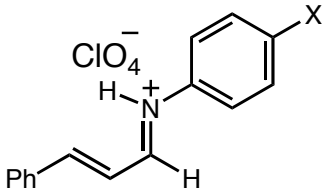
Pandit, U. K. *et al. J. Chem. Soc. Chem. Comm.* **1975**, 211.

Effect of substitution on hydride regioselection with α-β unsaturated iminium salts

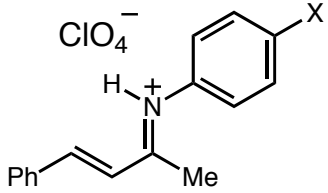
- Reductions proceed with 2 eq.HEH and are run in CH_3CN at RT. Yields are all > 90%.



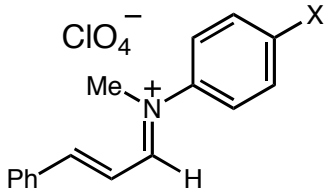
1



2



3



4

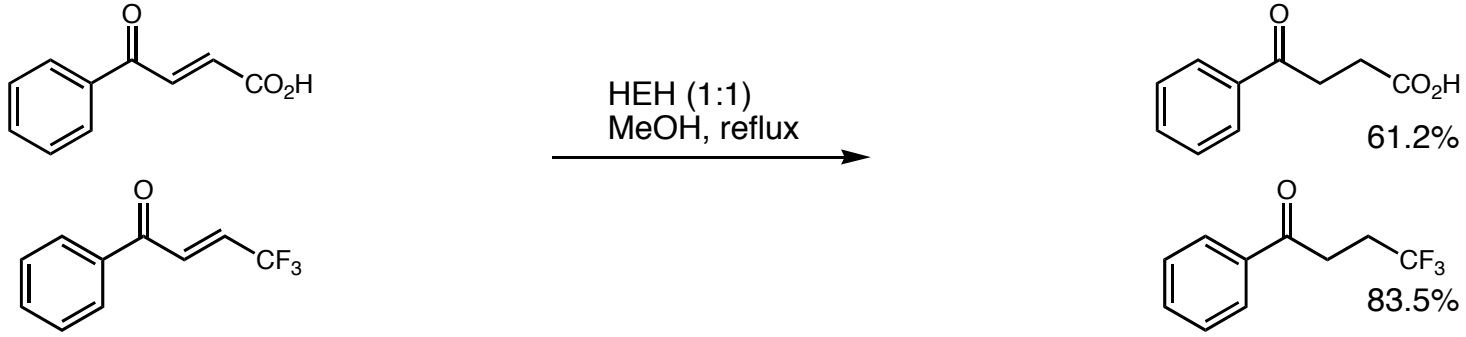
substrate	X	E1/2 (V)	pKa amine	ratio C=C:C=N attack
1	CH_2	-0.75	11.27	100:0
1	O	-0.66	8.33	100:0
2	OCH_3	-0.47	5.34	77:23
2	CH_3	-0.43	5.08	29:71
2	F	-0.38	4.65	28:72
2	H	-0.35	4.63	21:79
2	Br	-0.32	3.86	10:90
2	CO_2Et	-0.22	2.46	0:100
2	CN	-0.15	1.74	0:100
2	NO_2	+0.04	1.00	0:100
3	H	-0.59	4.63	100:0
3	Br	-0.49	3.86	100:0
4	-----	-0.44	4.8	100:0

- E1/2 is a measure of the relative LUMO energy. Data shows that E1/2 values below -0.59 lead to C=C attack. E1/2 values above -0.30 lead to iminium attack.
- Aromatic substituents have a significant effect on regioselectivity.
- Sterics are more important than FMO interactions as shown in 3(Br) and 4.

Nie-Sarink, M. J. and Pandit, U. K. *Tet. Lett.* **1979**, *26*, 2449.

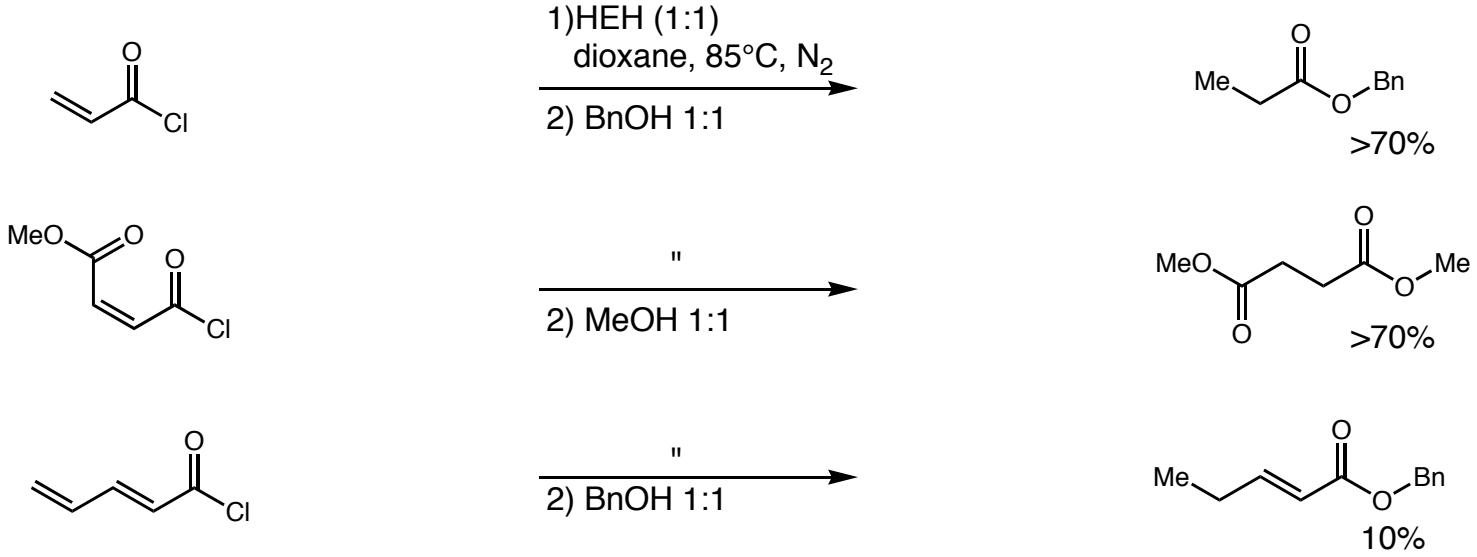
Hantzsch esters effectively reduce electrophilic olefins

- These substrates were shown earlier in a deuterium labeling experiment



Norcross, B. E., Klinedinst, Jr., P. E., Westheimer, F. H. *J. Amer. Chem. Soc.* **1962**, *84*, 797.

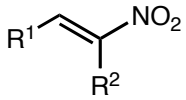
- The second step in these reactions proceeds using the crude reduced product



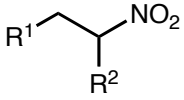
Pandit, U. K. *et al. Bioorg. Chem.* **1973**, *2*, 293.

Nitro- and carbonyl alkene reductions

β-nitroalkene derivatives



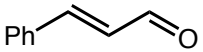
HEH (1.3 eq)
AcOH (0.18 eq)
benzene, N_2, 80°C, 15h

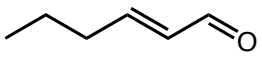


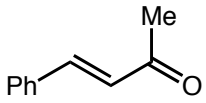
R^1	R^2	yield
Ph	H	100 (glc)
p-CH_3Ph	H	95
m-CH_3OPh	H	96
p-CH_3OPh	H	95 (glc)
p-ClPh	H	95
p-NO_2Ph	H	97
Ph	CH_3	70
m-CH_3OPh	CH_3	85

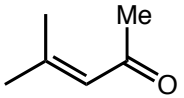
- Benzoic (pKa = 4.21), formic (pKa = 3.75), and chloroacetic (pKa = 2.87) acids also worked.
- Dichloroacetic (pKa = 1.26) and trifluoroacetic (pKa = 0.3) did not.

α-β unsaturated aldehydes and ketones

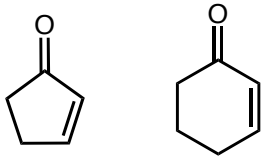




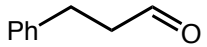
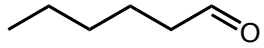
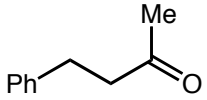
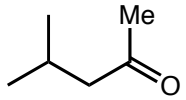
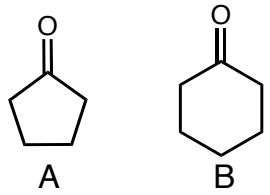




(Here used TFA)



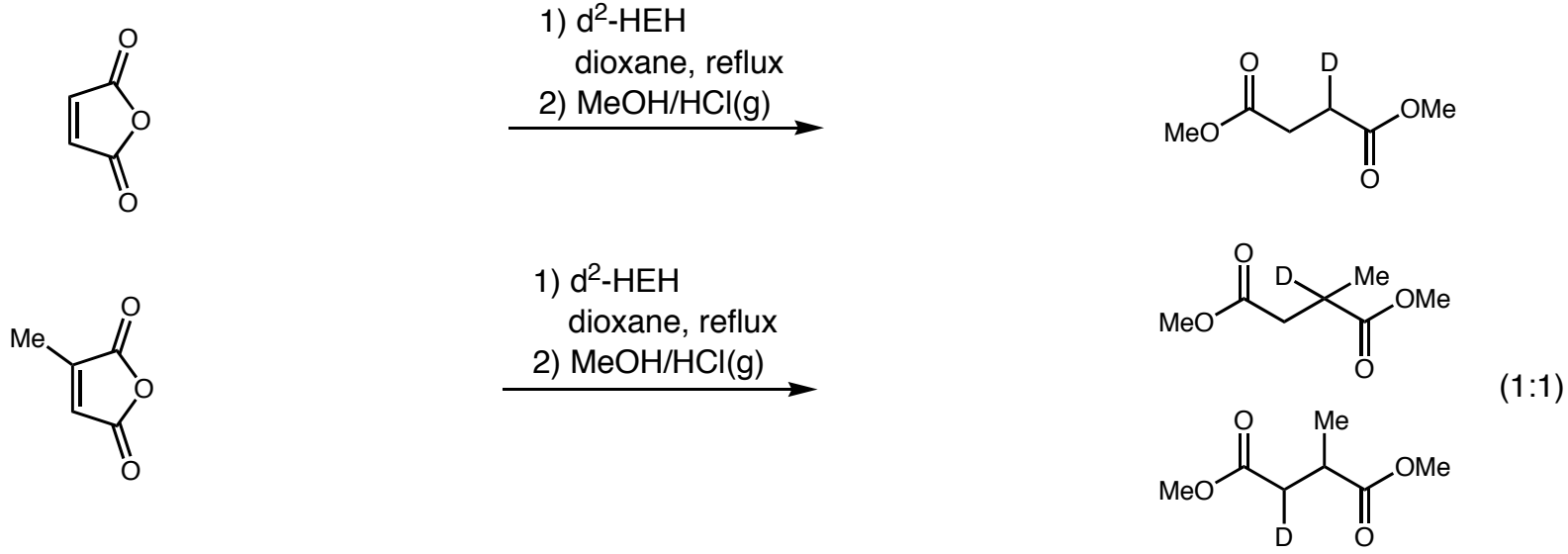
HEH (1.3 eq)
AcOH (0.18 eq)
toluene, N_2, 80°C, 15h

	yield
	76
	83
	54
	35
	A = 13 B = trace

Inoue, Y. *et al. Bull. Chem. Soc. Jpn.* **1988**, *61*, 3020

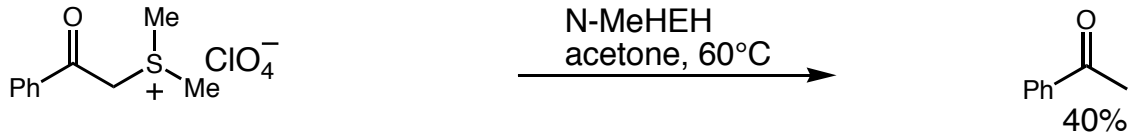
Various substrates

■ Maleic anydride is reduced non-regioselectively

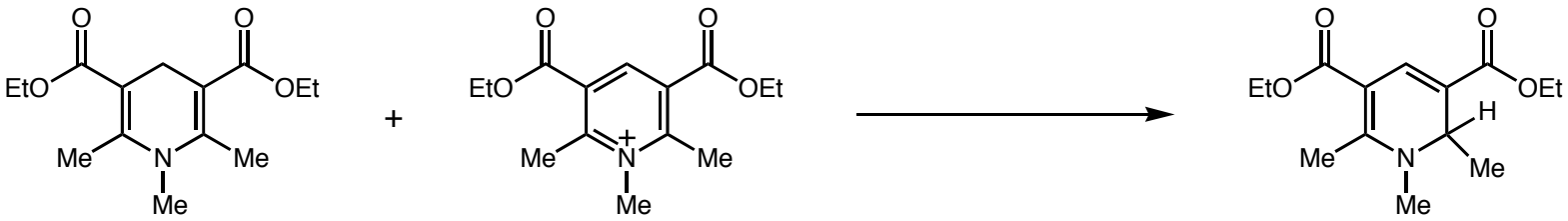


Pandit, U. K. *et al. Bioorg. Chem.* **1973**, *2*, 293.

■ Stabilized sulfonium salts are reduced by N-methylated Hantzsch esters



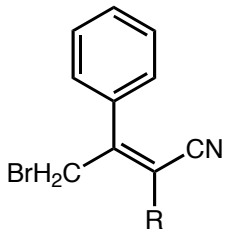
- Best case shown.



Van Bergen, T. J. and Kellogg, R. M. *J. Am. Chem. Soc.* **1964**, *98*, 1962.

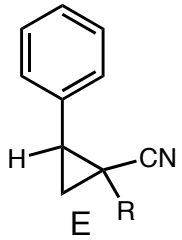
Other interesting reductions

■ Preparation of cyclic compounds

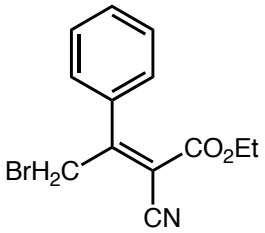


R = CN, CO_2Et

HEH (2.0 eq)
CH_3CN, deaerated, dark
Ar



	time (h)	% yield
CN	7-11	>90
CO_2Et	11-15	>91



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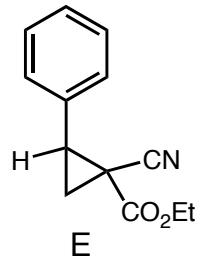
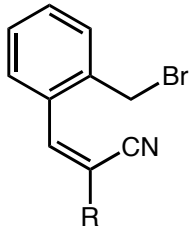
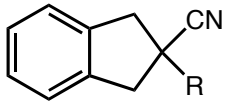


13-17 >92

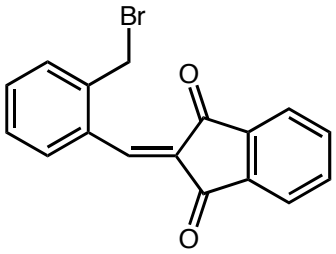


R = CN, CO_2Et, SO_2Ph

"



CN	15	89
CO_2ET	19	88
SO_2Ph	18	86



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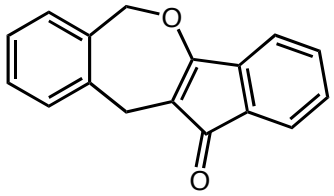
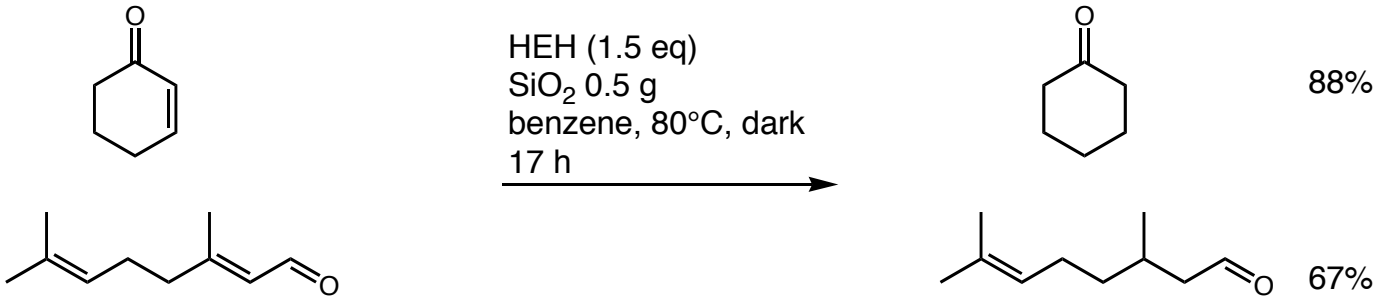


20 85

Zhu, X. -Q. *et al. J. Org. Chem.* **2001**, *66*, 344.

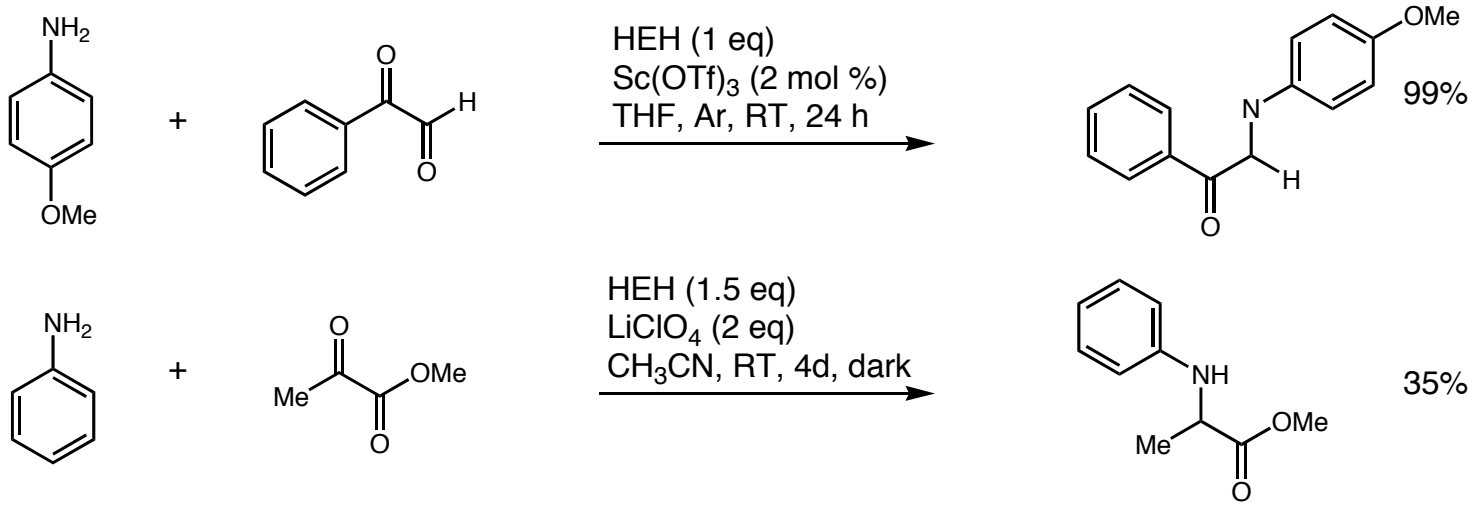
A brief look at Lewis acid catalyzed Hantzsch reactions

■ Olefin reduction with SiO_2



Ohno, A. *et al. Tet. Lett.* **1984**, *25*, 36.

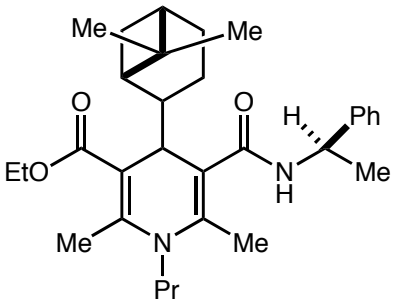
■ Reductive amination using $Sc(OTf)_3$ and $LiClO_4$

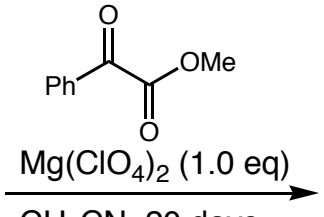


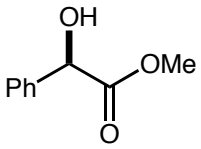
Ohsawa, A. *et al. Tet. Lett.* **2002**, *43*, 3105.
Ohno, A. *et al. Tet. Lett.* **1977**, *52*, 4593.

A look at asymmetric Hantzsch variants

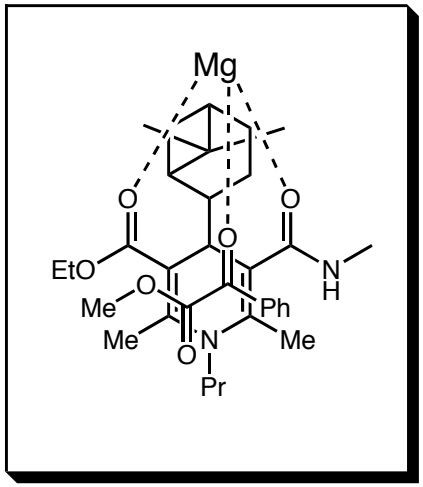
- Asymmetric versions



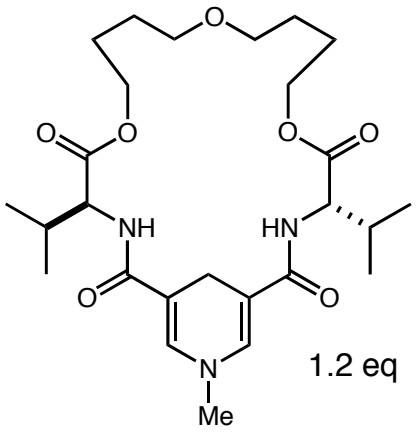




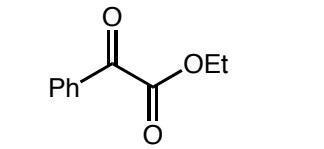
83% yield
72% ee

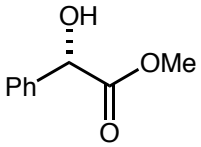


Tanner, D. and Li, X. *Tet. Lett.* **1996**, *37*, 3275.

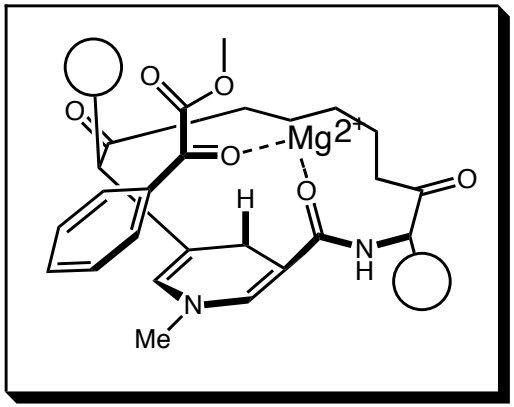


1.2 eq





80% yield
86% ee



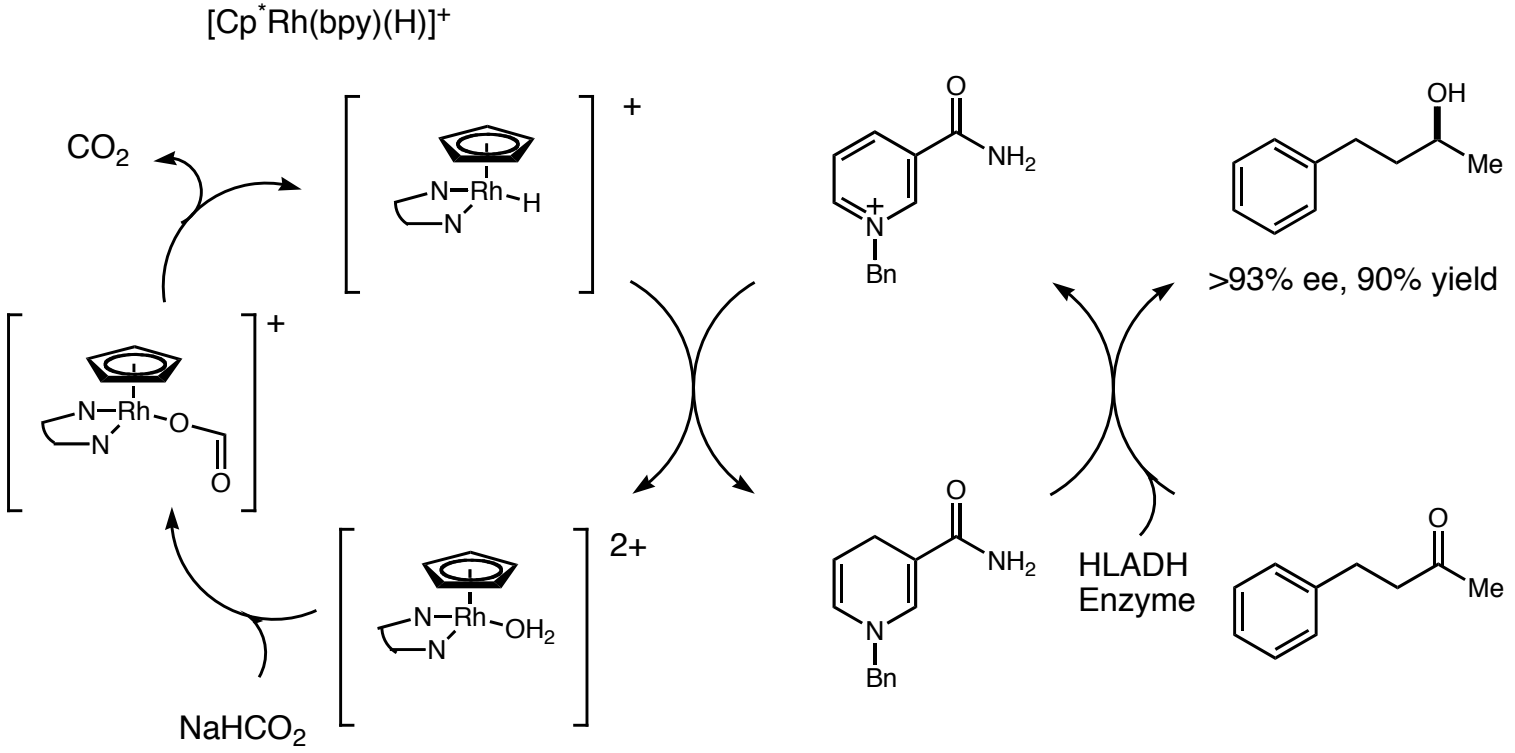
Kellogg, R. M. *et al. J. Am. Chem. Soc.* **1981**, *103*, 2091.

NADH regeneration

- Most of the current approaches require the use of enzymes or whole cell lysates

Kroutil, W. *et al. Curr. Op. Chem. Bio*. **2004**, *8*, 120.
van der Donk, W. A. and Zhao, H. *Curr. Op. Chem. Bio*. **2003**, *14*, 421.

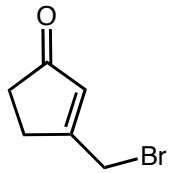
- A reasonable possibility

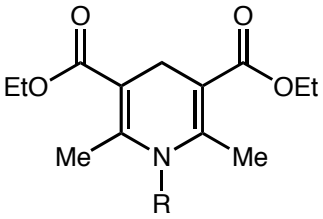


Lo, H. C. and Fish, R. H. *Angew. Chem. Int. Ed*. **2002**, *41*, 478

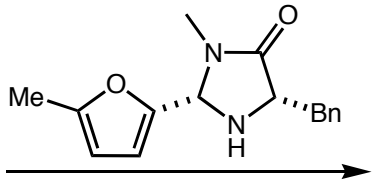
Future Directions

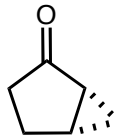
- Preparation of fused ring systems



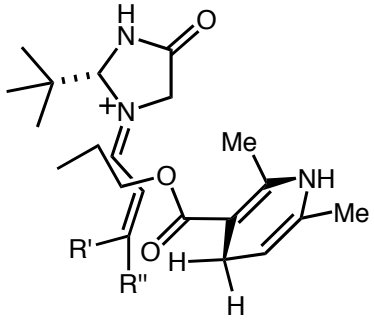


R = H, Me





- Extending 3,5 ester alkyl chains may increase enantioselectivity



- Develop a catalytic cycle

Conclusions

- Reduction mechanisms are highly dependent on substrates
- Effectively lowering the LUMO of electrophiles facilitates reduction with Hantzsch esters
- Based on mechanistic postulates, enantioselectivity may be increased with different Hantzsch derivatives
- A catalytic cycle may be created with careful selection of the second reductant and hydride source