Peptide Based Acylammonium Salts in Asymmetric Diels-Alder Reactions

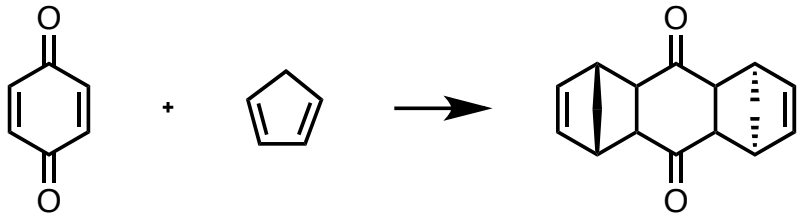
Seminar talk presented by
Christian Eschmann

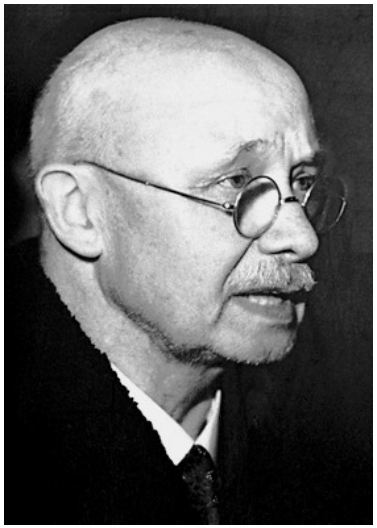
October 21st, 2016

Institute of Organic Chemistry
Justus-Liebig University Giessen

pericyclic reaction

[4+2] cycloaddition





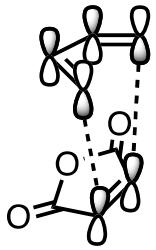
Otto Diels

Kurt Alder

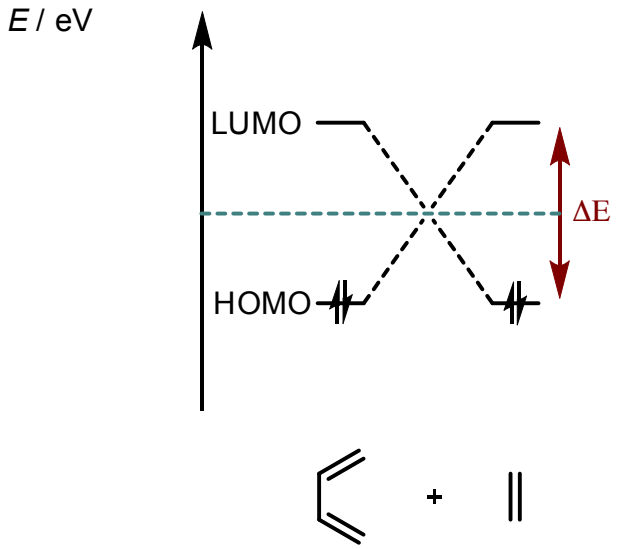
diene in *s-cis* conformation

6 delocalized π-electrons in transition state

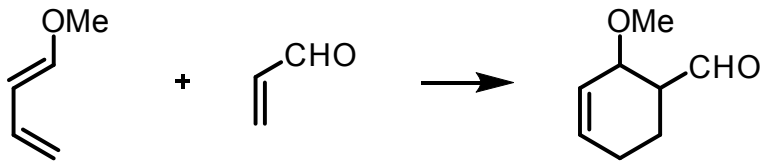
1950 noble price



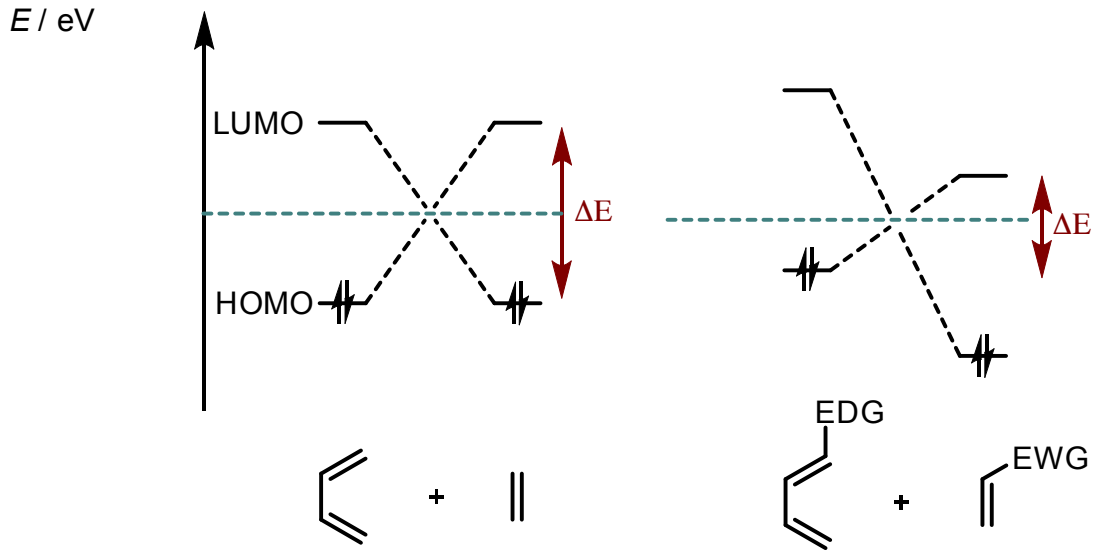
O. Diels, K. Alder, *Justus Liebigs Ann. Chem.* **1928**, *460*, 98-122.
I. Fleming, *Molecular Orbitals and Organic Chemical Reactions*, Wiley, London, **2009**.



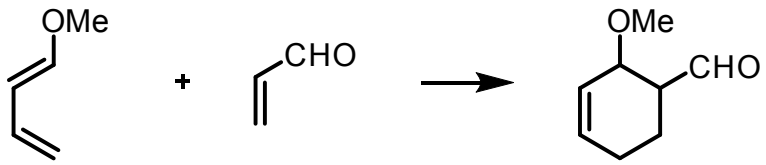
for example:



I. Fleming, *Molecular Orbitals and Organic Chemical Reactions*, Wiley, London, **2009**.



for example:



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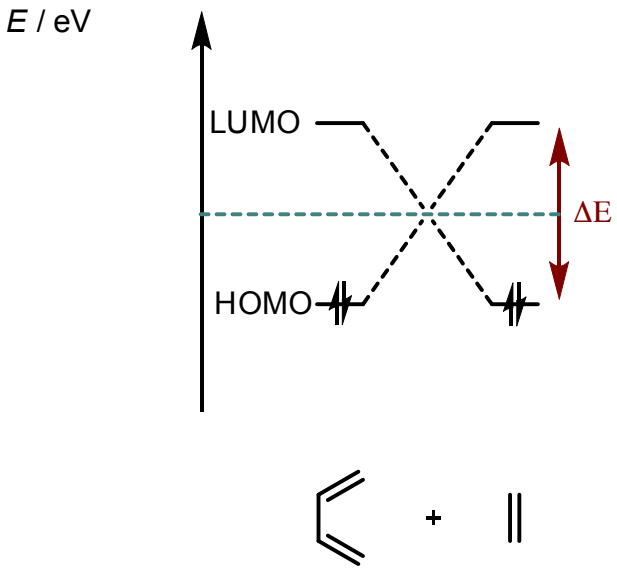

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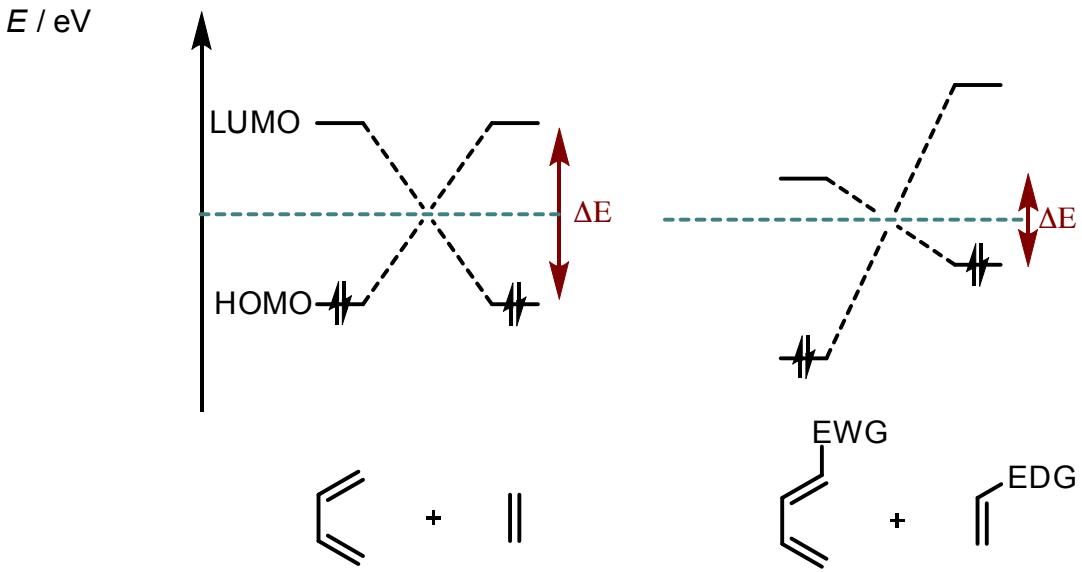
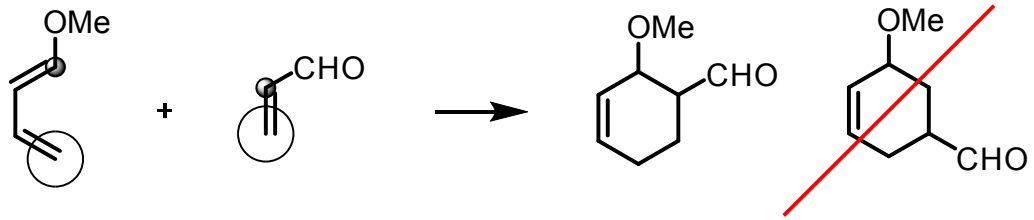
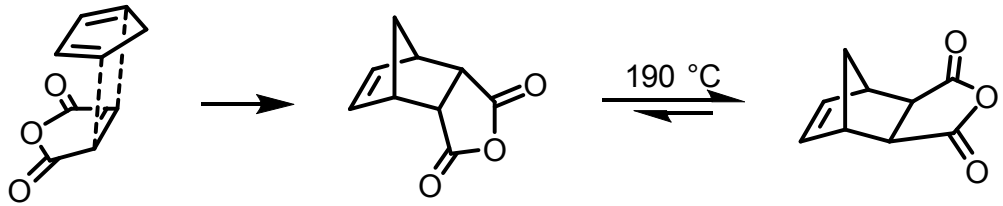


I. Fleming, *Molecular Orbitals and Organic Chemical Reactions*, Wiley, London, **2009**.

regioselectivity: coefficients of frontier orbitals



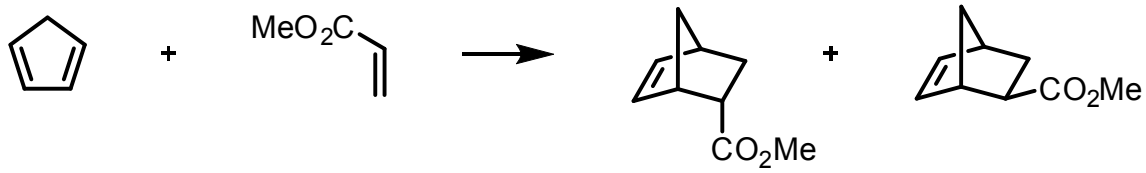
stereoselectivity: Alder‘s endo rule (secondary orbital interaction)



endo *exo*

I. Fleming, *Molecular Orbitals and Organic Chemical Reactions*, Wiley, London, **2009**.

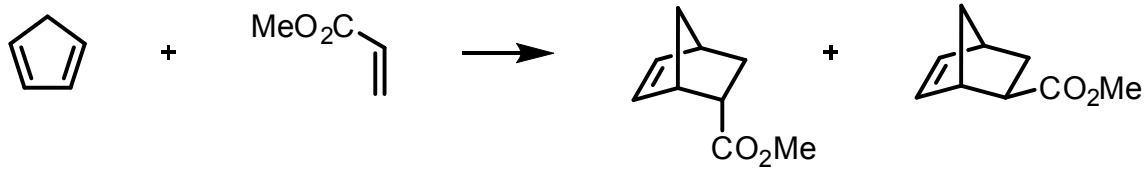
lewis acid catalyzed



without $AlCl_3$ at 0 °C: 88:12
with $AlCl_3$ at -80 °C: 99:1

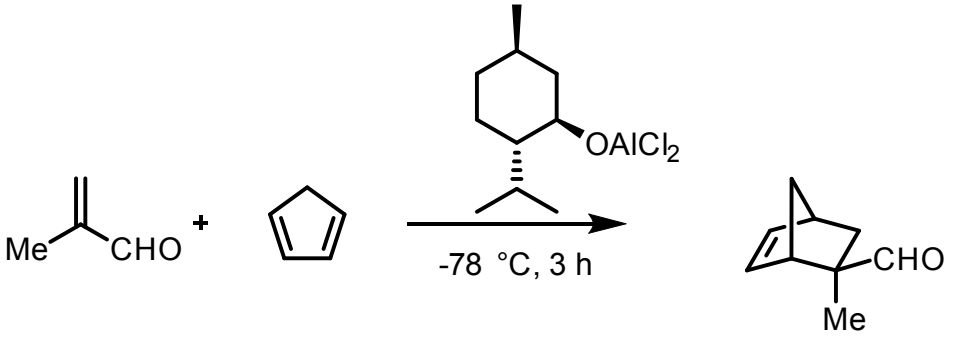
J. Sauer, J. Kredel, *Tetrahedron Lett.* **1966**, *7*, 731-736.
S.-i. Hashimoto, N. Komeshima, K. Koga, *Chem. Commun.* **1979**, 437-438.

lewis acid catalyzed



without $AlCl_3$ at 0 °C: 88:12
with $AlCl_3$ at -80 °C: 99:1

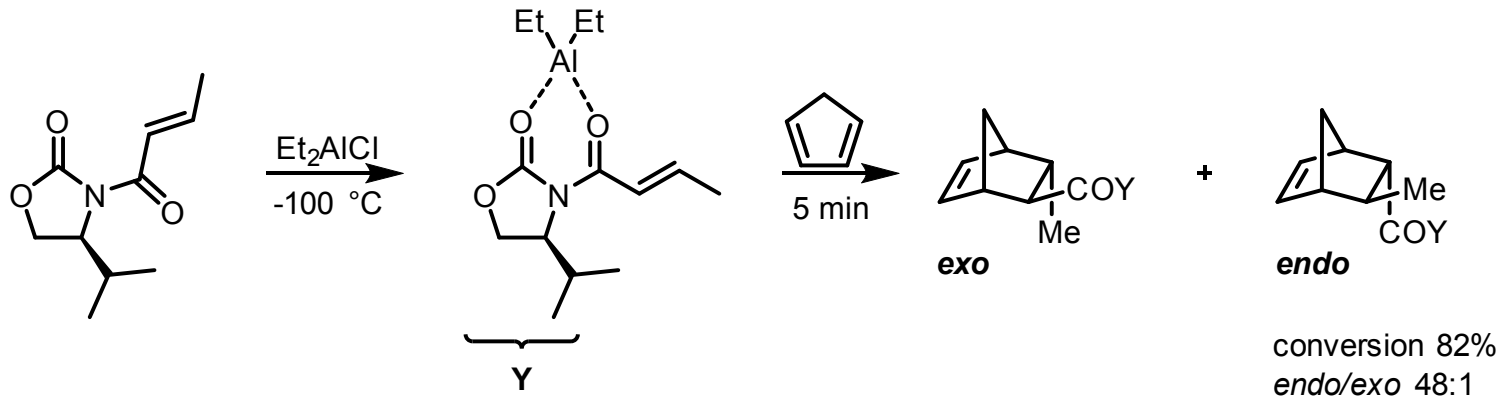
chiral lewis acid



79% yield
72% *ee*
exo/endo: 98:2

J. Sauer, J. Kredel, *Tetrahedron Lett.* **1966**, *7*, 731-736.
S.-i. Hashimoto, N. Komeshima, K. Koga, *Chem. Commun.* **1979**, 437-438.

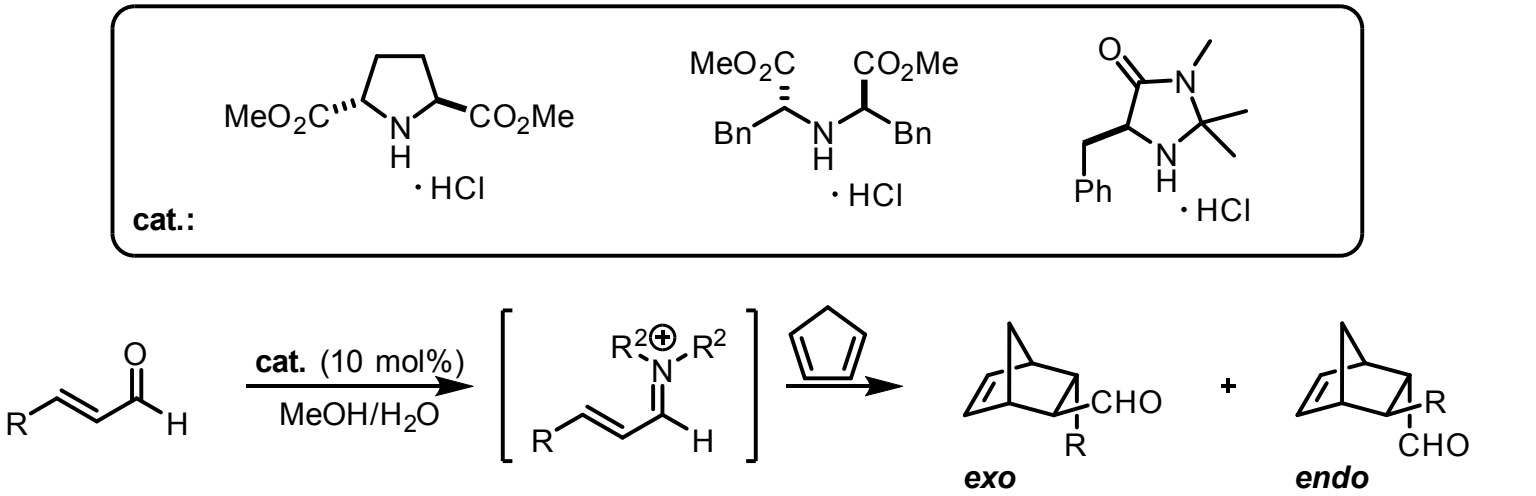
Evans chemistry



conversion 82%
endo/exo 48:1
90% ee

D. A. Evans, K. T. Chapman, J. Bisaha, *J. Am. Chem. Soc.* **1988**, *110*, 1238-1256.

MacMillan

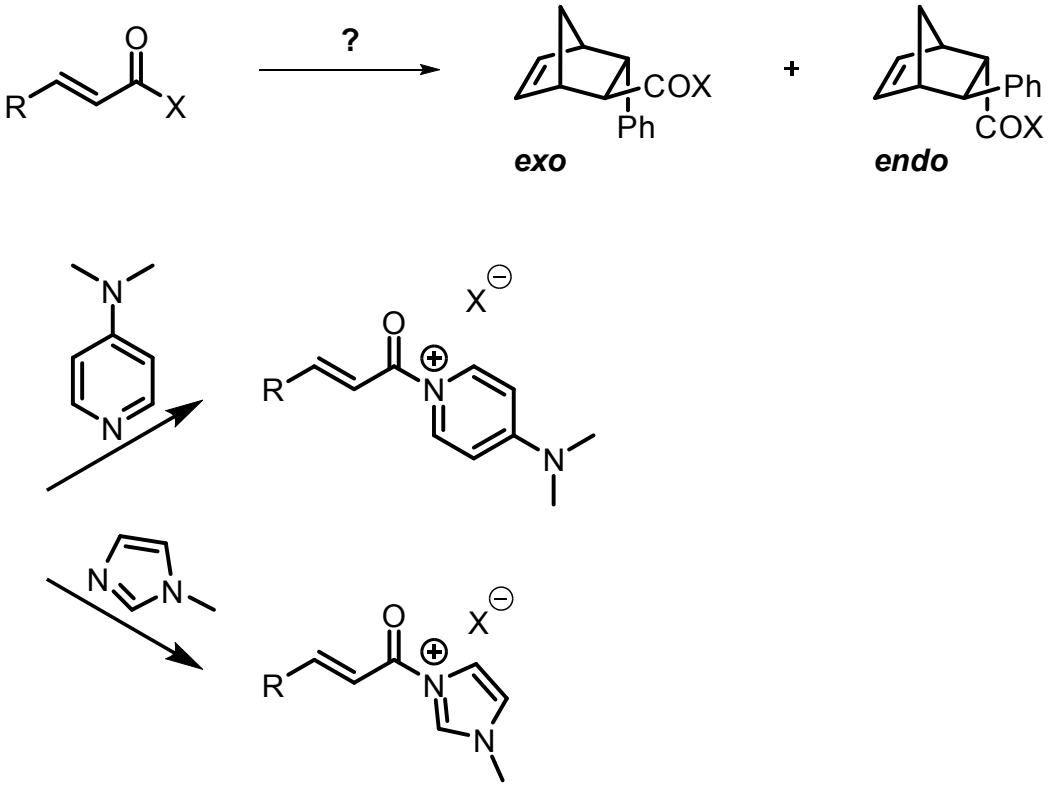


up to:
conversion 99%
endo/exo 1,0:1,3
93% ee

acids and acid derivatives??

W. Steglich, G. Höfle, *Angew. Chem. Int. Ed.* **1969**, *8*, 981-981.
C. E. Müller, L. Wanka, K. Jewell, P. R. Schreiner, *Angew. Chem. Int. Ed.* **2008**, *47*, 6180-6183.

acids and acid derivatives??



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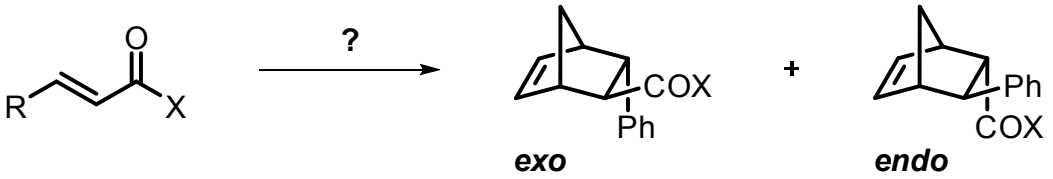

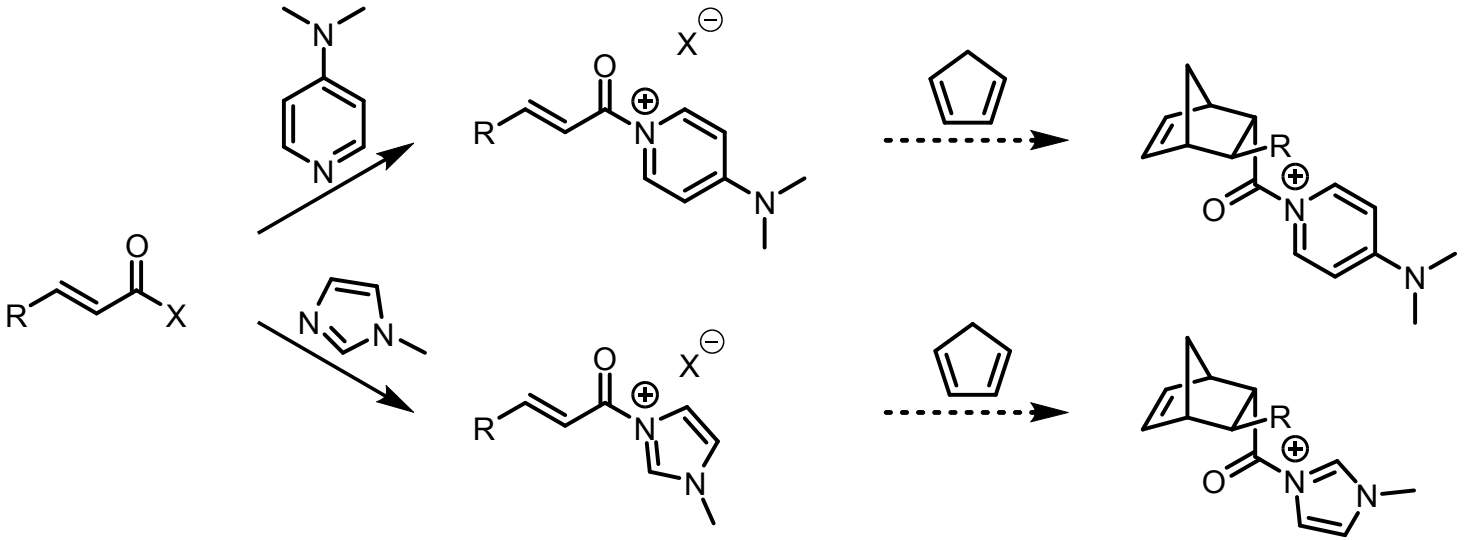

acylammonium salts
as activated dienophiles

W. Steglich, G. Höfle, *Angew. Chem. Int. Ed.* **1969**, *8*, 981-981.
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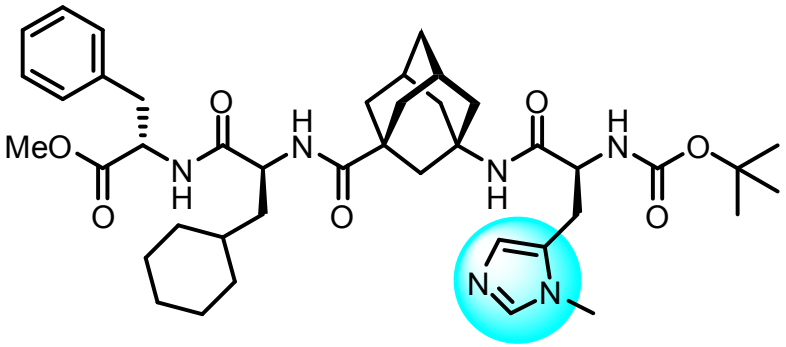
acids and acid derivatives??



W. Steglich, G. Höfle, *Angew. Chem. Int. Ed.* **1969**, *8*, 981-981.
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Organocatalysis

International Edition: DOI: 10.1002/anie.201602217
German Edition: DOI: 10.1002/ange.201602217

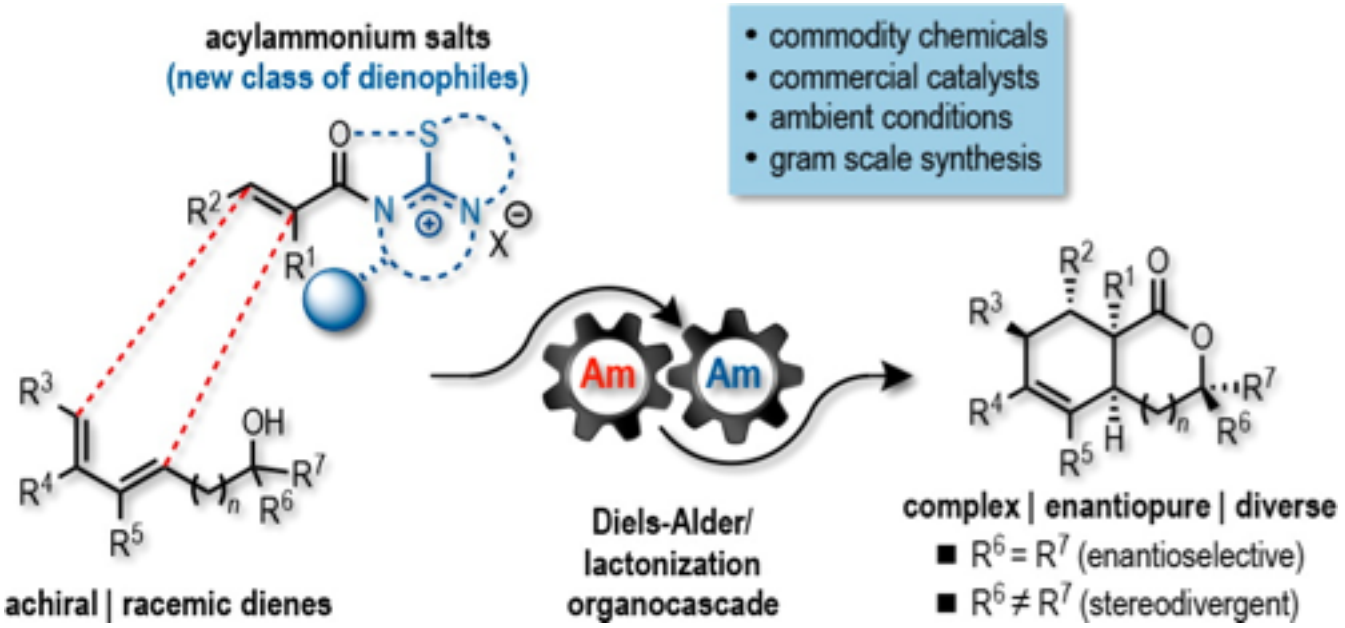
Asymmetric Organocatalysis: The Emerging Utility of α,β-Unsaturated Acylammonium Salts

*Sreekumar Vellalath and Daniel Romo**

alkaloids · enantioselectivity · cyclizations · Lewis bases · organocatalysis

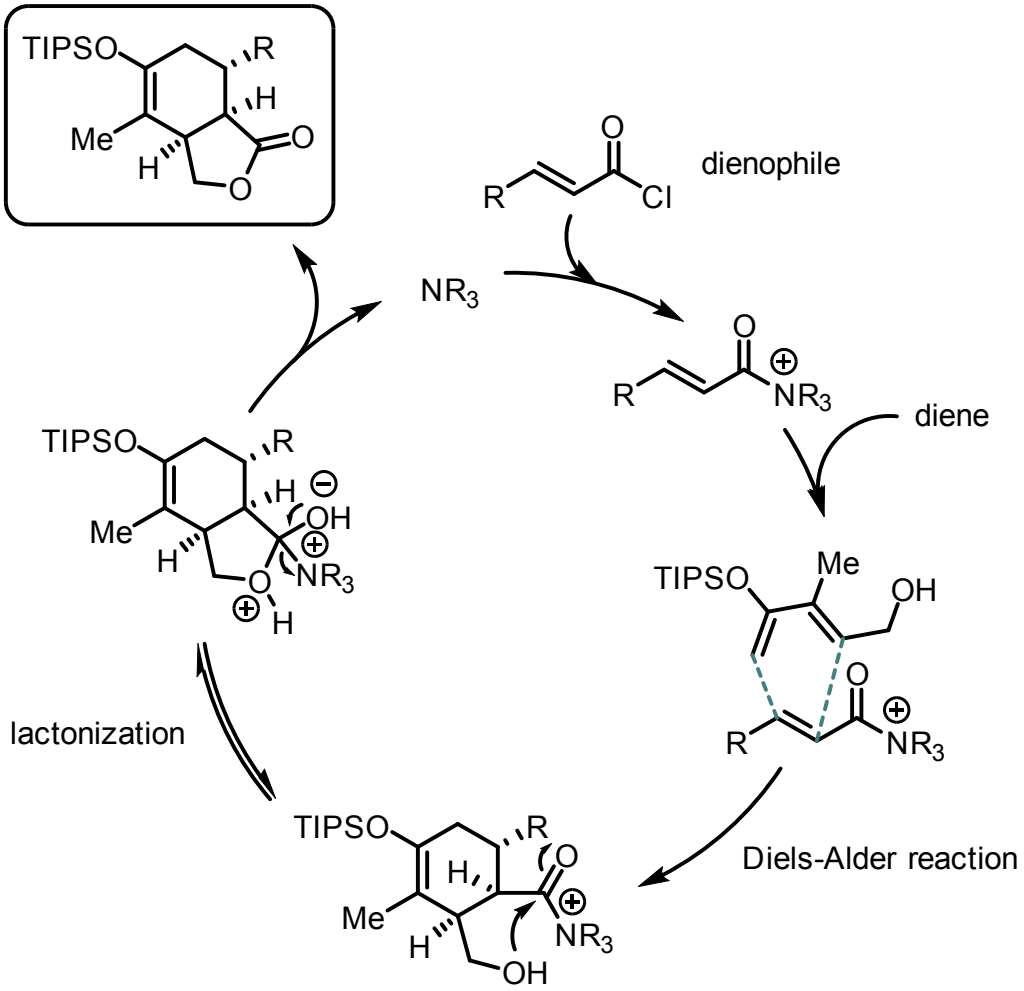
Although acylammonium salts are well-studied, chiral α,β-unsaturated acylammonium salts have received much less attention. While these intermediates are convenient synthons, which are readily available from several commodity unsaturated acids and acid chlorides, and possess three reactive sites, their application in organic synthesis has been limited because of the lack of appropriate chiral Lewis bases for their generation. In recent years, the utility of chiral, unsaturated acylammonium salts has expanded considerably, thus demonstrating the unique reactivity of this intermediate leading to the development of a diverse array of catalytic, asymmetric transformations including organocascade processes. This Minireview highlights the recent and growing interest in these intermediates which might spark further research into their untapped potential for asymmetric organocascade catalysis. A cursory comparison is made to related unsaturated iminium and acylazolium intermediates.

Romo‘s asymmetric Diels-Alder lactonization cascade

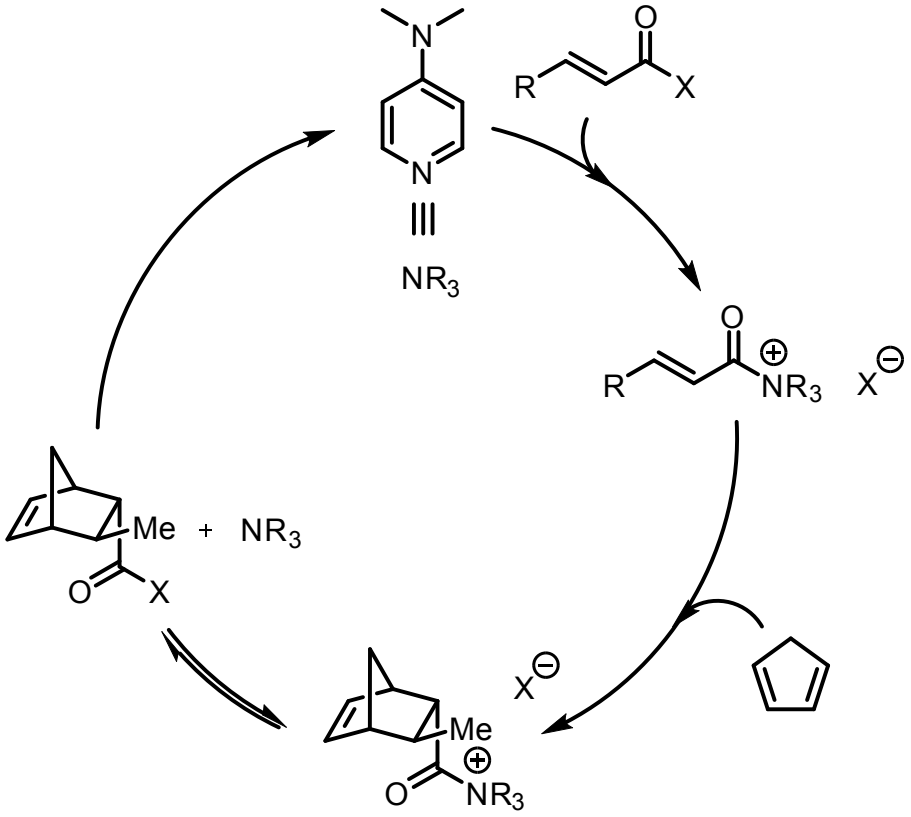


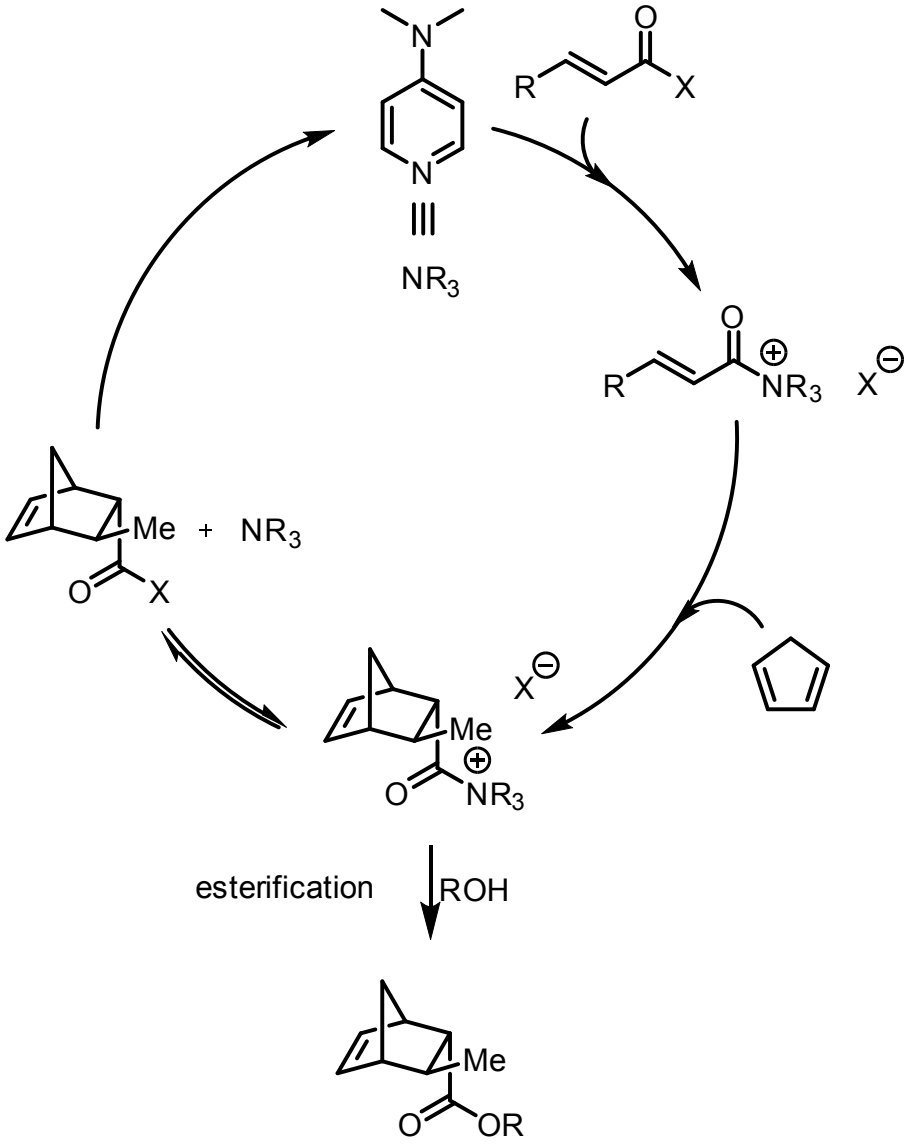
M. E. Abbasov, B. M. Hudson, D. J. Tantillo, D. Romo, *J. Am. Chem. Soc.* **2014**, *136*, 4492-4495.

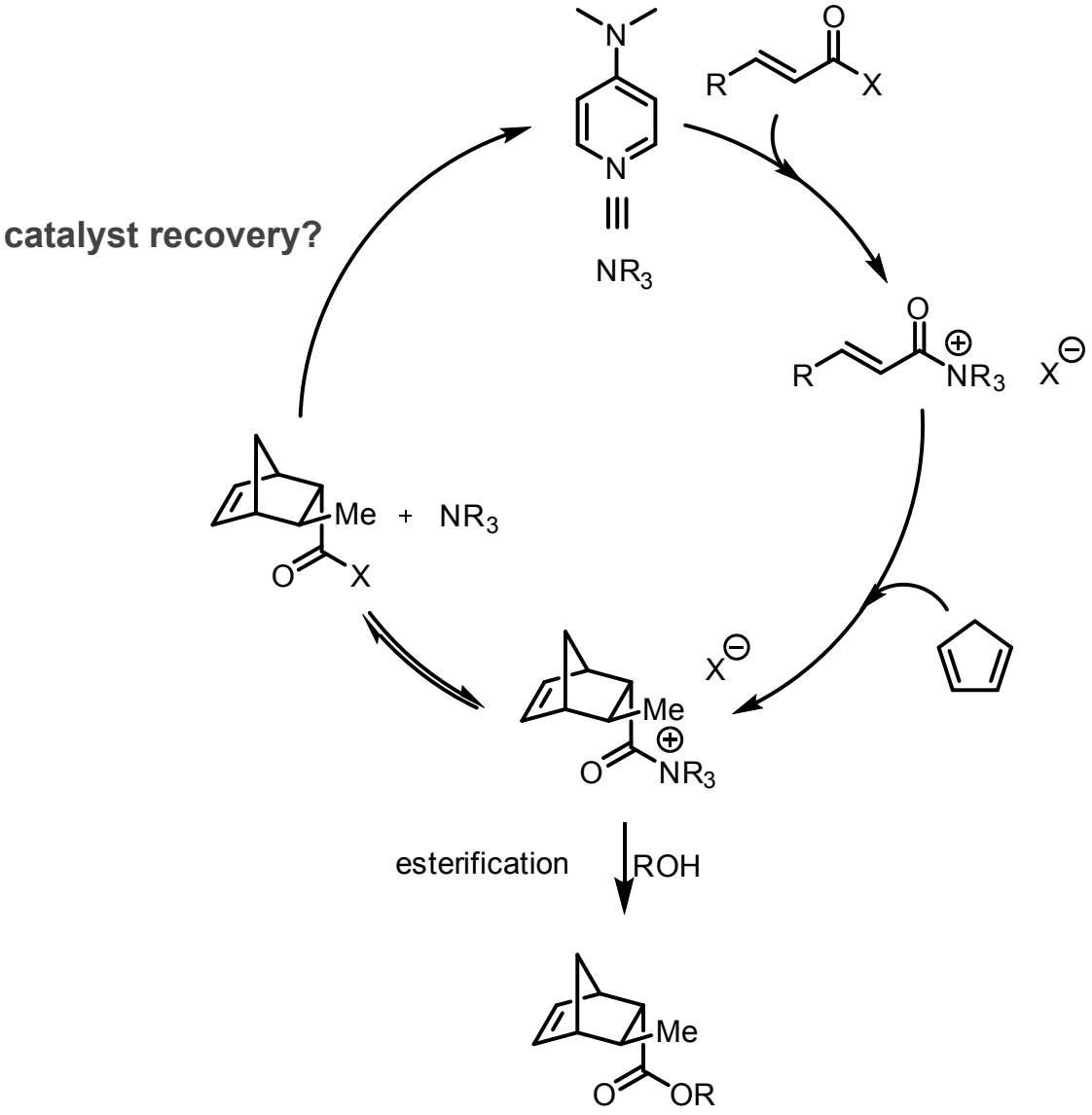
Mechanism of Romo‘s Diels-Alder lactonization cascade



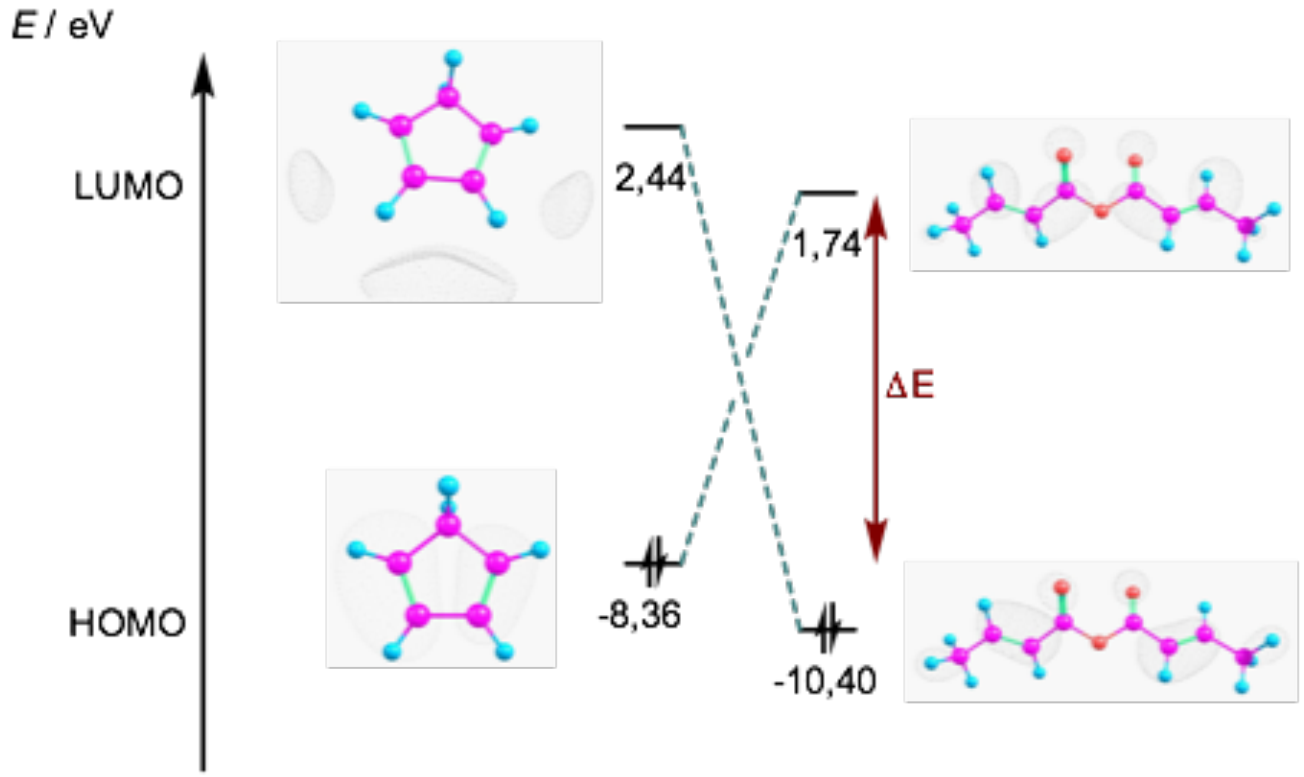
M. E. Abbasov, B. M. Hudson, D. J. Tantillo, D. Romo, *J. Am. Chem. Soc.* **2014**, *136*, 4492-4495.


N
N
NR3
O
R
X
O
R
NR3
X
Me + NR3
O
X
X
Me
O
NR3


N
N
NR3
O
R
X
O
R
NR3
X
Me
+
NR3
O
X
X
Me
O
NR3
esterification
ROH
Me
O
OR

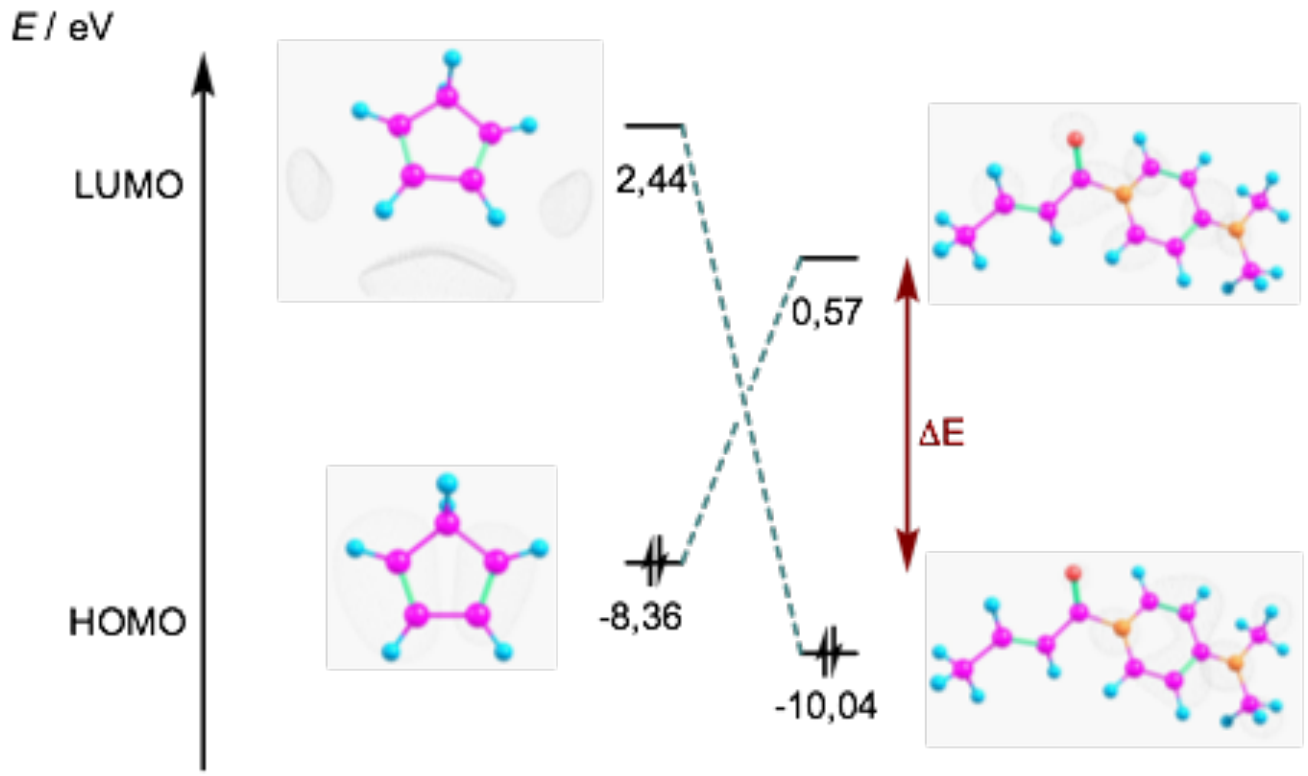

catalyst recovery?
N
N
NR3
O
R
X
O
R
NR3
X
Me
+
NR3
O
X
X
Me
O
NR3
esterification
ROH
Me
O
OR

HOMO-LUMO gap

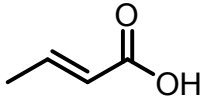


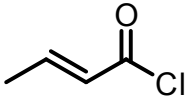
B3LYP/6-31+G**//MP2/6-31+G**

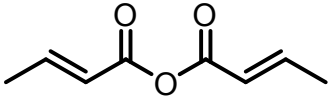
HOMO-LUMO gap



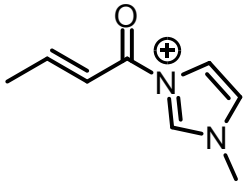
B3LYP/6-31+G**//MP2/6-31+G**

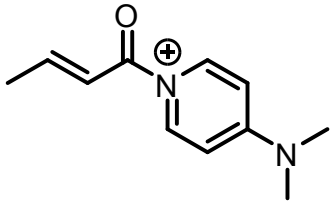


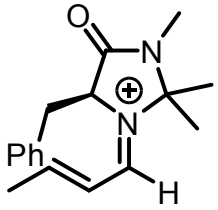




LUMO / eV	2,06	1,63	1,74

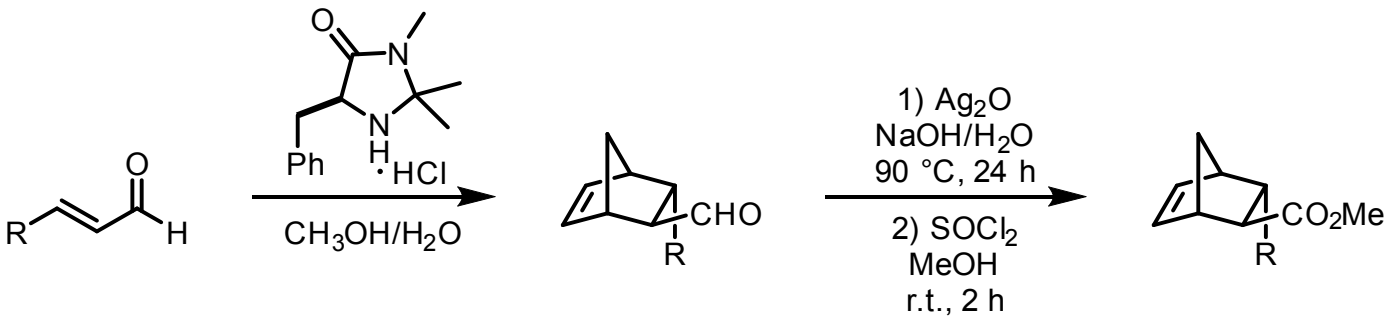






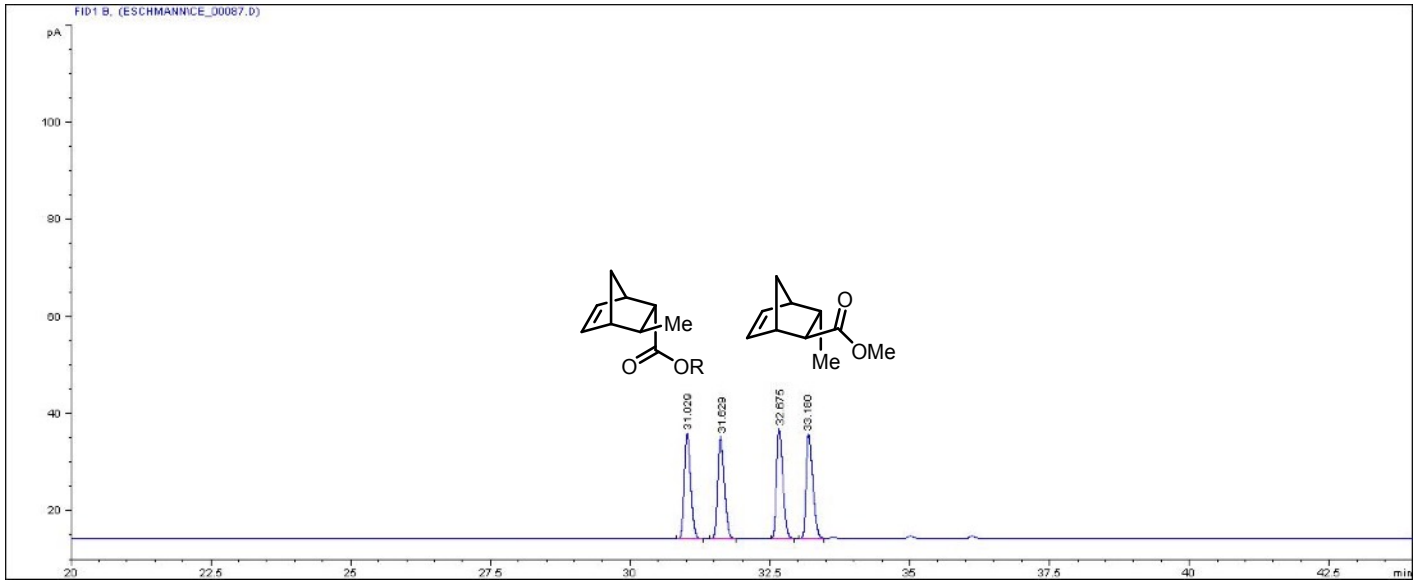
LUMO / eV	0,70	0,57	0,41

B3LYP/6-31+G**//MP2/6-31+G**

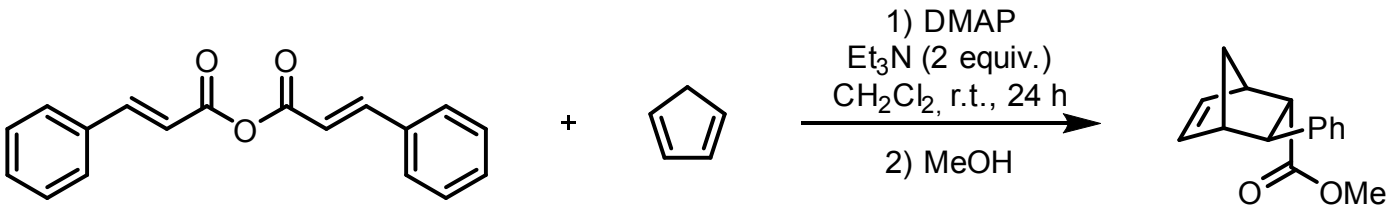


R = Ph 89% (*endo/exo* 1,0:1,3)
Me 60% (*endo/exo* 1,0:1,1)

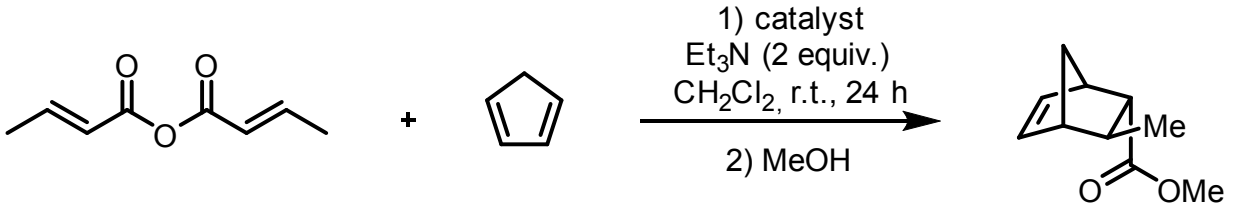
R = Ph 48%
Me 22%



K. A. Ahrendt, C. J. Borths, D. W. C. MacMillan, *J. Am. Chem. Soc.* **2000**, *122*, 4243-4244.
M. Hatano, T. Mizuno, A. Izumiseki, R. Usami, T. Asai, M. Akakura, K. Ishihara, *Angew. Chem. Int. Ed.* **2011**, *50*, 12189-12192.

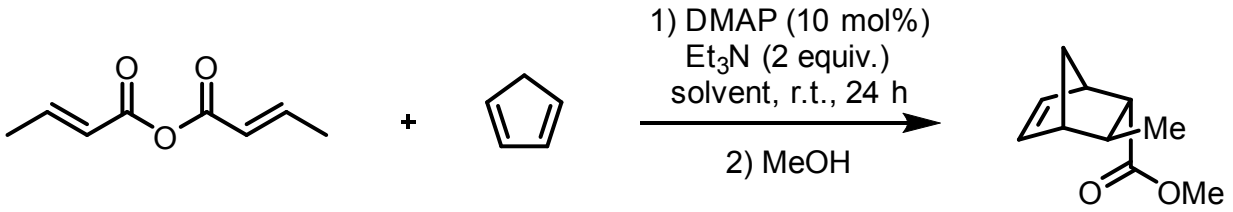


DMAP
10 mol%: 0% conversion
100 mol%: 0% conversion



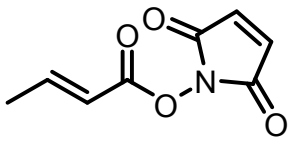
catalyst	mol%	conversion[a]	*endo/exo*
-	-	0%	-
DMAP	10	22%	1,0:1,6
DMAP	100	traces	-
NMI	10	19%	1,0:1,6
NMI	100	32%	1,0:1,8

a: determined *via* chiral GC with undecan as internal standard

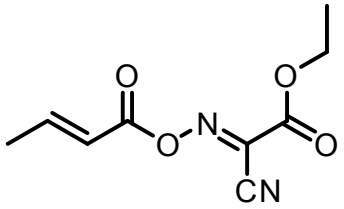


solvent	conversion[a]	*endo*/*exo*
neat	31%[b]	1,0:1,8
dichloromethane	22%	1,0:1,6
toluene	26%	1,0:1,6
chloroform	6%	1,0:1,8

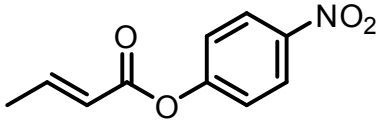
a: determined *via* chiral GC with undecan as internal standard
b: isolated yield



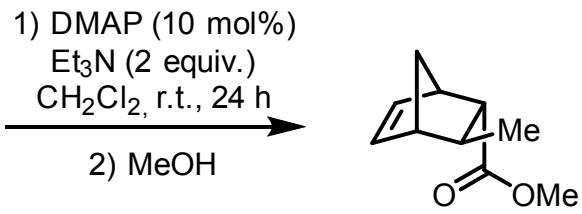
1



2

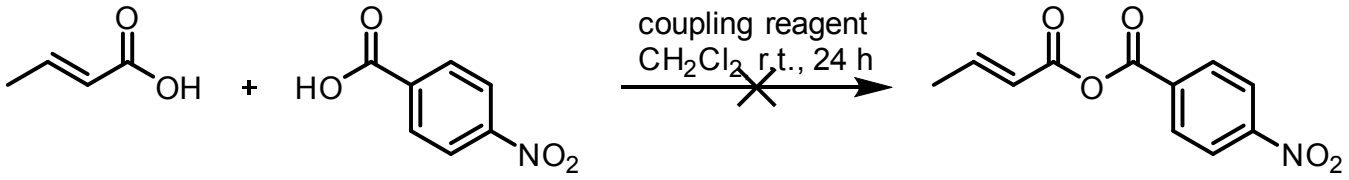


3

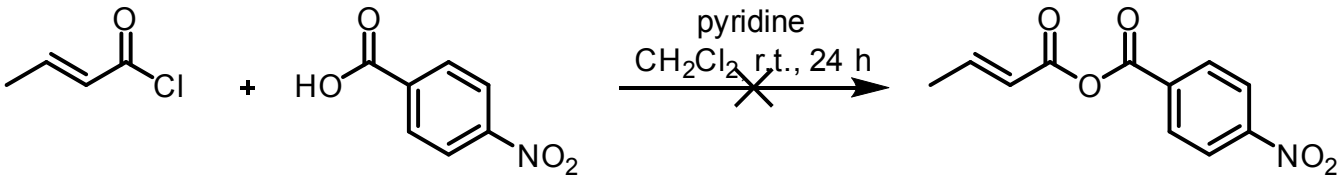


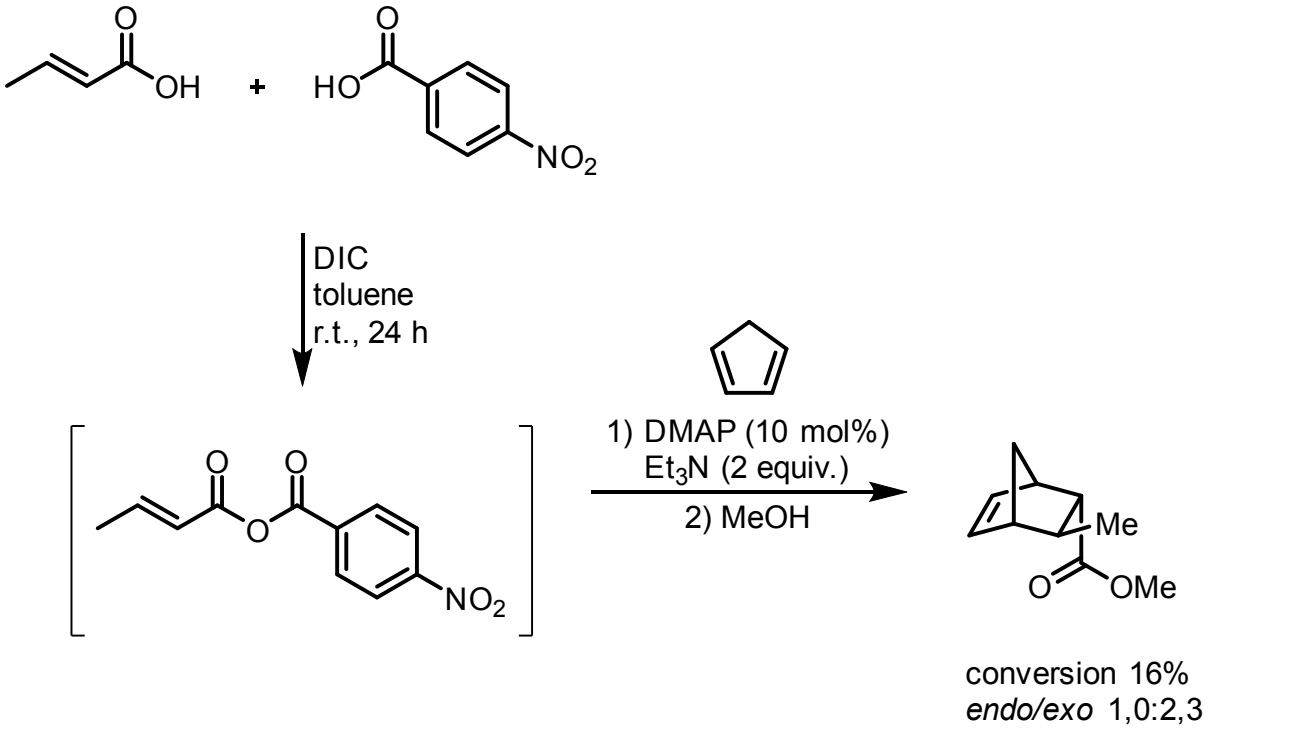
substrate	conversion[a]	*endo/exo*
1	<1%	2,1:1
2	0%	-
3	<1%	1,6:1

a: determined *via* chiral GC with undecan as internal standard

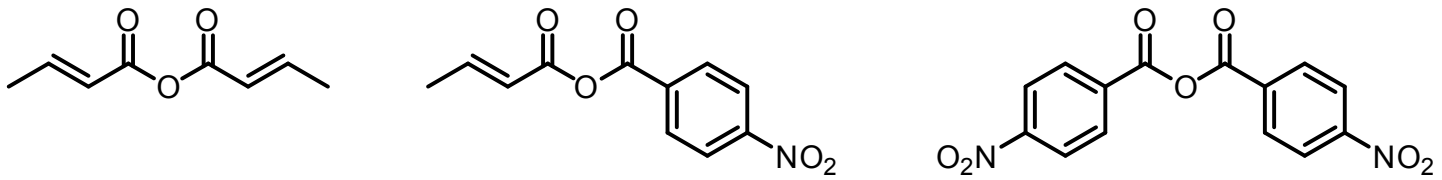


coupling reagent: DIC, EDC·HCl

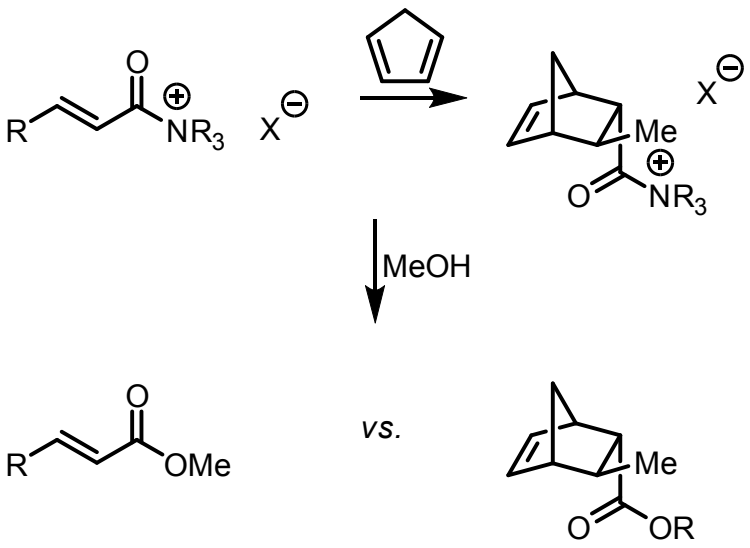


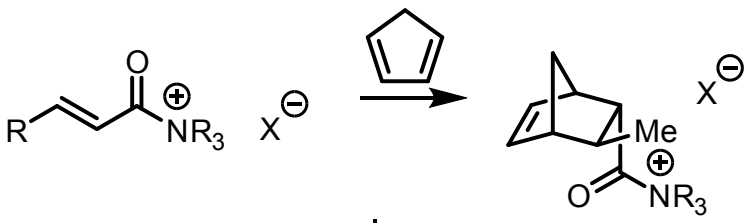

DIC
toluene
r.t., 24 h
1) DMAP (10 mol%)
Et3N (2 equiv.)
2) MeOH
Me
OMe
conversion 16%
endo/exo 1,0:2,3

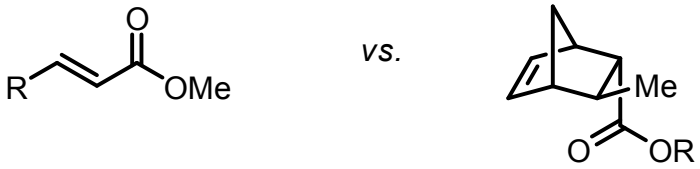
ratio?

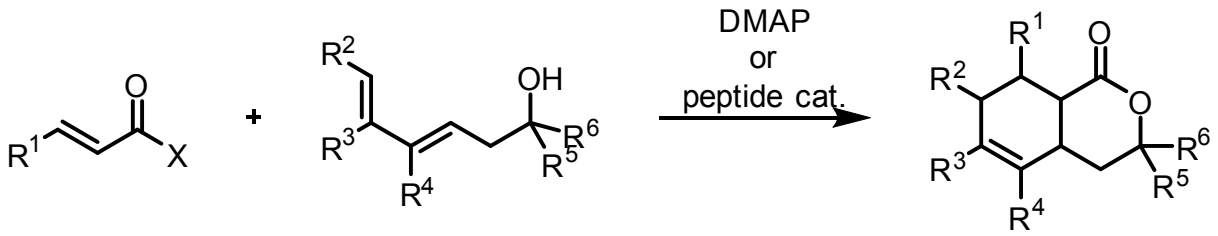


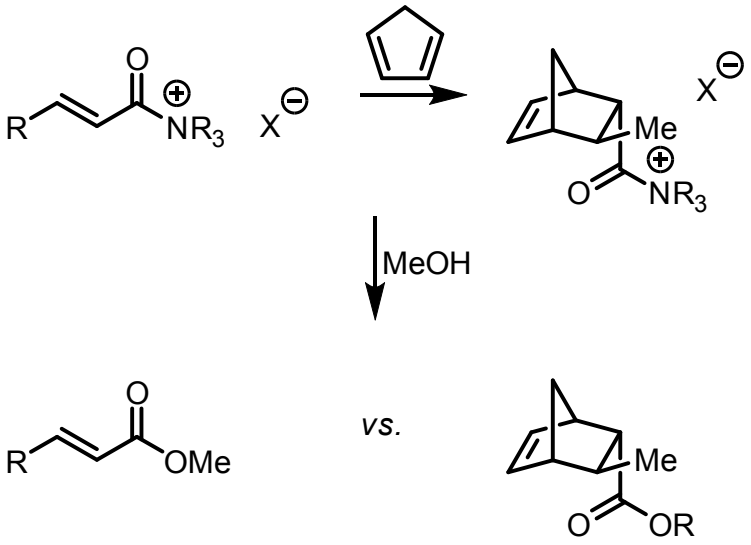
Outlook – Catalyst Recovery?

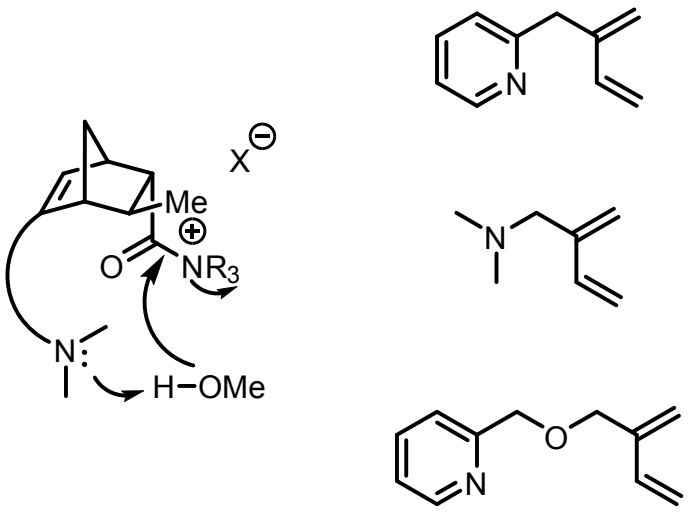



O
R
NR3
X
Me
O
NR3
X
MeOH

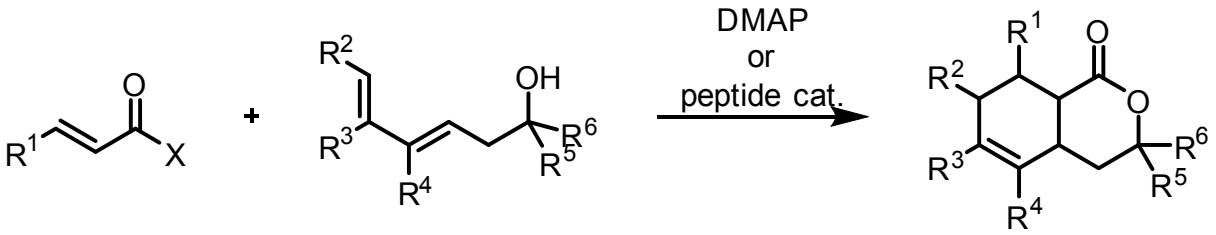

O
R
OMe
vs.
Me
O
OR


O
R1
X
+
R2
OH
R3
R6
R5
R4
DMAP
or
peptide cat.
R1
O
R2
O
R6
R3
R5
R4

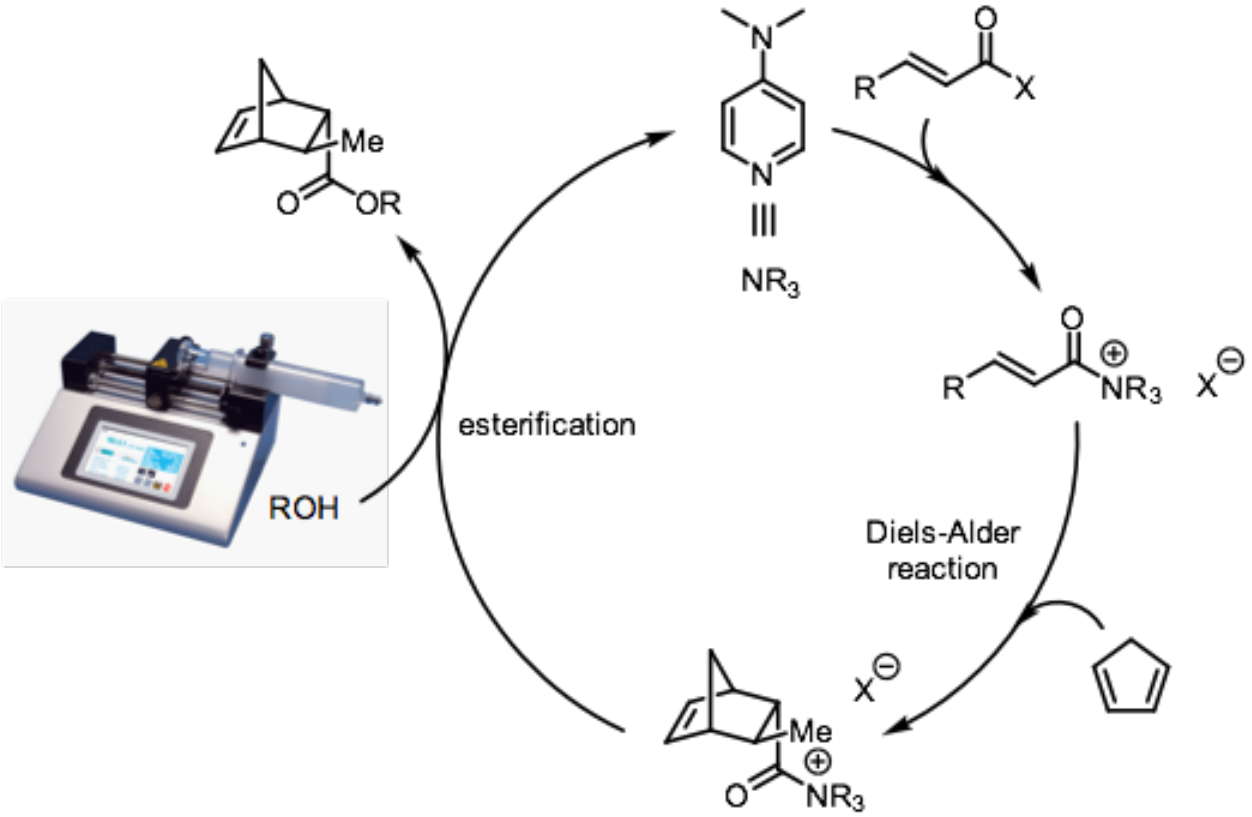


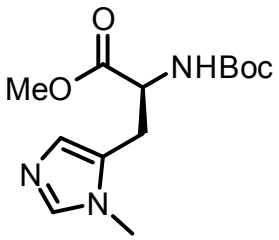


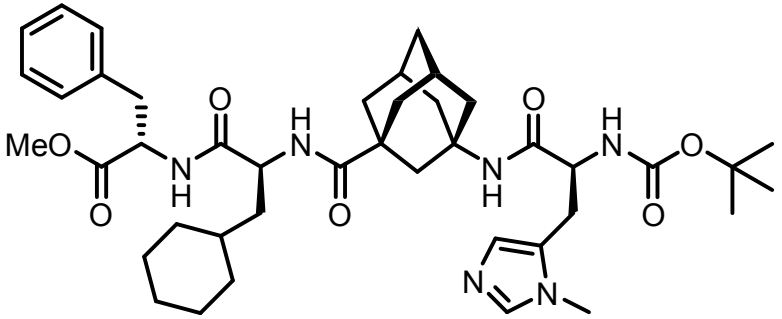
enhance hydrolysis of product



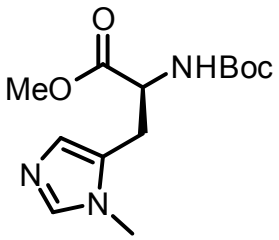
continuous addition of reactants over time (syringe pump)

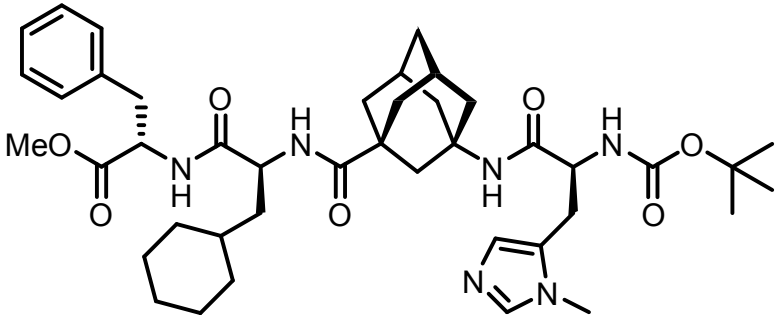




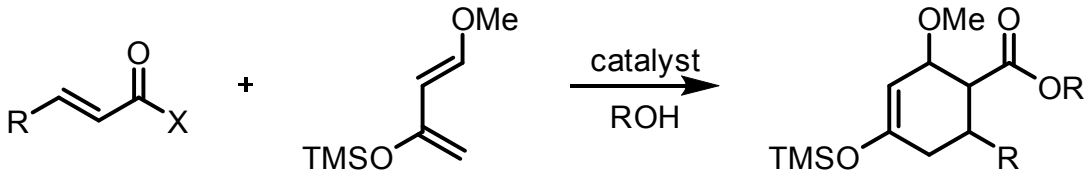


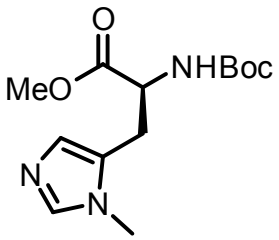
S. Danishefsky, T. Kithara, *J. Am. Chem. Soc.* **1974**, *96*, 7807-7808

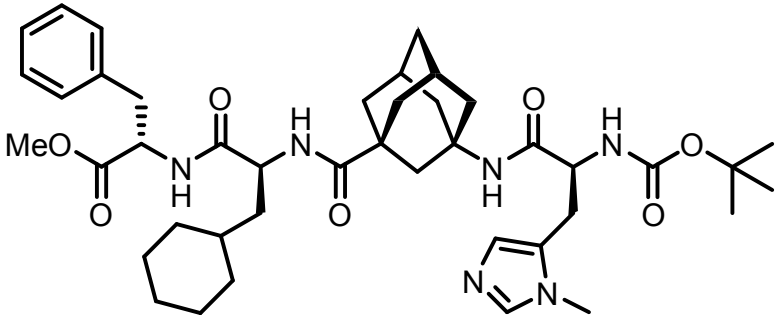




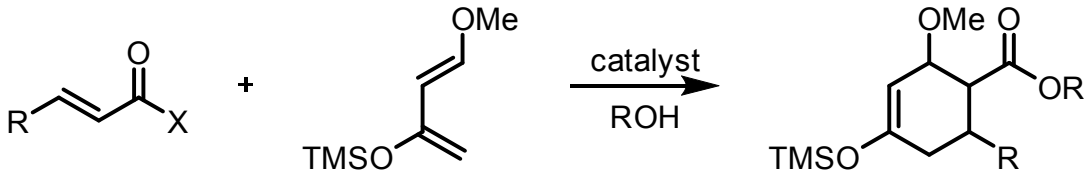
Danishefsky diene



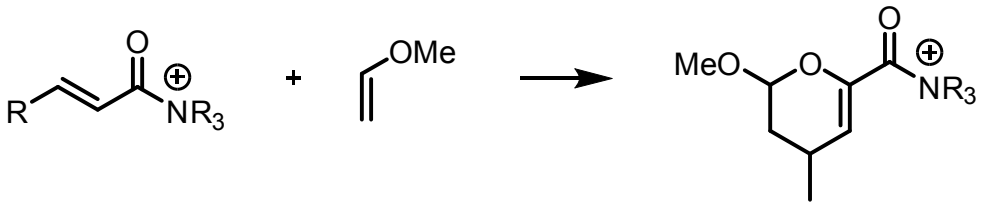




Danishefsky diene

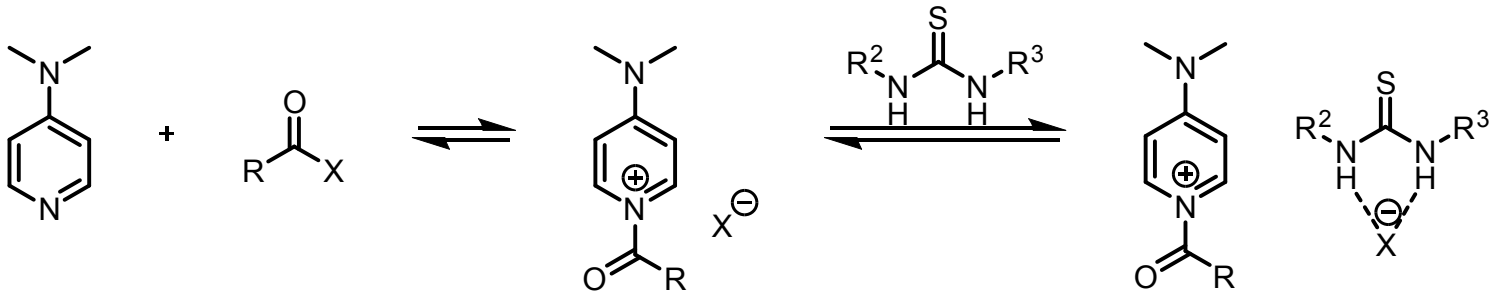


Inverse electron demand (Hetero-Diels-Alder reaction)



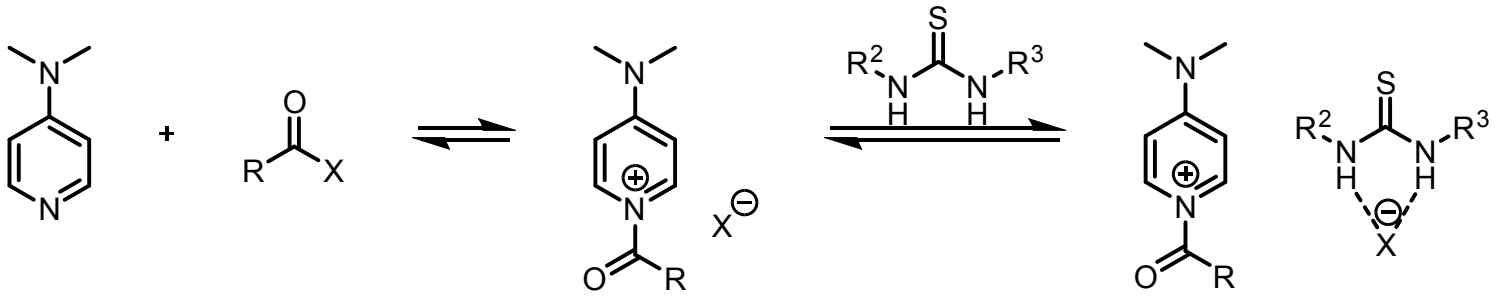
$LUMO_{diene}$ $HOMO_{dienophile}$

S. Danishefsky, T. Kithara, *J. Am. Chem. Soc.* **1974**, *96*, 7807-7808

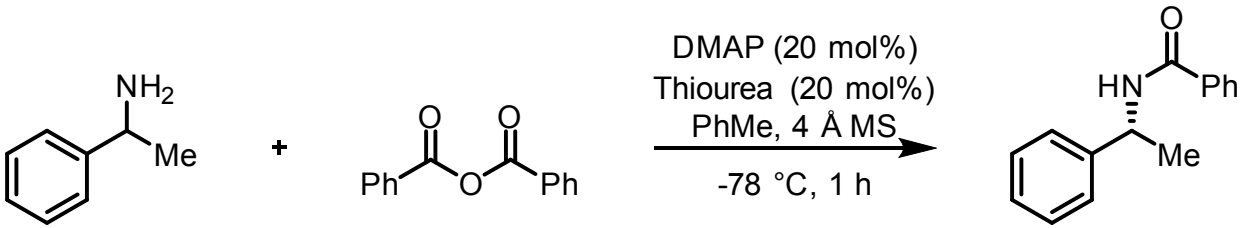


achiral *chiral*

D. Seidel, *Synlett* **2014**, *25*, 783-794.
Z. G. Zhang, P. R. Schreiner, *Chem. Soc. Rev.* **2009**, *38*, 1187-1198.

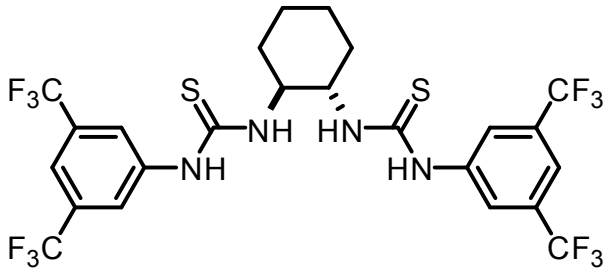


achiral *chiral*

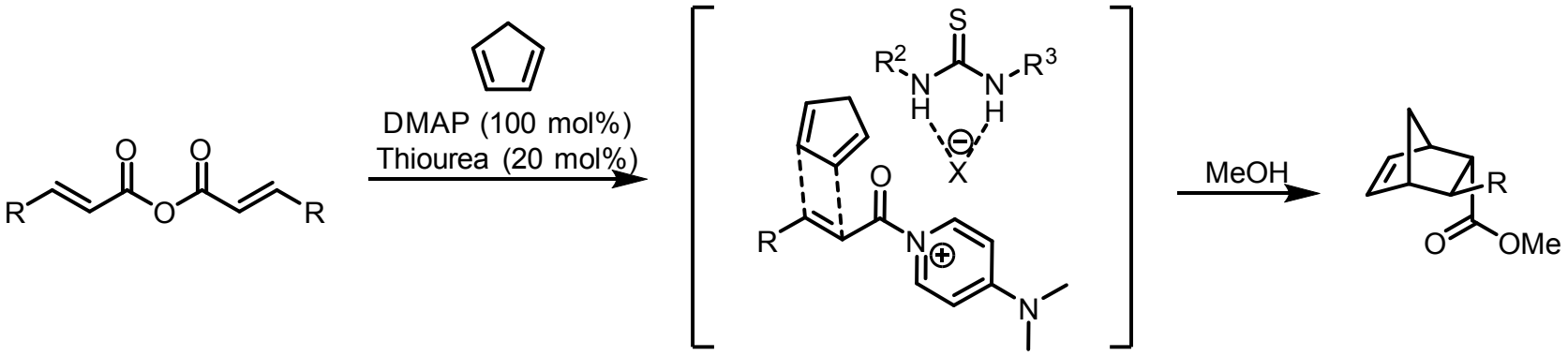


conversion 45%
s-factor 10

Thiourea:



D. Seidel, *Synlett* **2014**, *25*, 783-794.
Z. G. Zhang, P. R. Schreiner, *Chem. Soc. Rev.* **2009**, *38*, 1187-1198.



D. Seidel, *Synlett* **2014**, *25*, 783-794.
Z. G. Zhang, P. R. Schreiner, *Chem. Soc. Rev.* **2009**, *38*, 1187-1198.

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Alex, Raffi
PRS Group