Enantioselectively Organocatalytic Michael Reactions and Tandem Reactions

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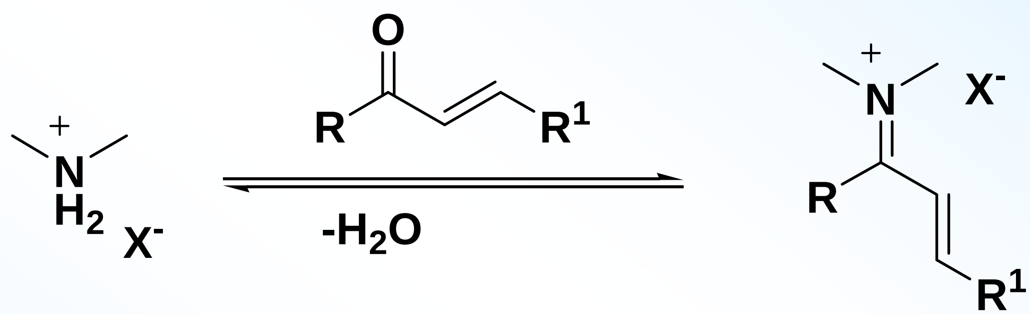
Contents

1. The synthesis of the newly designed pyrrolidine-urea(thiourea) catalysts

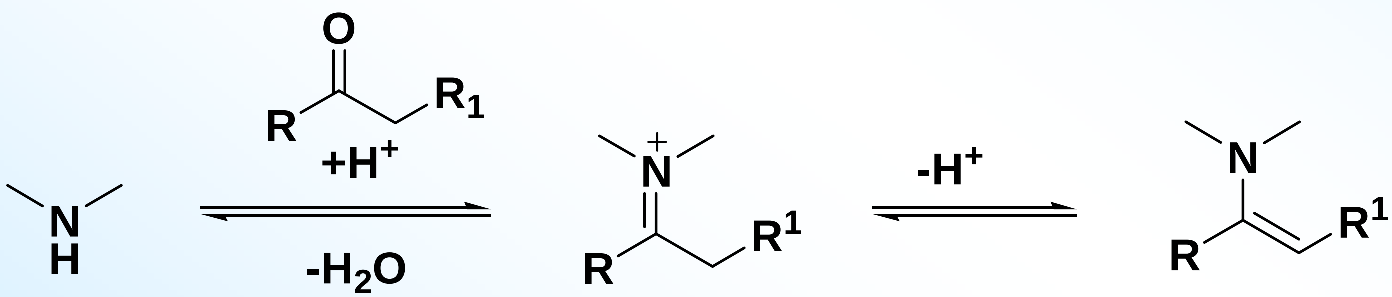
2. Michael addition of cyclic ketones to
   - nitroolefins
   - alkylidene malonates

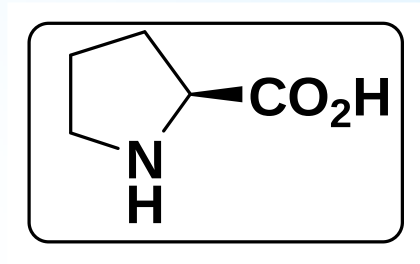
3. Tandem reactions
   - Michael/Aldol reaction
   - Michael/Elemination/Michael reaction

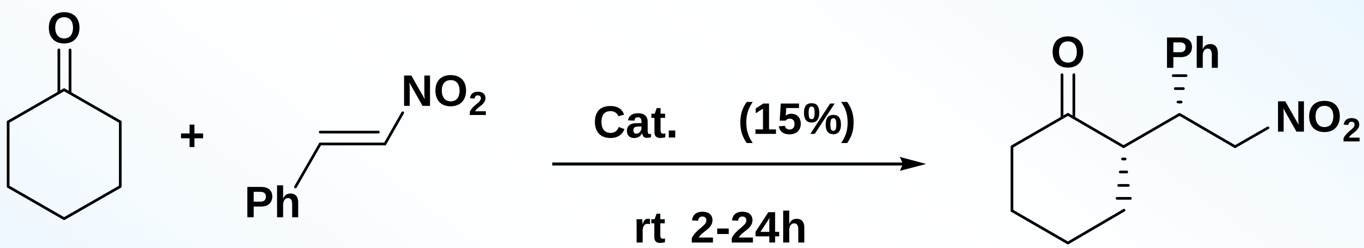
Iminium catalysis



Enamine catalysis

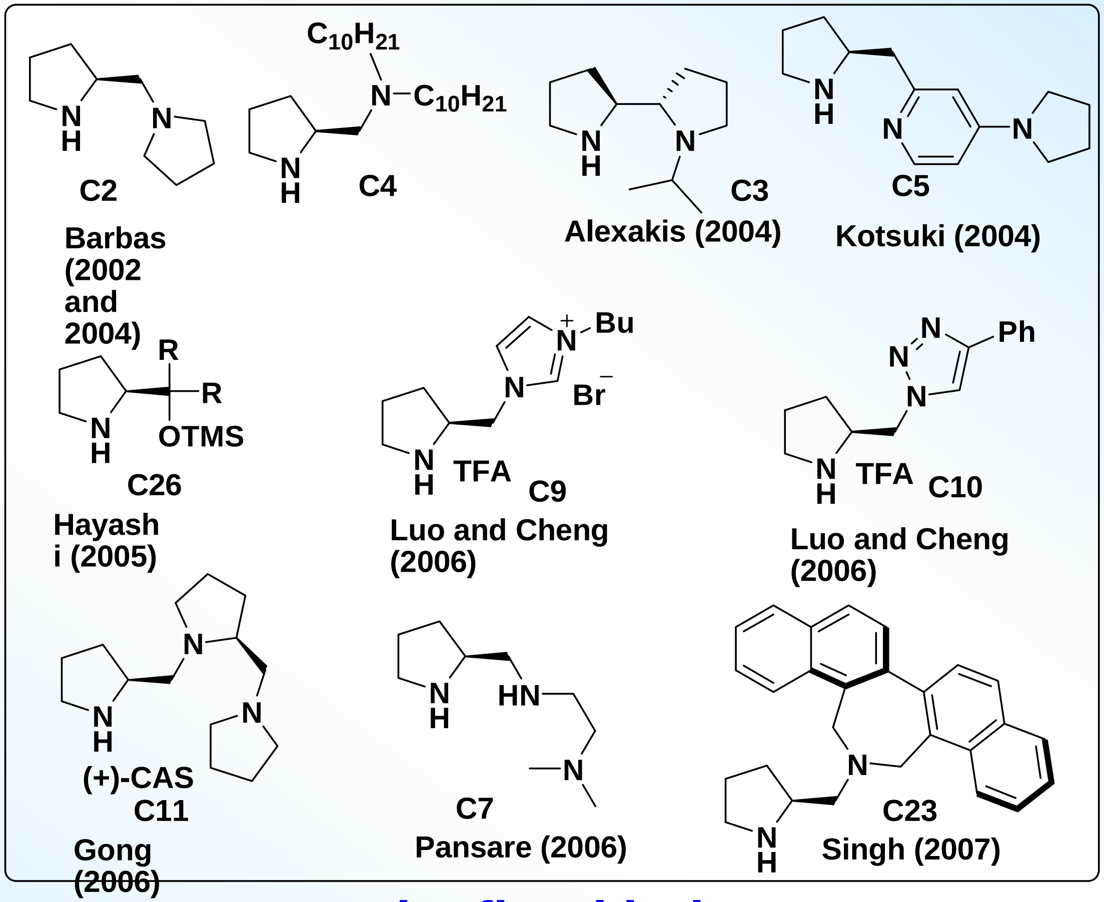


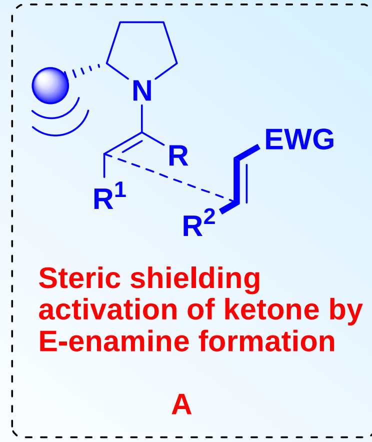




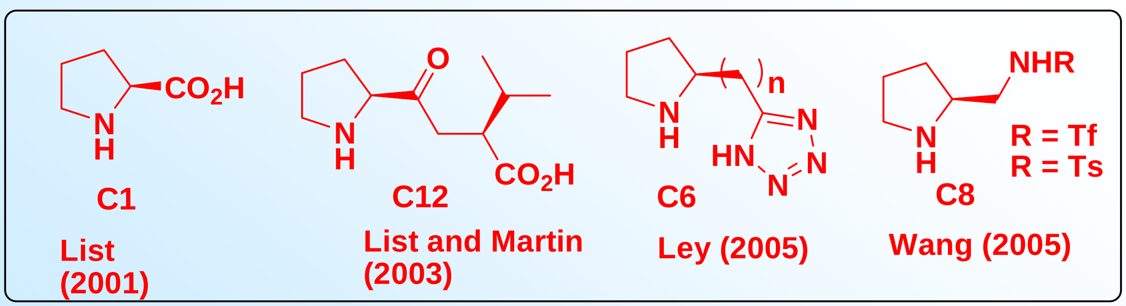
DMSO, 94% yield, de>90%, 23% ee

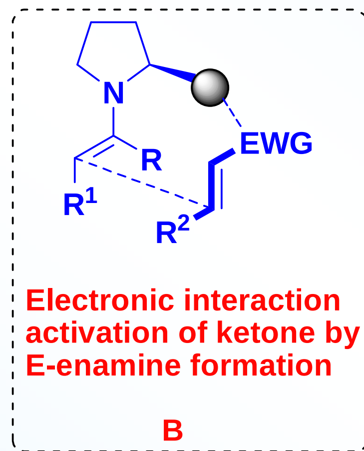
List, B. *Org. Lett.* 2001, *3*, 2324



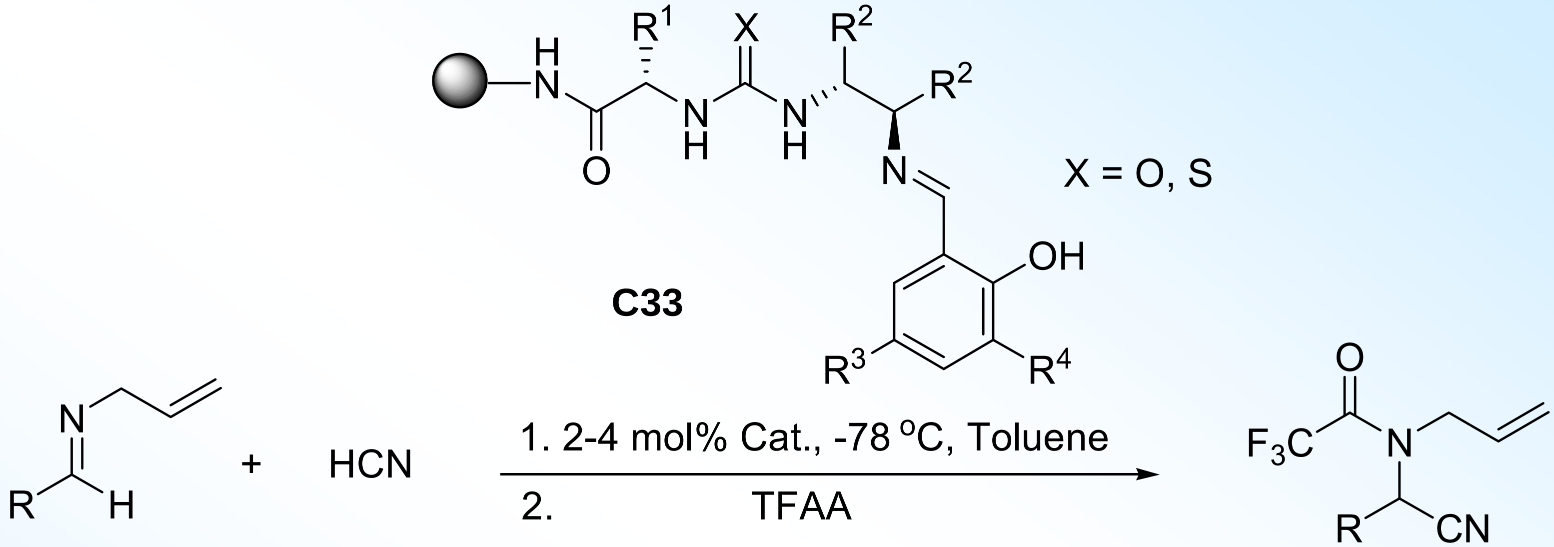


The first kind



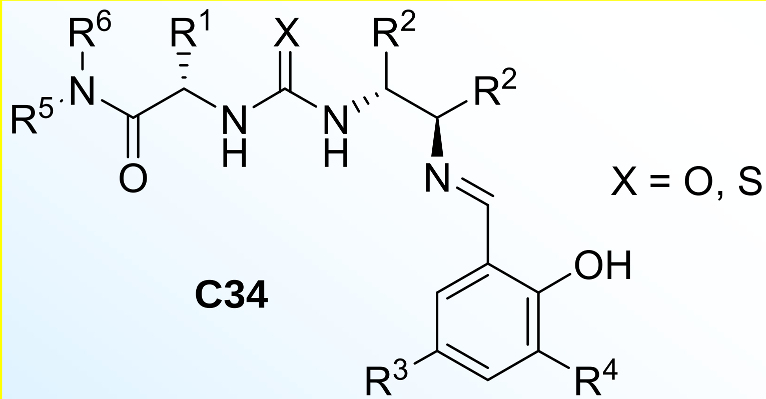


The second kind



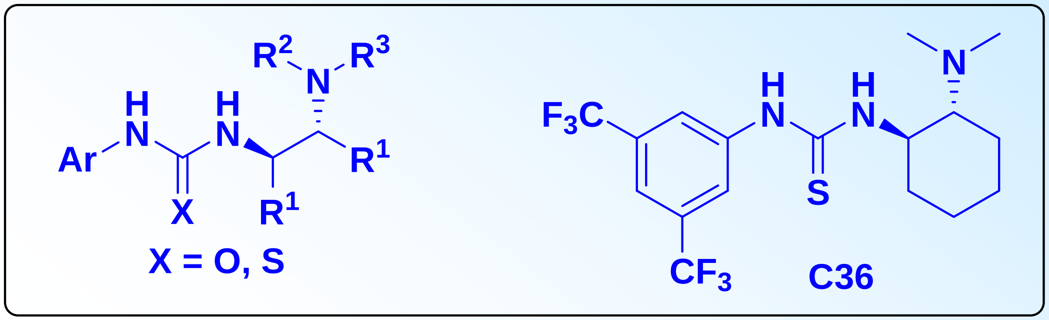
up to 91% ee
65-92% yield

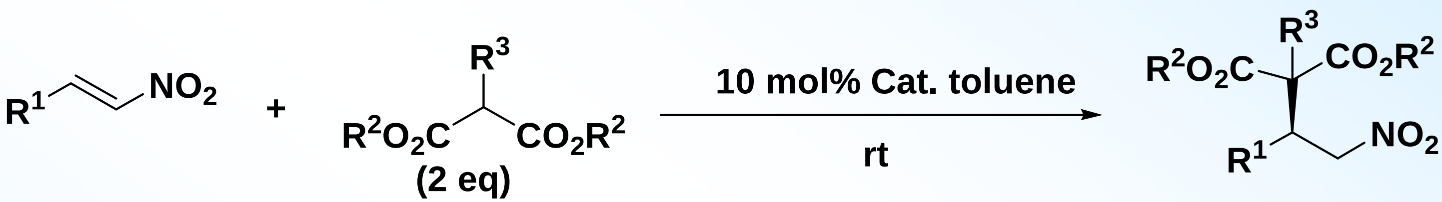
Jacobsen, E. N.et al. *J.Am.Chem. Soc.* **1998**, *120*, 491



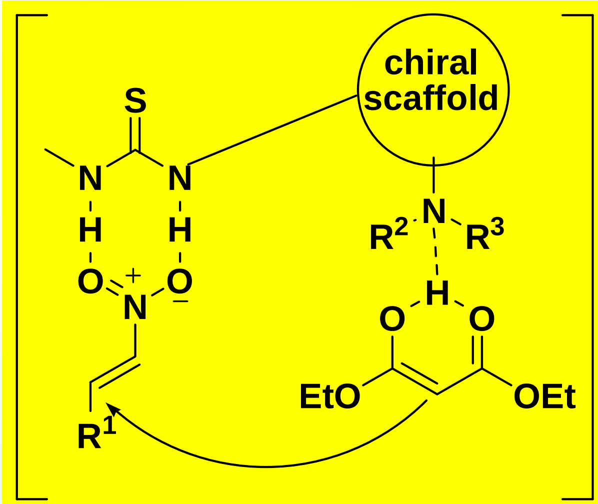
C34

Strecker reaction, Mannich reaction,
Pictet-Spengler reaction et al.





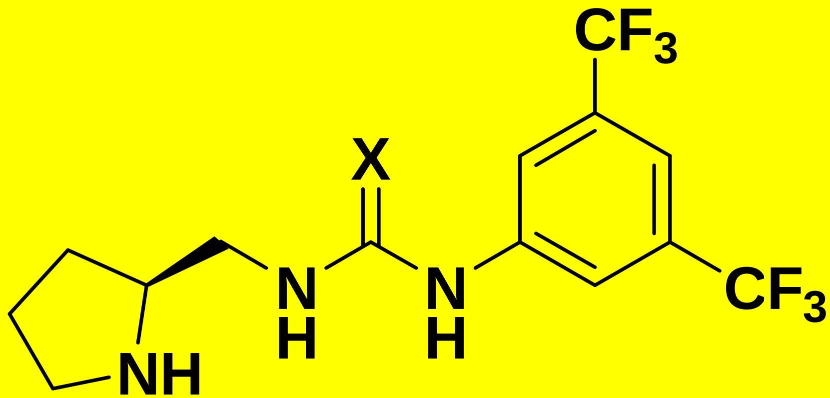
up to 93% ee
74-95% yield



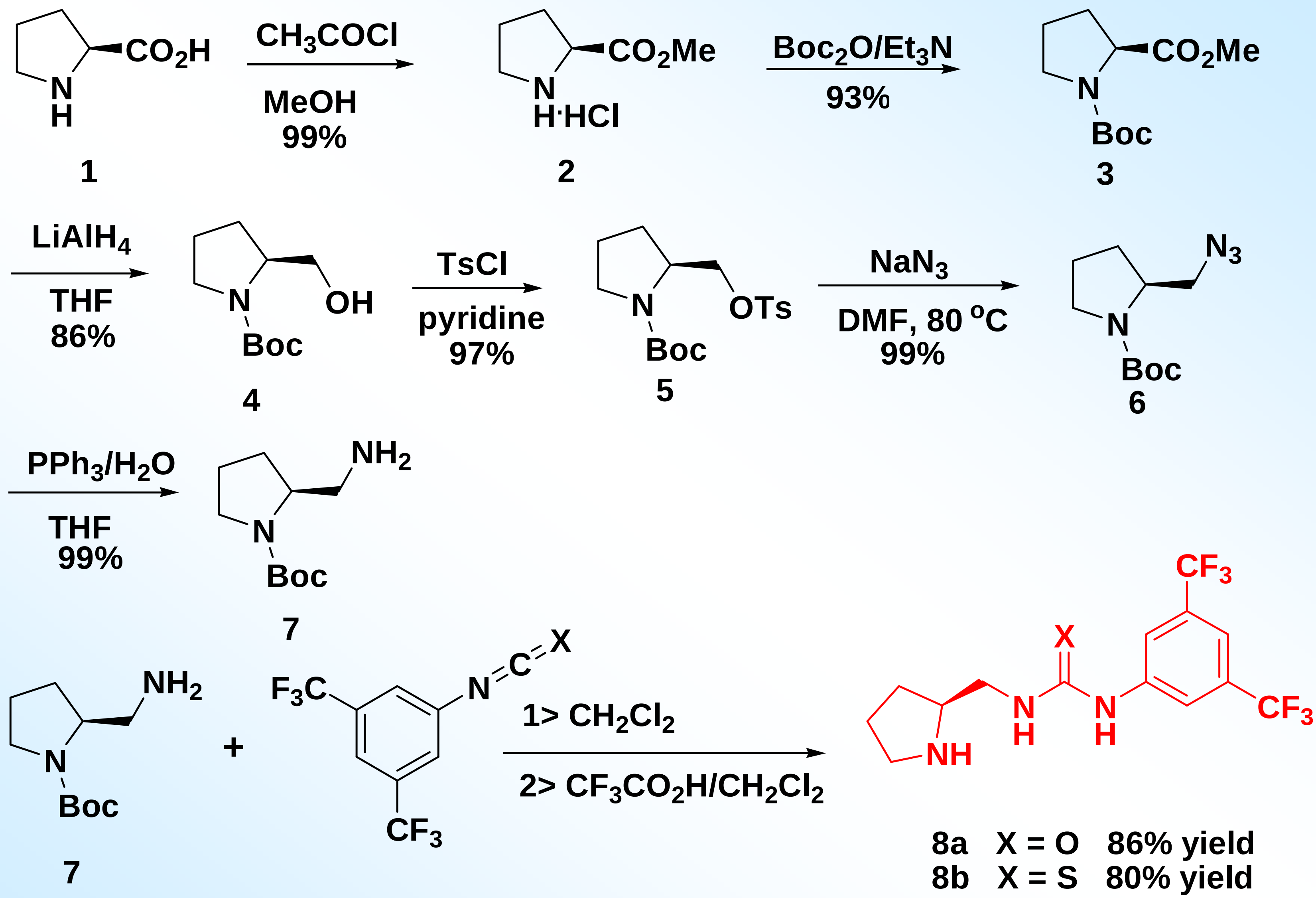
double activation

Takemoto, Y. et al. *J. Am. Chem. Soc.* **2003**, *125*, 12672

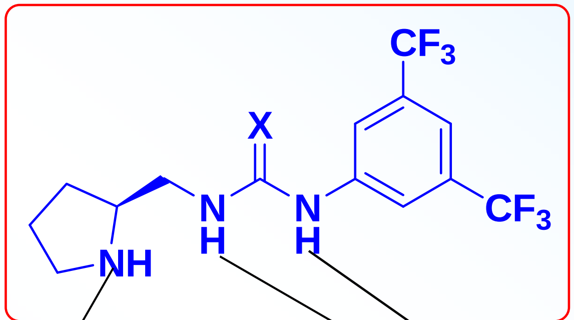
The newly designed catalysts:



8a X = O
8b X = S


CO2H
CH3COCl
MeOH
99%
CO2Me
H·HCl
Boc2O/Et3N
93%
CO2Me
N
Boc
1
2
3
LiAlH4
THF
86%
OH
Boc
4
TsCl
pyridine
97%
OTs
Boc
5
NaN3
DMF, 80 °C
99%
N3
Boc
6
PPh3/H2O
THF
99%
NH2
Boc
7
NH2
Boc
7
+
F3C
CF3
N=C=X
1> CH2Cl2
2> CF3CO2H/CH2Cl2
X
NH
CF3
CF3
8a X = O 86% yield
8b X = S 80% yield

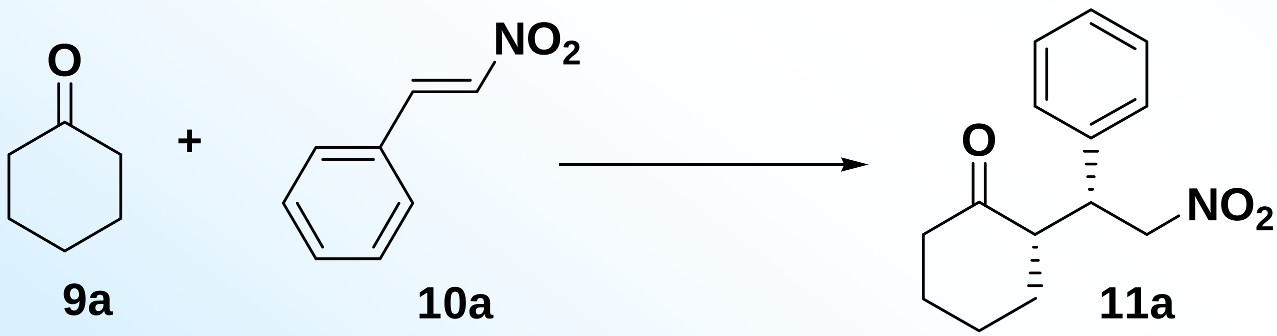
2. Enantioselective Michael Addition of Cyclic Ketones to Nitroolefins



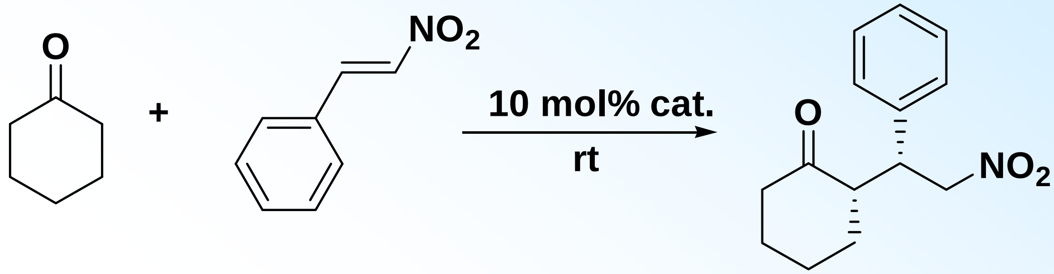
8a X = O
8b X = S

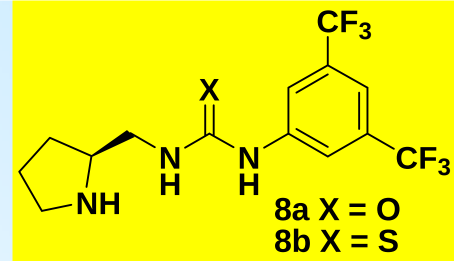
can form enamine with ketones

active nitro and carbonyl groups

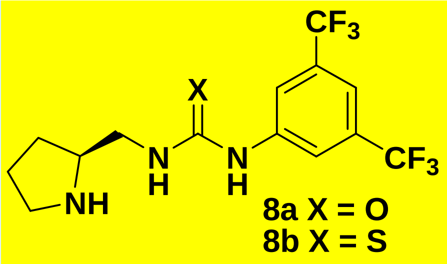


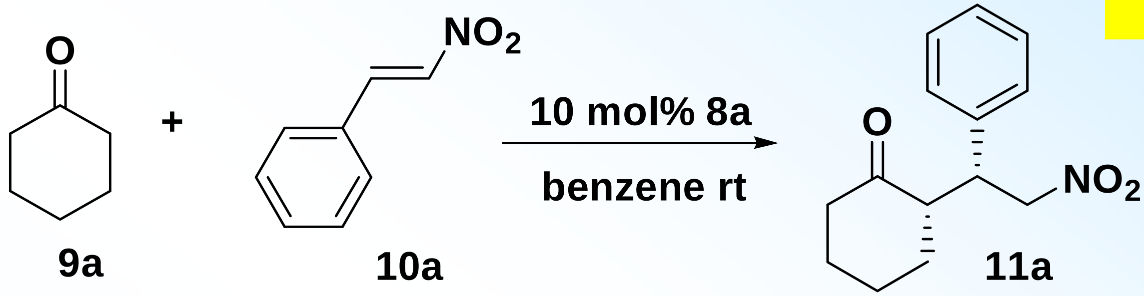
Effects of Solvents





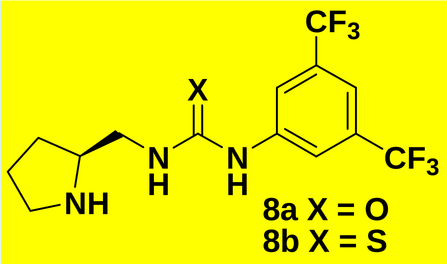
Entry	Cat	Solvent	Time (d)	Conv. (%)	Syn/anti	Ee (%)
1	8a	MeOH	6	trace	-	-
2	8a	*i*-PrOH	4	trace	-	-
3	8a	THF	6	trace	-	-
4	8a	CH_2Cl_2	5	25	-	76
5	8a	DCE	8	27	84/16	79
6	8a	Toluene	4	33	91/9	82
7	8b	Toluene	4	36	87/13	84
8	8a	Benzene	4	56	92/8	84
9	8b	BTF	4	24	-	82
10	8b	PhCl	4	17	-	86

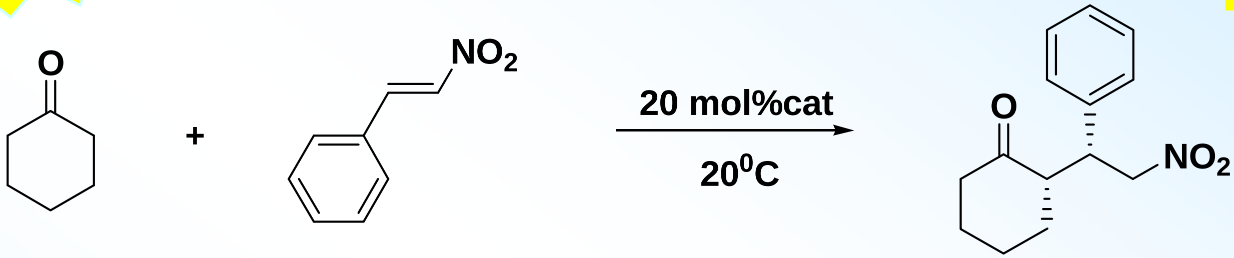




Entry	1	2	3	4
Time (days)	1	2	3	4
Conv.(%)	45	45	45	45 (84%ee)

Why?

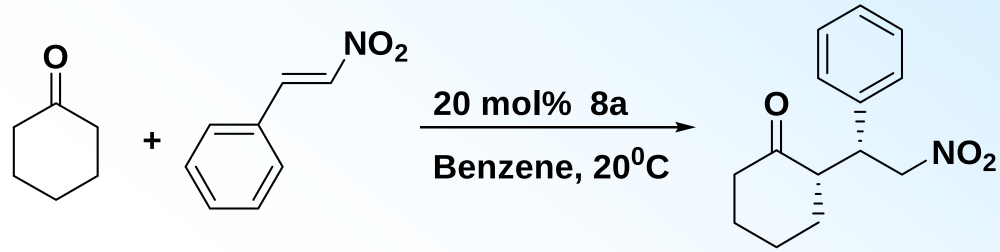


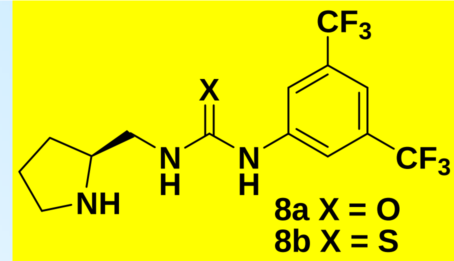


Entry	Cat	Solvent	Time (d)	Conv. (%)	Cis/trans	Ee (%)
1	8a	Benzene	2	68	92/8	67
2[a]	8a	Benzene	1	>99	93/7	81

[a] Commercial available cyclohexanone

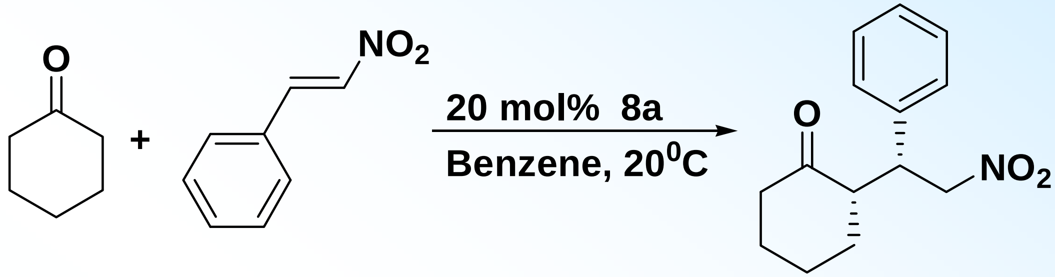
Additive

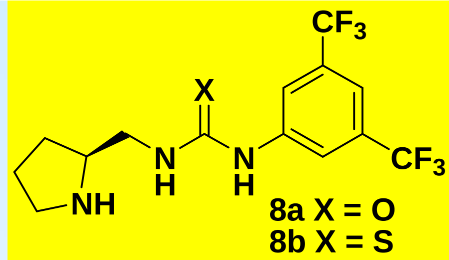




Entry	Additive (mol%)	Time (d)	Conv. (%)	Syn/anti	Ee (%)
1	$(CH_2)_5CHOH$ (20)	2	53	83/17	80
2	PhOH (20)	2	43	80/20	75
3	HFIP (10eq)	4	16	-	-
4	HCl (20)	3.5	trace	-	-
5	TsOH (20)	8	trace	-	-
6	CF_3COOH (10)	1	41	-	70
7	PhCOOH (10)	1	100	90/10	68
8	PhCOOH (20)	1	100 (94)	89/11	65
9	CH_3COOH (10)	1	100	90/10	77
10	CH_3COOH (5)	1	100	90/10	77
11	CH_3COOH (1)	3d	95	88/12	77

Additive

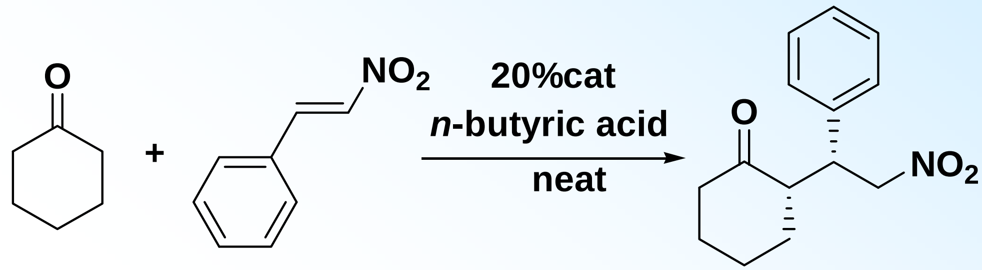


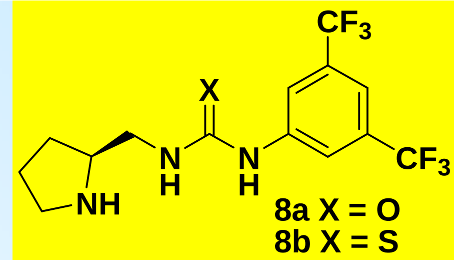


Entry	Additive (mol%)	Time (h)	Conv. (%)	Syn/anti	Ee (%)
1	CH_3CO_2H (10)	24	100	90/10	77
2	$HO_2C(CH_2)_3CO_2H$ (10)	24	100	93/7	73
3	$CH_3CH_2CO_2H$ (10)	24	100	83/17	77
4	$CH_3(CH_2)_2CO_2H$ (10)	11	100	94/6	80
5	$(CH_3)_2CHCO_2H$ (10)	11	100	93/7	79
6	$CH_3(CH_2)_5CO_2H$ (10)	11	100	96/4	78
7	$CH_3(CH_2)_3CH(CH_2CH_3)CO_2H$ (10)	11	100	91/9	76

Screening the temperature:

Solvent free

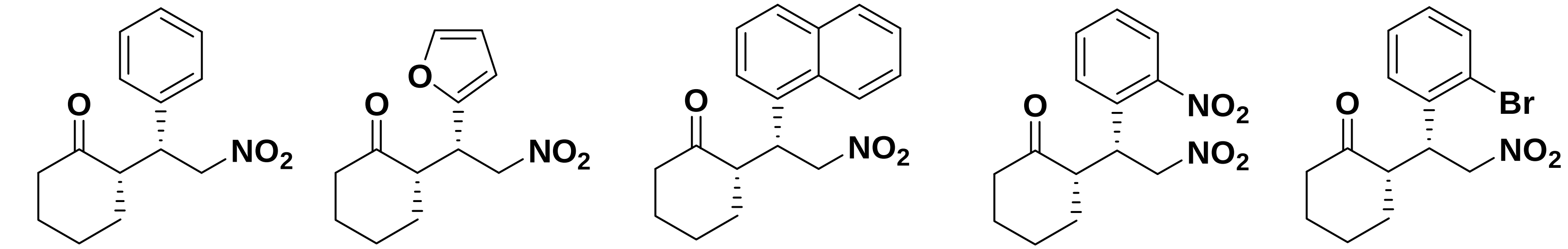




Entry	Cat.	T (℃)	Time (h)	Conv. (%)	Syn/anti	Ee (%)
1	8a	20	11	98	94/6	88
2	8a	0	30	99	97/3	89
3	8b	0	30	99	95/5	90
4	8a	-15	48	97	97/3	89
5	8b	-15	48	95	96/4	90
6[a]	8b	0	48	60	93/7	90

[a] 10 mol% catalyst was used.

Generality:



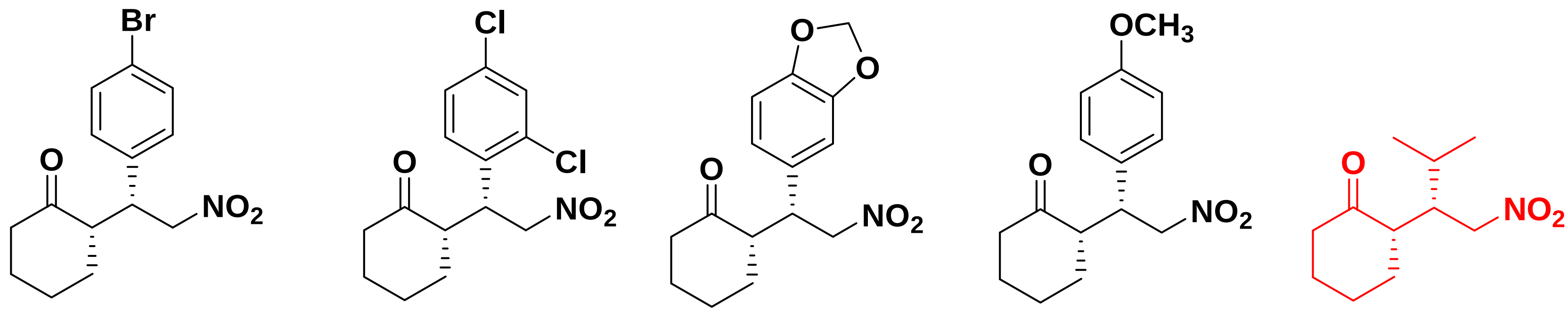
38h, 96/4, 93%, 90% ee

36h, 91/9, 99%, 90% ee

60h, 99/1, 93%, 95% ee

38h, 96/4, 95%, 97% ee

29h, 99/1, 88%, 96% ee



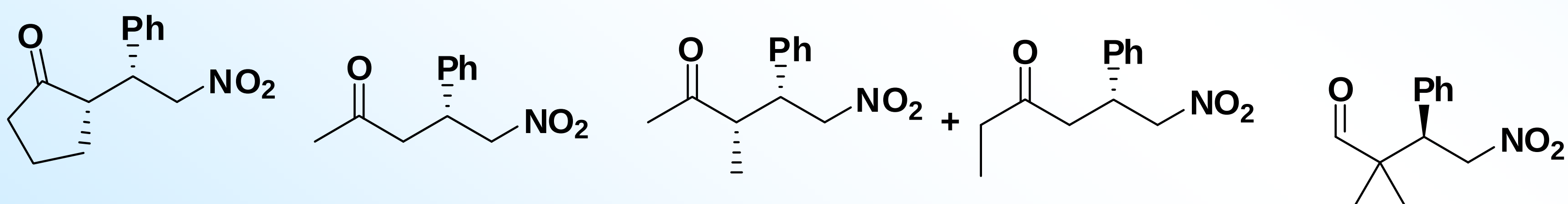
38h, 95/5, 90% 95% ee

49h, 97/3, 89%, 97% ee

38h, 94/6, 87%, 98% ee

44h, 97/3, 95%, 88% ee

6d, >99/1, 63%, 94% ee



7d, 27%, syn/anti:75/25 ee_{syn}: 71% ee_{anti}: 58%

2d, 80%, ee: 48%

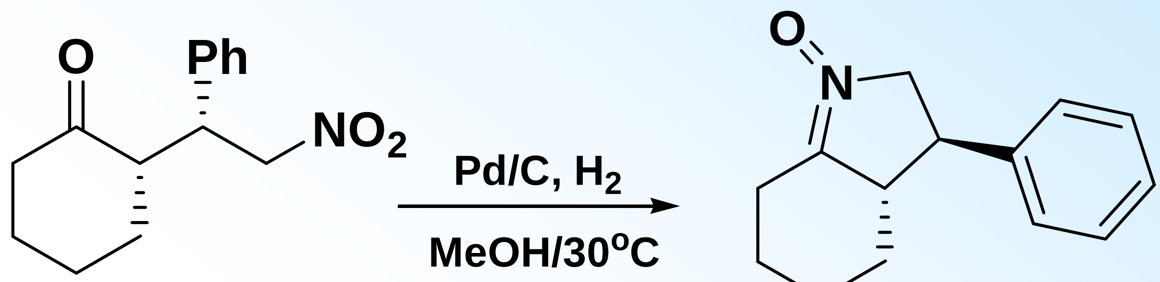
54 : 46

syn/anti: 99/1 ee: 70%

ee: 71%

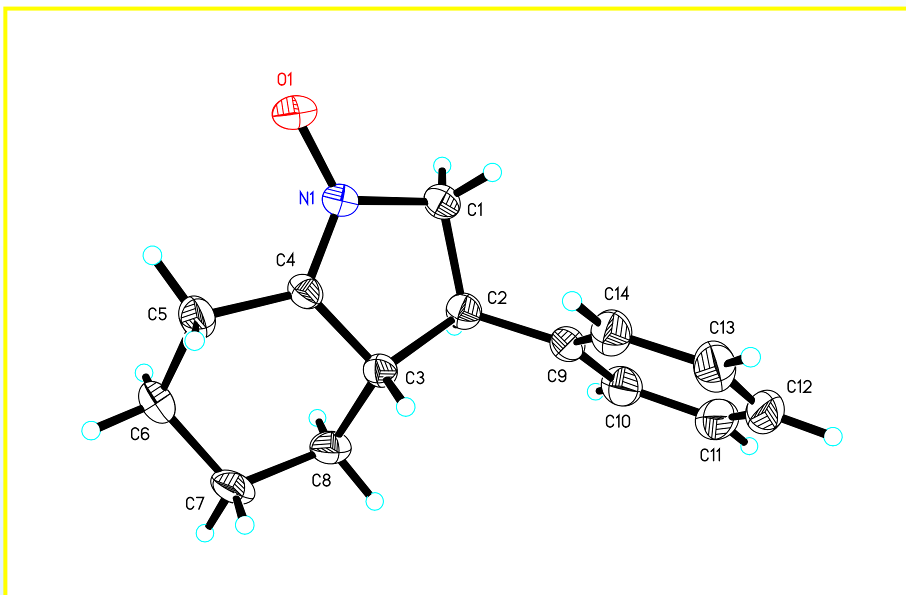
2d, 90% yield

2d, 61%, ee: 82%

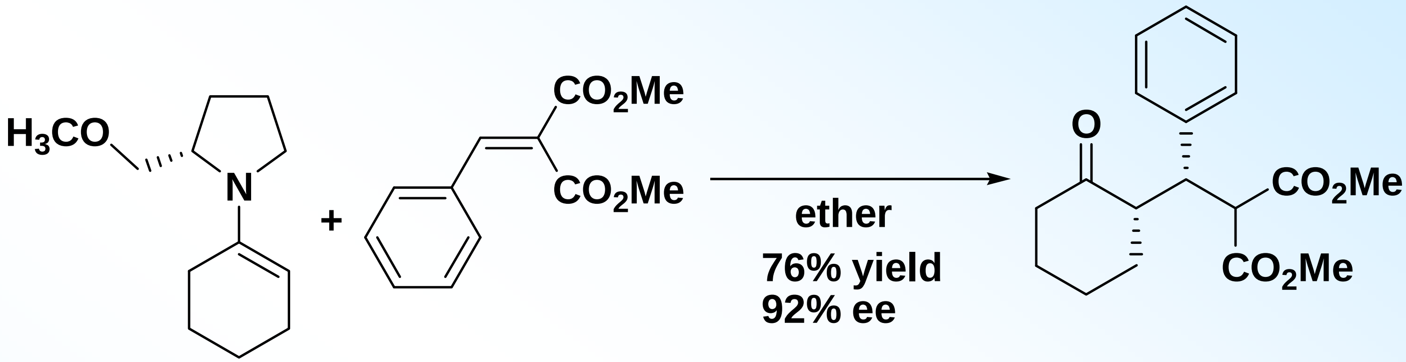


11a 90% ee

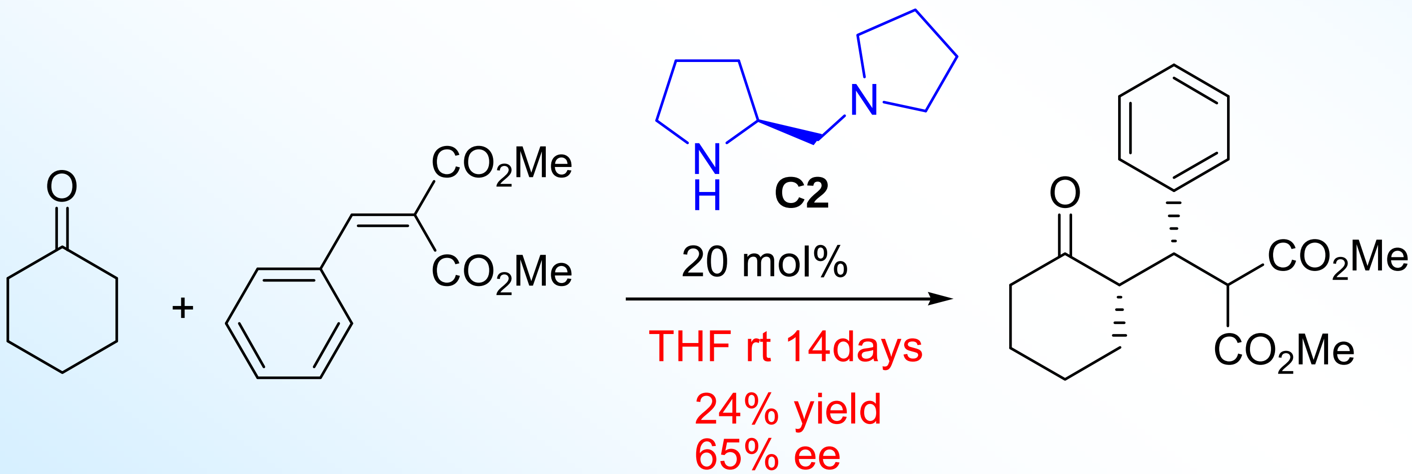
12 95% yield
92% ee



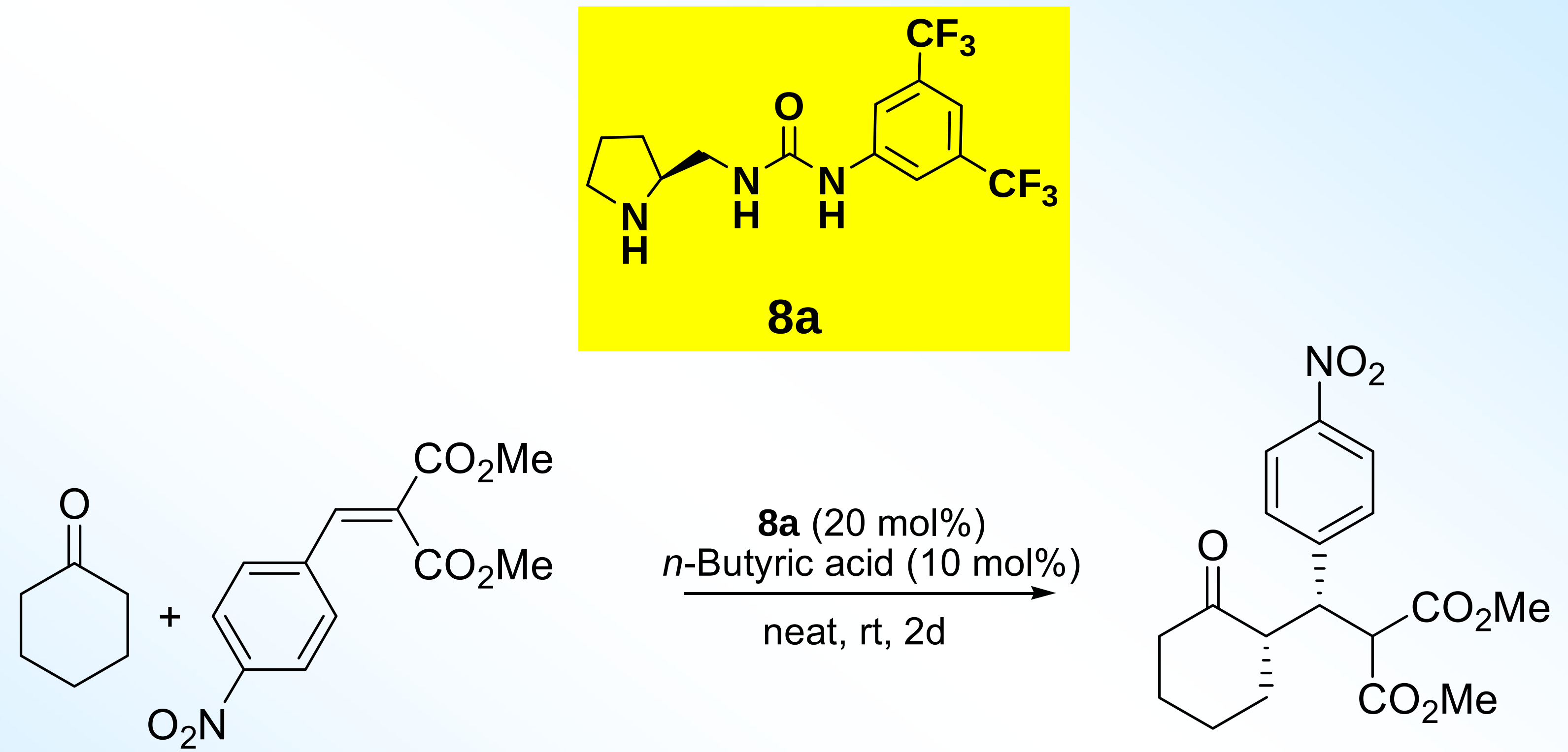
2. Enantioselective Michael Addition of Cyclic Ketones to Alkylidene Malonates



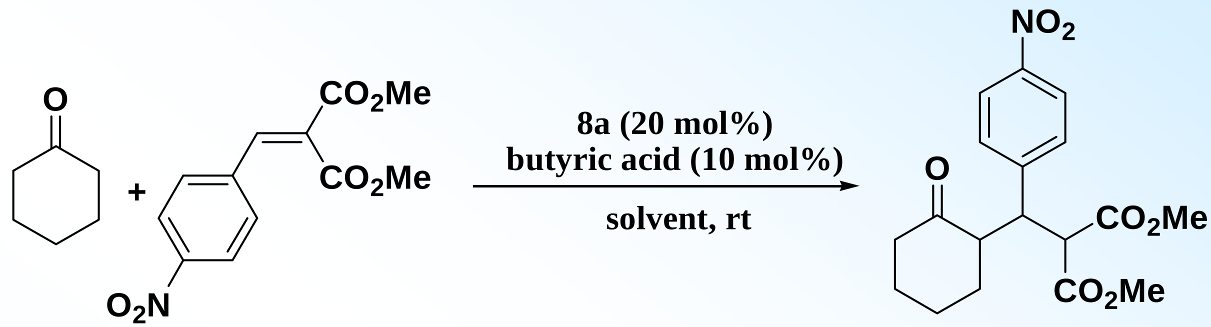
Seebach, D. *Chem. Ber.* **1983**, 2251

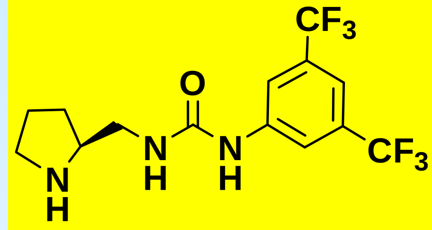


Barbas . et al. *Tetrehedron Lett.* **2001**, 4441.



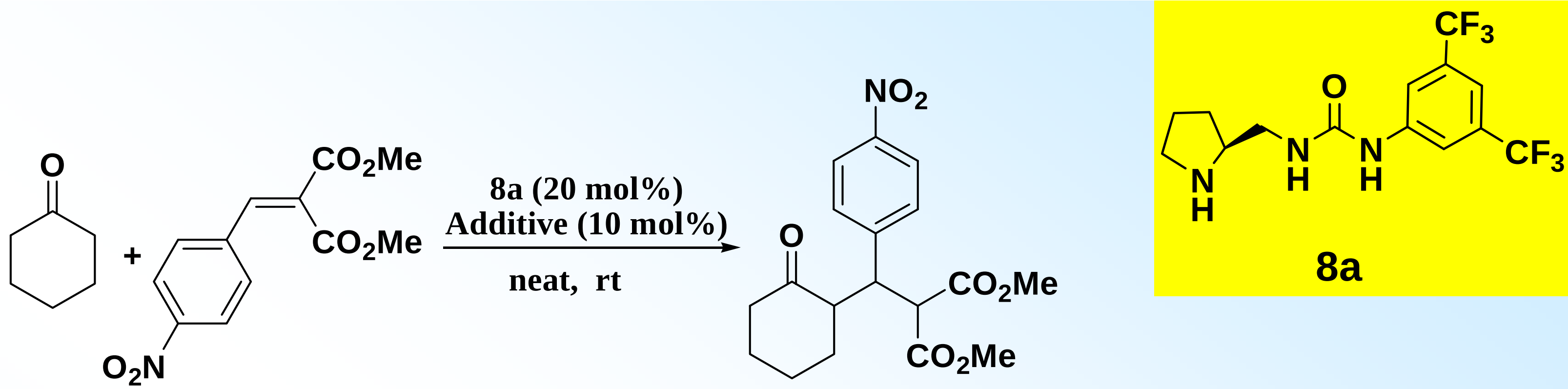
72% yield
syn/anti: 90/10
90% ee



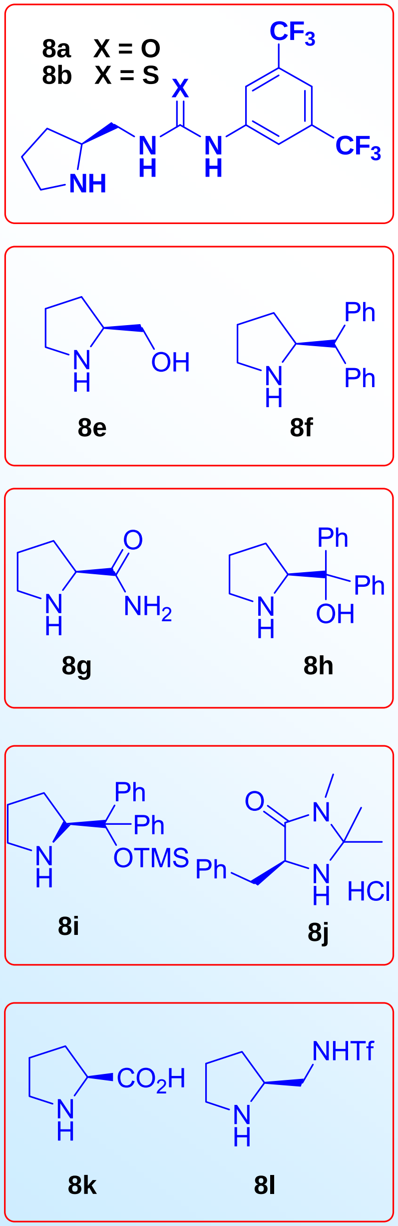


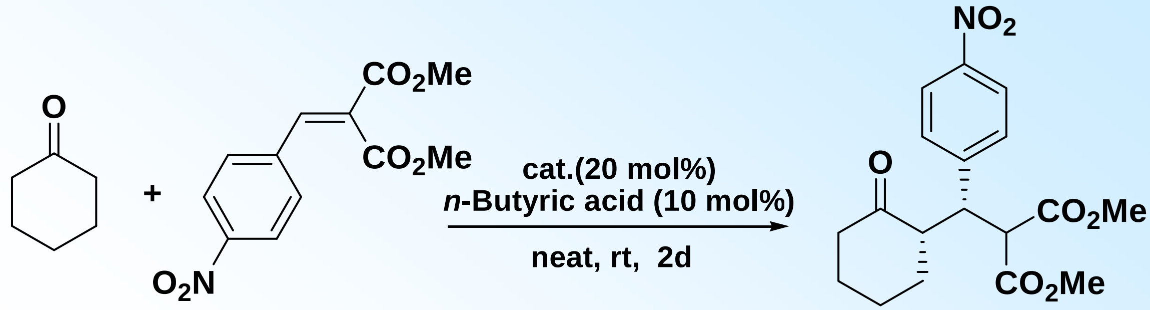
8a

Entry	Solvent	Time (d)	Conv. (%)	Syn/anti	Ee (%)
1	benzene	2	51	87/13	86
2	*i*-BuOH	2	50	90/10	87
3	*t*-BuOH	2	33	90/10	88
4	EA	2	33	88/12	87
5	THF	2	26	82/18	88
6	CH_2Cl_2	2	25	88/12	86
7	Solvent free	4	99	90/10	90
8	Solvent free	2	72	90/10	90



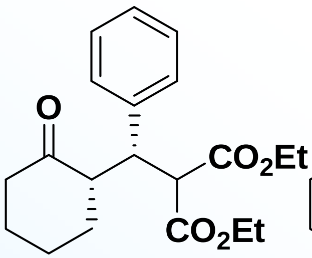
Entry	Additive (10 mol%)	Time (d)	Conv. (%)	Syn/anti	Ee (%)
1	*n*-butyric acid	4	99	90/10	90
2	*n*-butyric acid	2	72	90/10	90
3	*i*-butyric acid	2	76	90/10	89
4	heptanoic acid	2	68	91/9	87
5	D-campher-10 -sulfonic acid	2	15	-	-
6	4-methylbenzene sulfonic acid	2	10	-	-



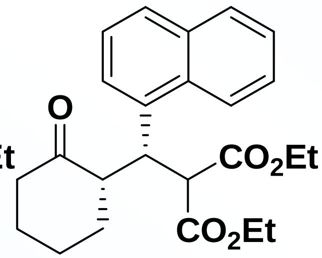


Entry	Catalyst	Conv.[b] (%)	syn/anti[b]	ee[c] (%)
1	8a	72	90/10	90
2	8b	43	80/20	88
3	8e	17	-	-
4	8f	17	-	-
5	8g	13	-	-
6	8h	NR	-	-
7	8i	NR	-	-
8	8j	NR	-	-
9	8k	85	85/15	33
10	8l	99	93/7	90
11[d]	8l	91	93/7	90

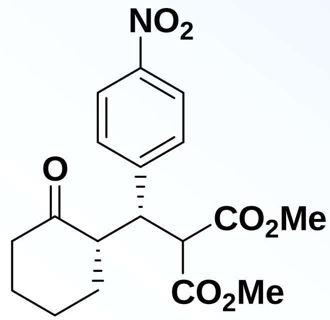
Generality:



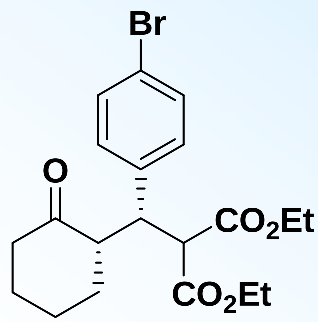
36%, 90/10,
88% ee



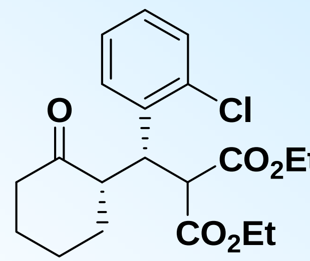
20%, 95/5,
87% ee



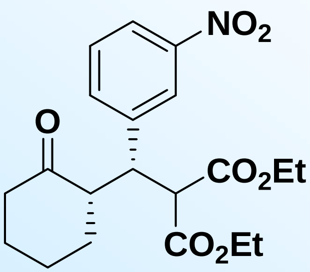
98%, 93/7,
90% ee



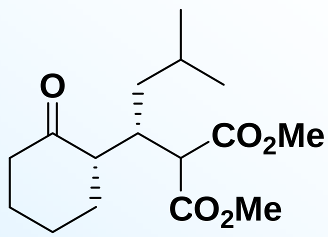
71%, 93/7,
90% ee



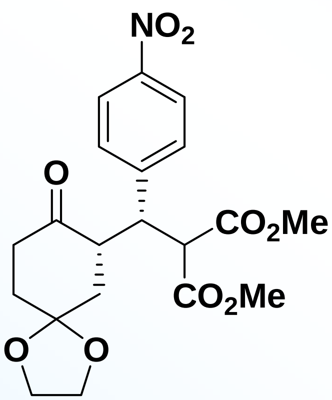
48%, 95/5,
88% ee



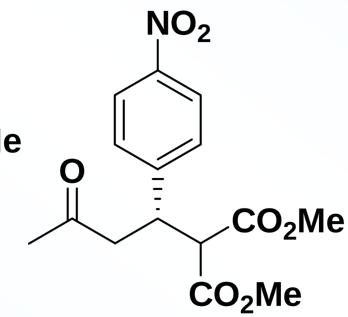
95%, 91/9,
90% ee



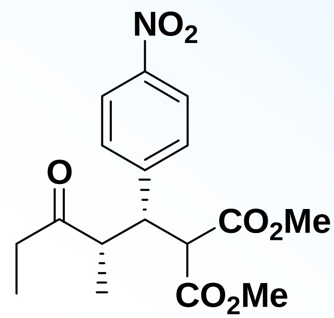
27%, ND



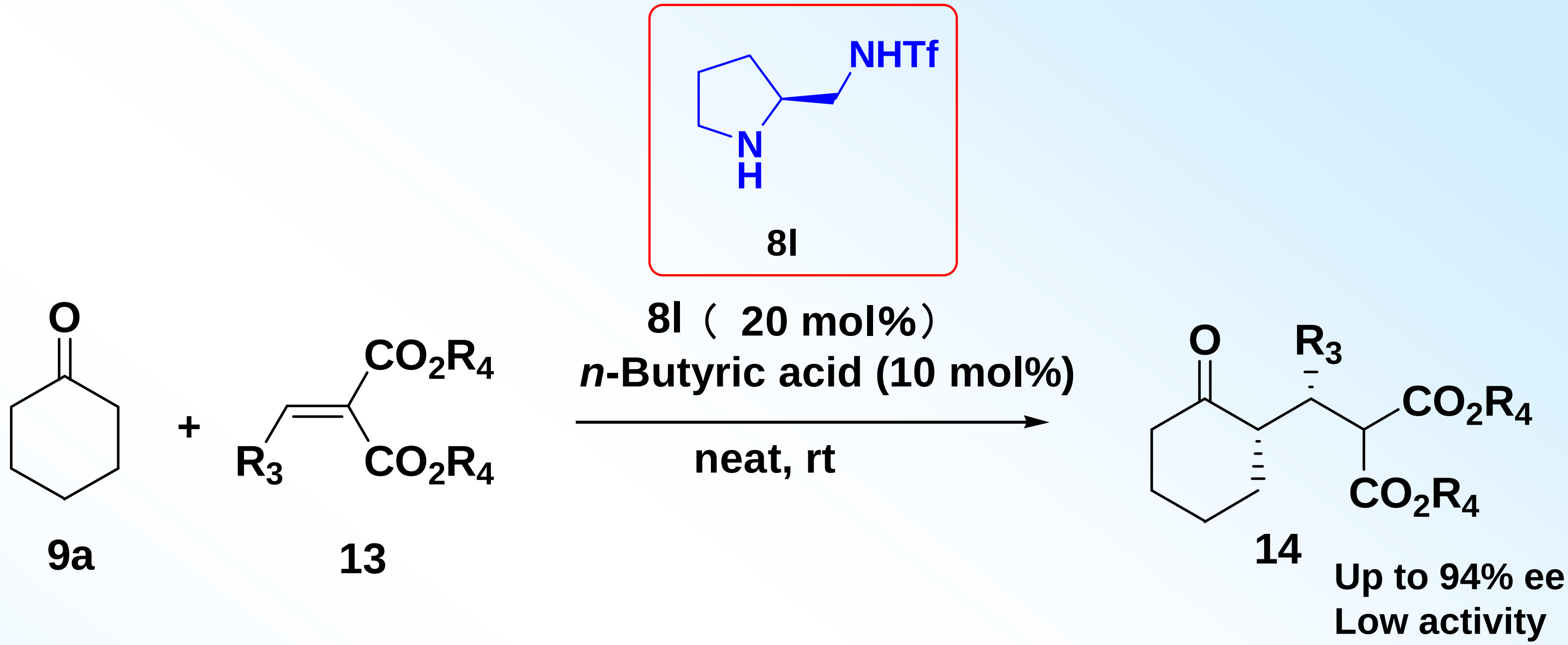
60%, 89/11,
94% ee



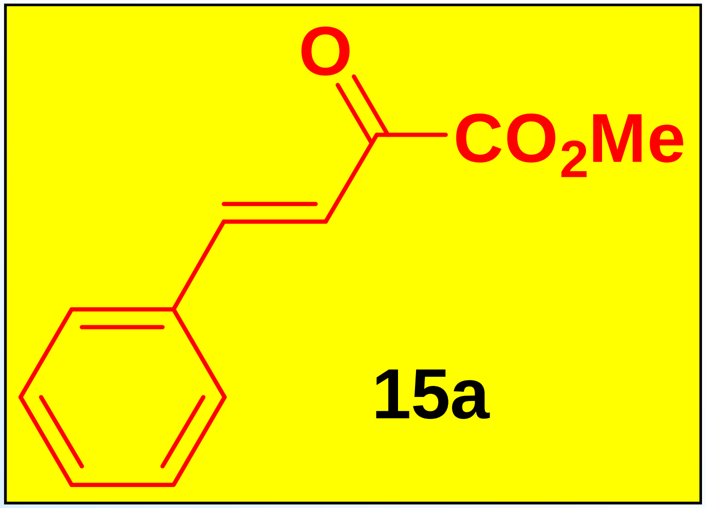
74%
54% ee



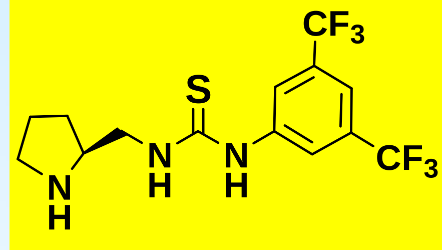
NR



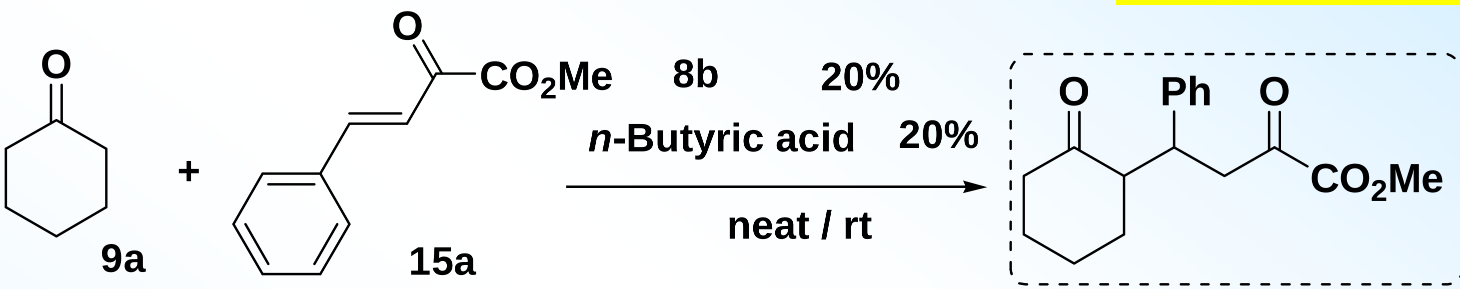
In order to improve the activity of the Michael reaction, then we synthesized the more active Michael acceptor



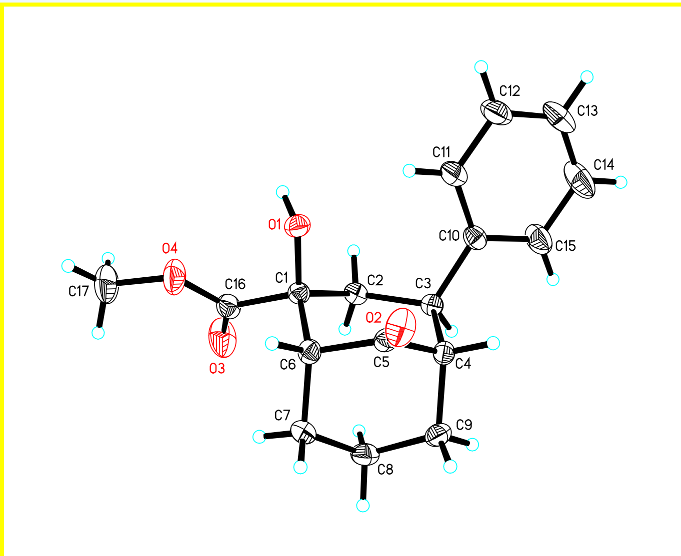
3. Organocatalytic Tandem Michael/Aldol Reactions

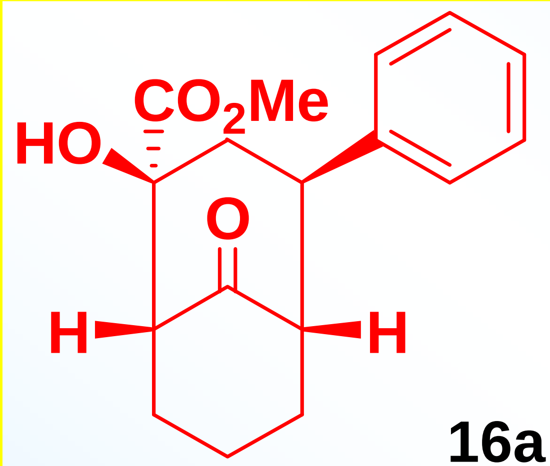


8b



3.5 days
conv.: 83%
ee: 88%

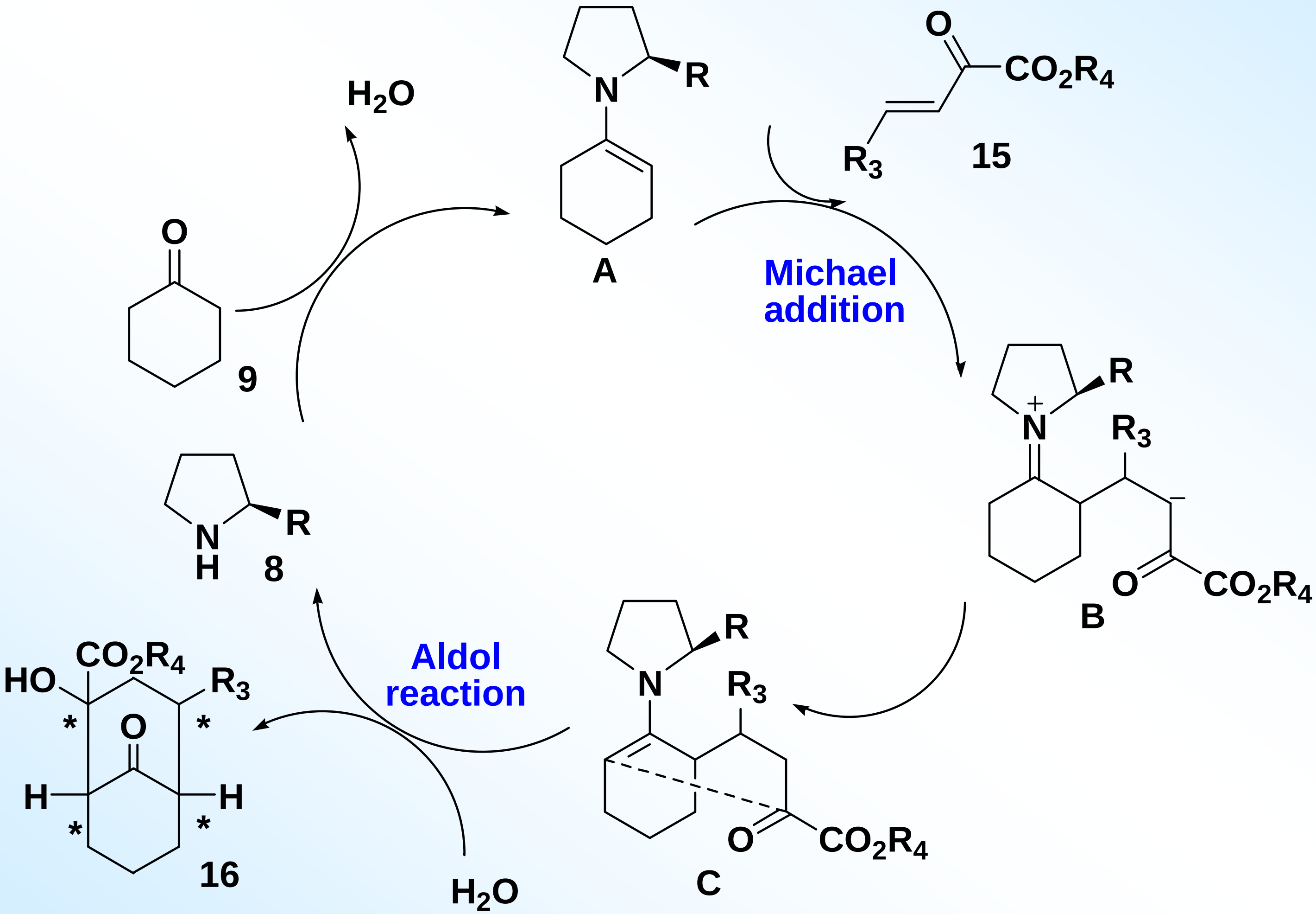


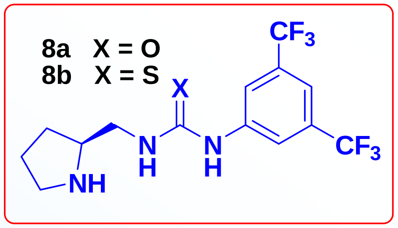


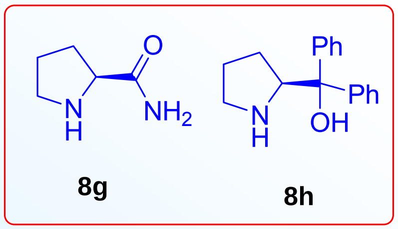
16a

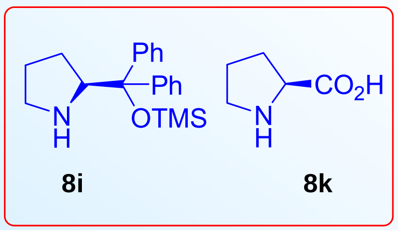
Plausible mechanism:

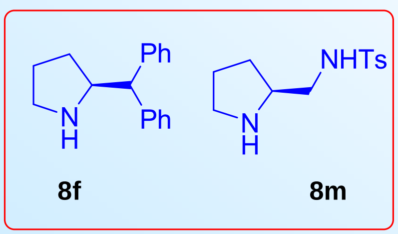
Michael/Aldol Tandem Reaction

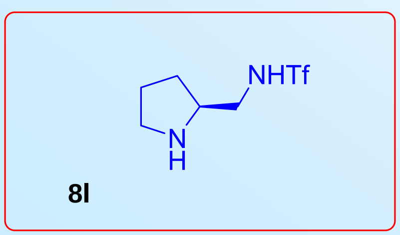


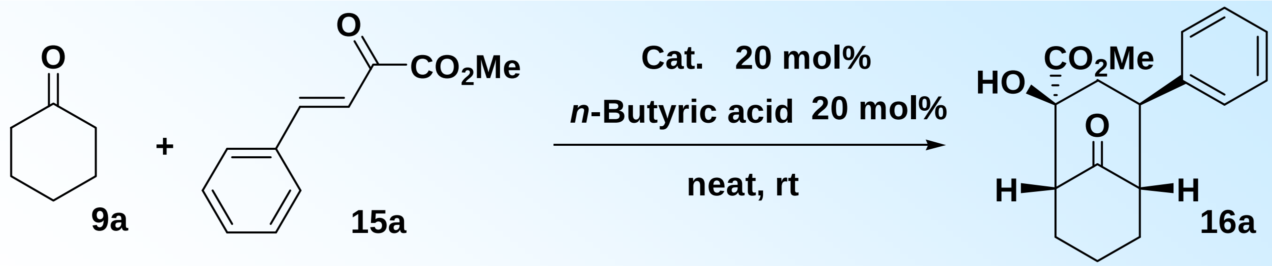




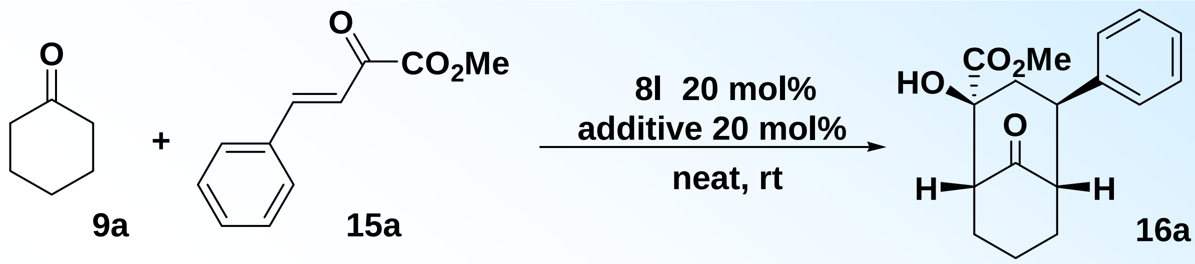


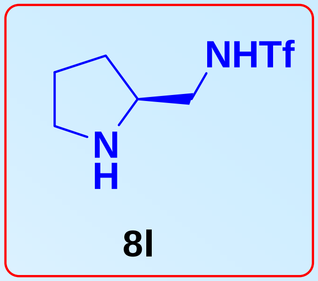






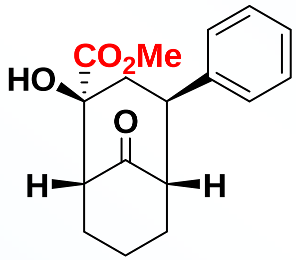
Entry	Catalyst	Time (day)	Conv.[b] (%)	Ee[c] (%)
1	8a	2	99	85
2	8b	2	88	88
3	8g	3.5	<5	-
4	8h	3.5	<5	-
5	8i	3.5	<5	-
6	8k	3.5	20	-
7[d]	8k	3	99	23
8	8f	2	53	66
9	8m	2	50	85
10	8l	2	99（80）	90
11[e]	8l	2	89	90
12[f]	8l	2	45	90



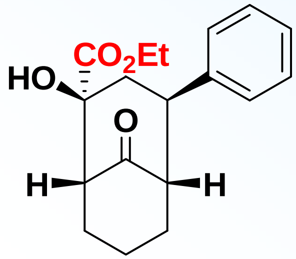


Entry	Additive (10 mol%)	Conv.[b] (%)	Ee[c] (%)
1	D-campher-10-sulfonic acid	<5	-
2	CF_3CO_2H	<5	-
3	TsOH	<5	-
4	$PhCO_2H$	99	87
5	p-NO_2-C_6H_4-CO_2H	99	84
6	3, 5-diNO_2-C_6H_4-CO_2H	80	87
7	o-OMe-C_6H_4-CO_2H	80	87
8	p-OMe-C_6H_4-CO_2H	99	90
9	m-OMe-C_6H_4-CO_2H	99	89
10	p-OH-C_6H_4-CO_2H	99	90
11	o-OH-C_6H_4-CO_2H	72	23
12	o-OH-C_6H_4-CO_2Na	99	87
13	*n*-butyric acid	99	90

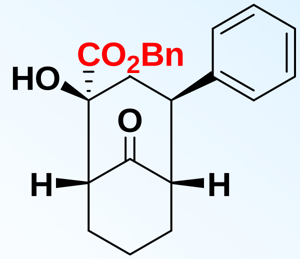
普 适 性:



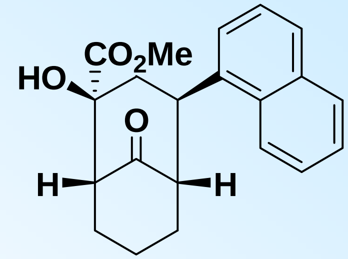
48h, 80%
90% ee



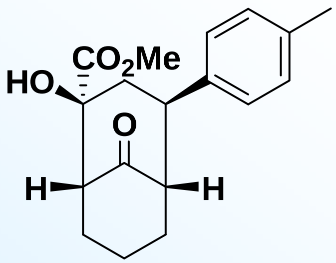
40h, 74%,
91% ee



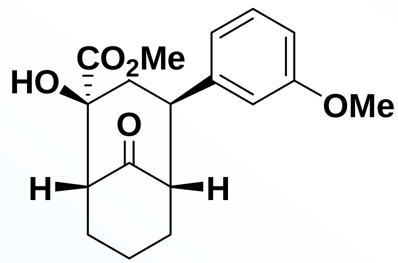
24h, 76%,
91% ee



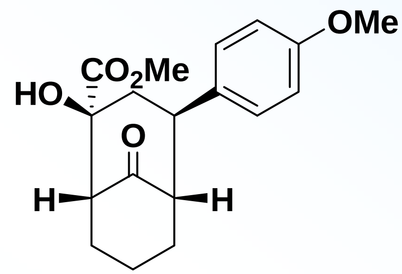
50h, 73%,
91% ee



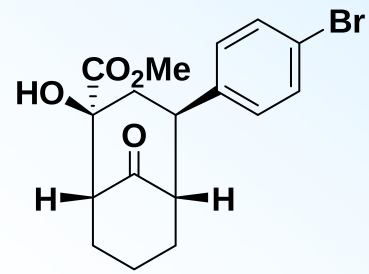
40h, 80%
90% ee



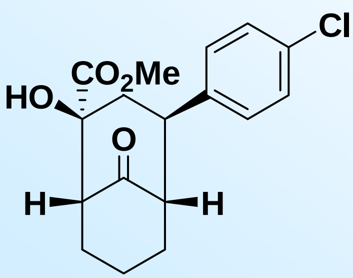
48h, 81%
86% ee



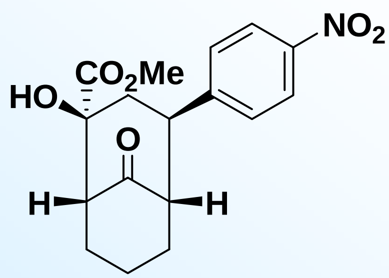
64h, 77%
87% ee



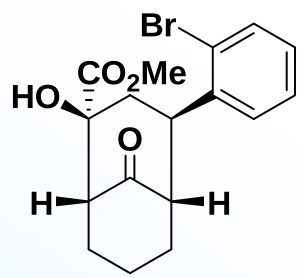
24h, 77%,
90% ee



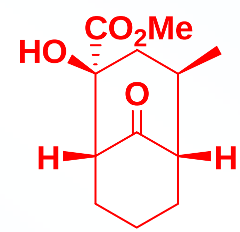
40h, 85%,
93% ee



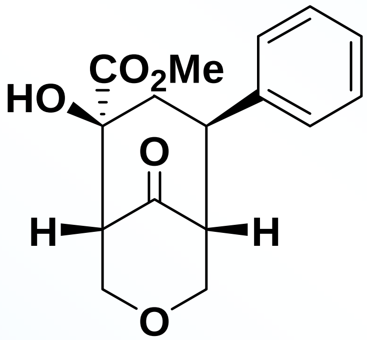
120h, 90%,
92% ee



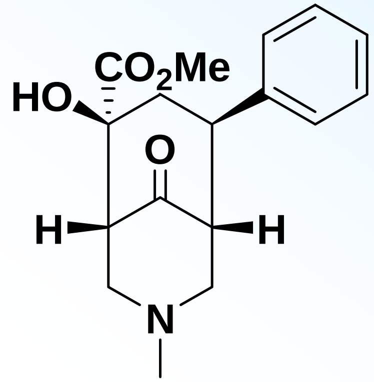
48h, 74%,
93% ee



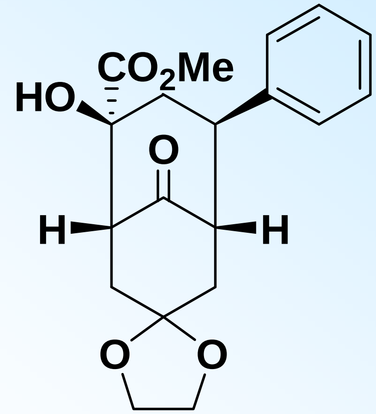
60h, 56%,
94% ee



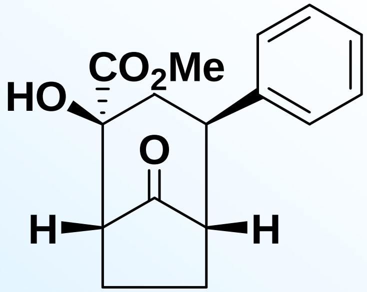
7d, 66%,
90% ee



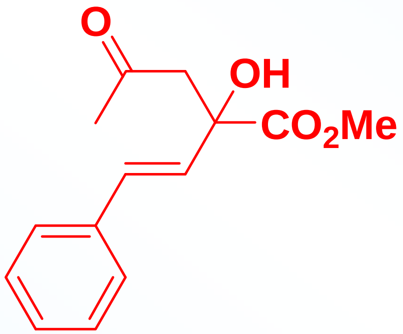
72h, 92%,
80% ee



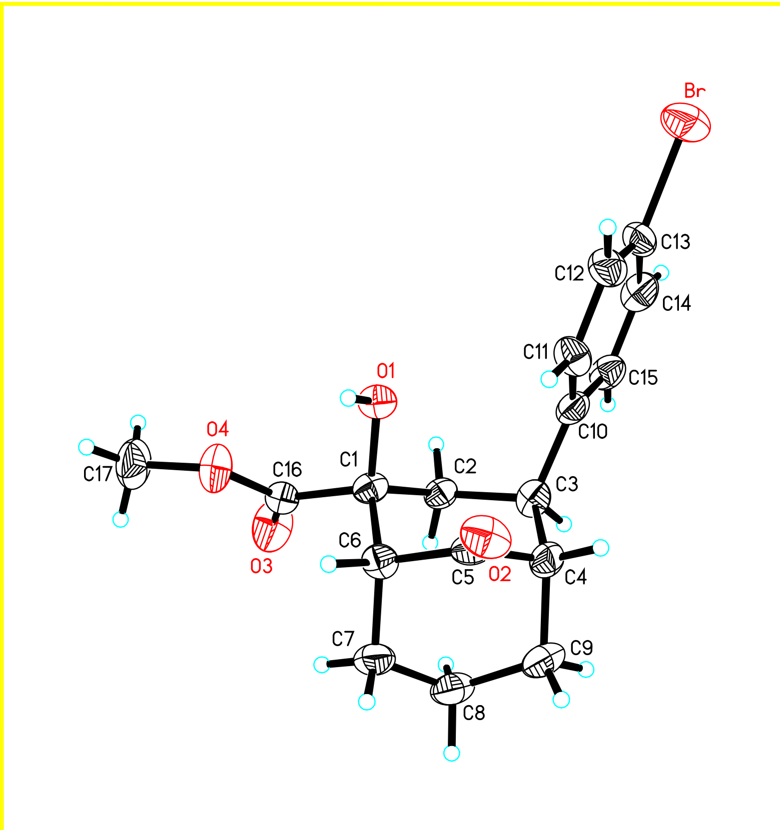
72h, 49%,
84% ee

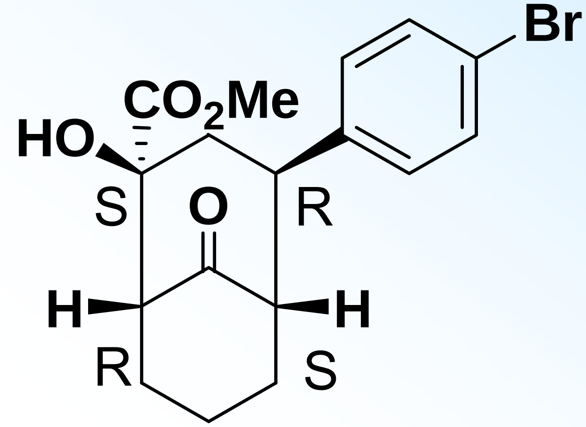


40h, 98%,
64% ee

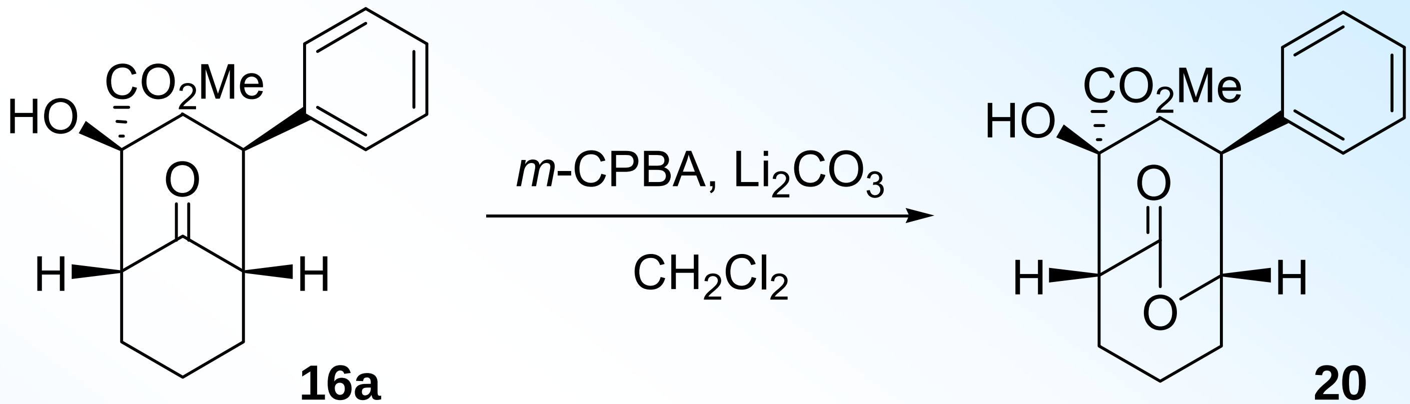


20h, 99%,
14% ee


Br
C13
C12
C14
C11
C15
O1
C10
O4
C16
C1
C2
C3
C17
C6
O3
C5
O2
C4
C7
C9
C8

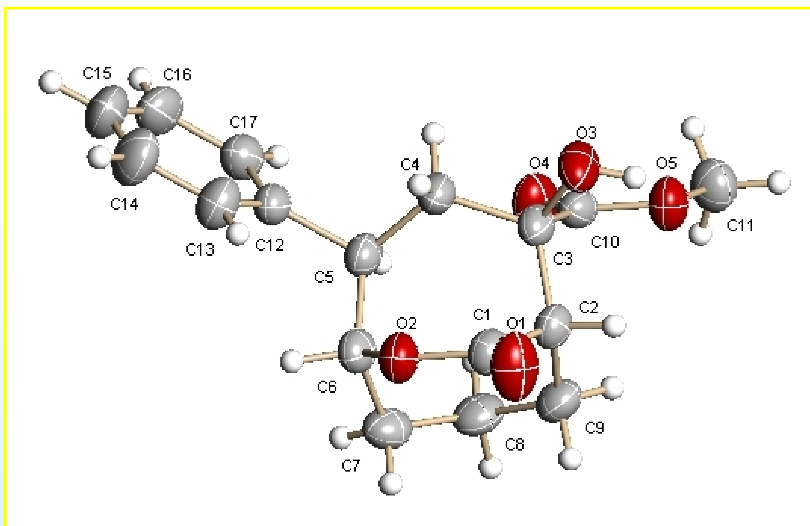

Br
CO2Me
HO
S
O
R
H
H
R
S

16h

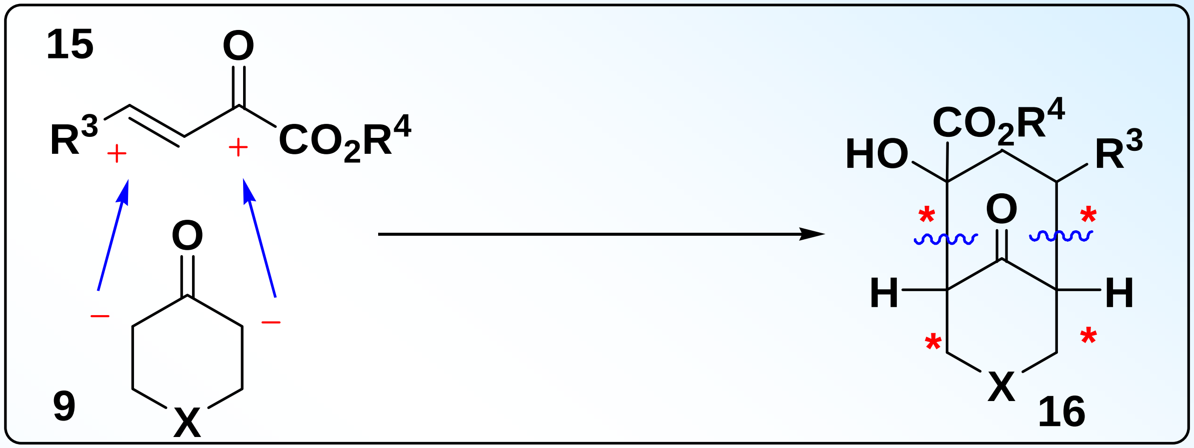


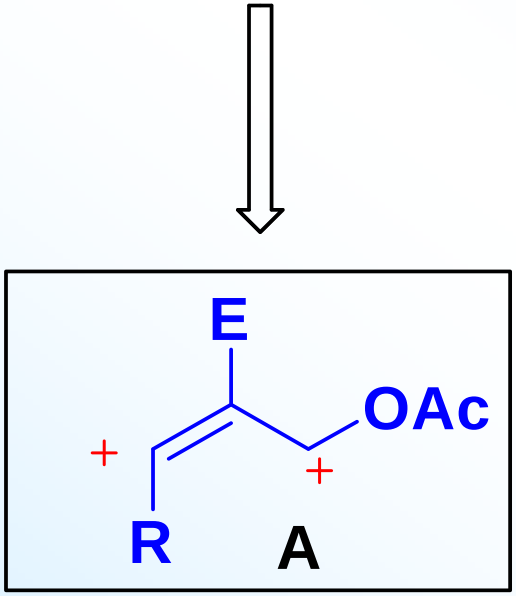
16a **20**

single product
yield: 83%

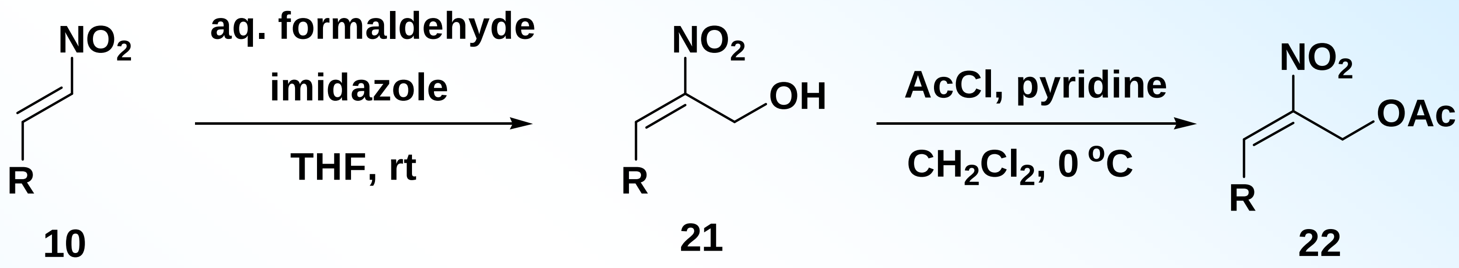


Formal [3+3] reaction

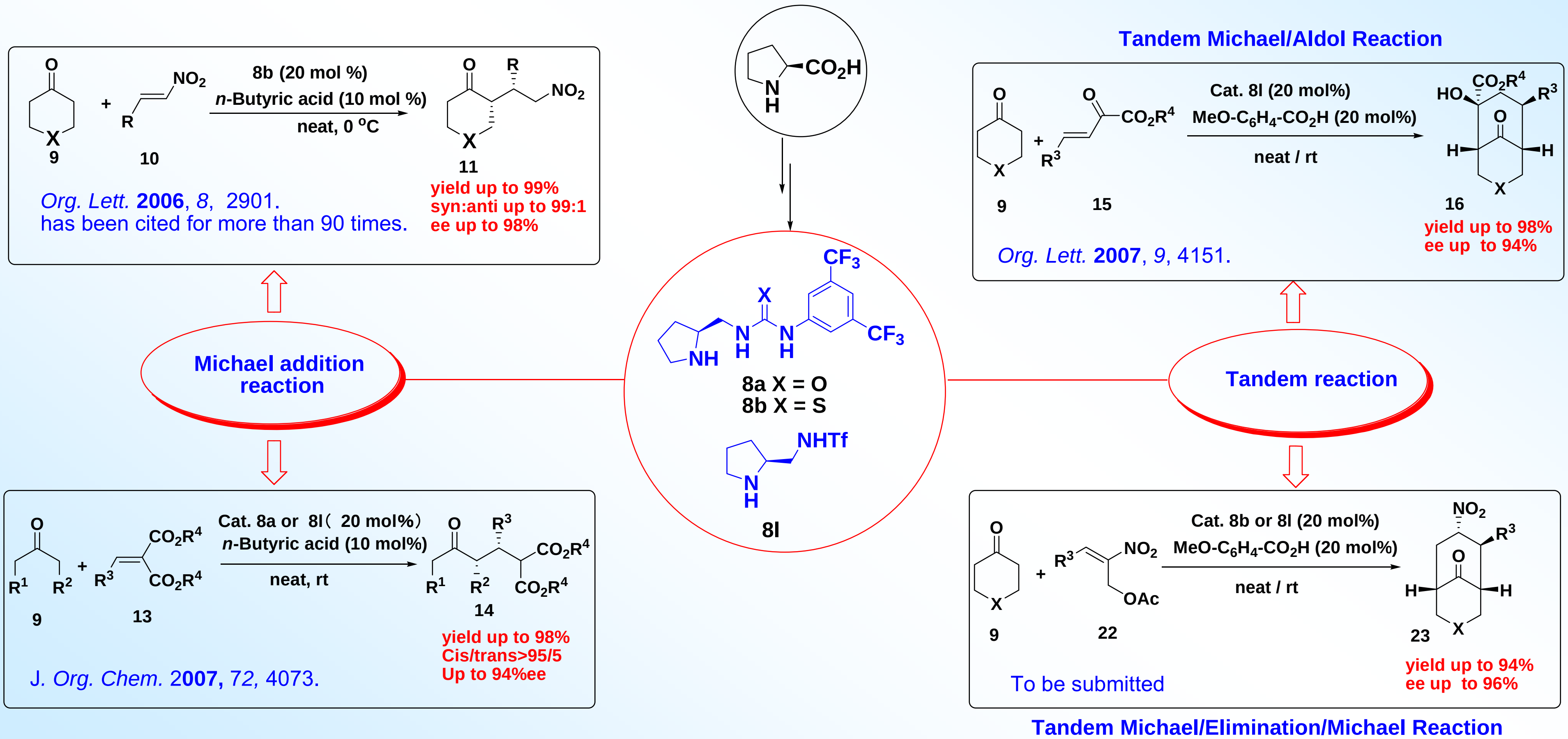




3. Organocatalytic Tandem Michael-Elemination/Michael Reactions



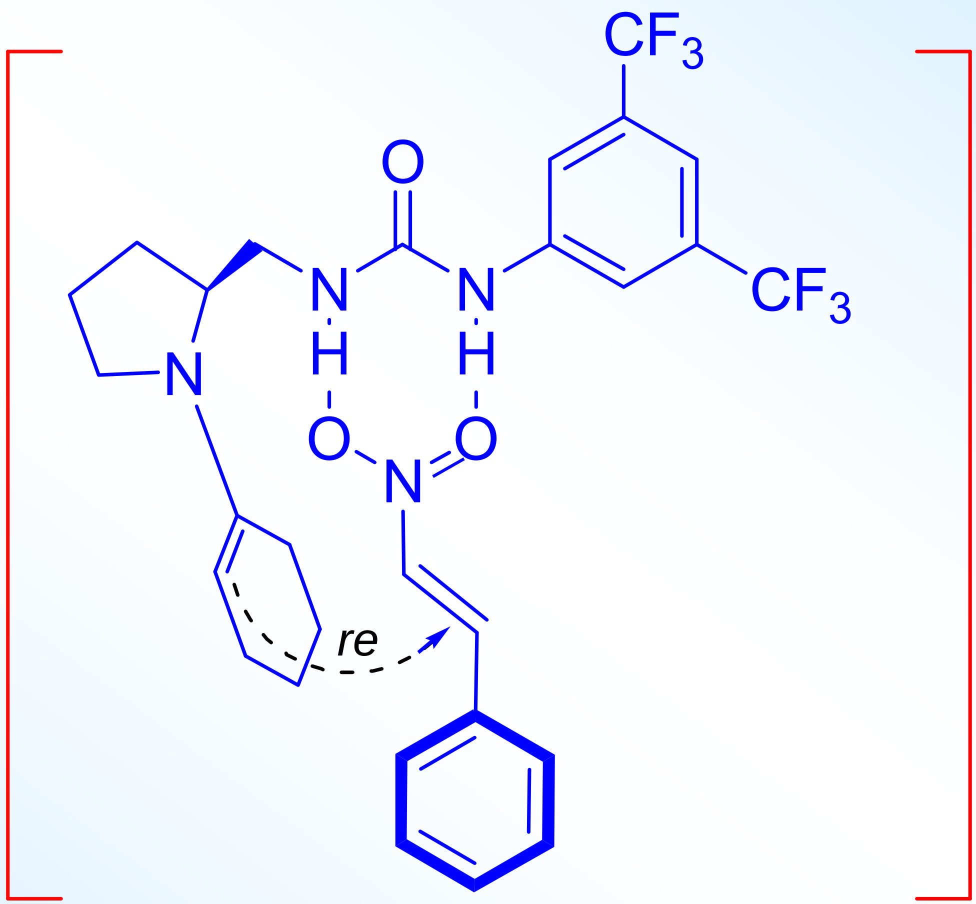
Conclusion



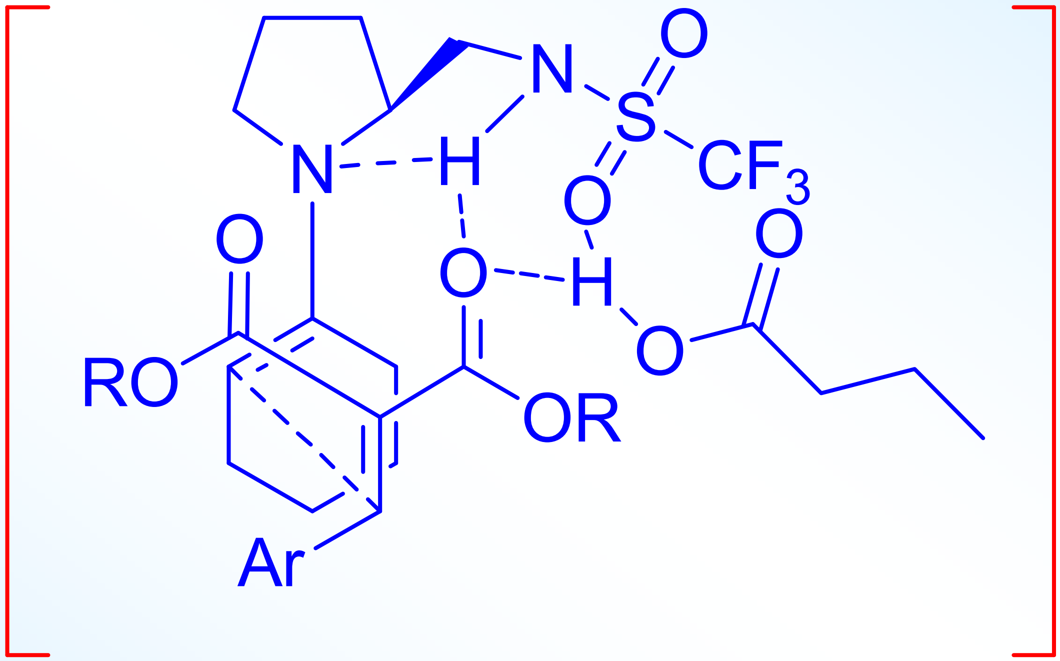
Michael addition reaction
Tandem reaction
8a X = O
8b X = S
NHTf
8l
CO2H
8b (20 mol %)
n-Butyric acid (10 mol %)
neat, 0 °C
9
10
11
Org. Lett. 2006, 8, 2901.
has been cited for more than 90 times.
yield up to 99%
syn:anti up to 99:1
ee up to 98%
Cat. 8a or 8l（ 20 mol%）
n-Butyric acid (10 mol%)
neat, rt
9
13
14
J. Org. Chem. 2007, 72, 4073.
yield up to 98%
Cis/trans>95/5
Up to 94%ee
Tandem Michael/Aldol Reaction
Cat. 8l (20 mol%)
MeO-C6H4-CO2H (20 mol%)
neat / rt
9
15
16
Org. Lett. 2007, 9, 4151.
yield up to 98%
ee up to 94%
Cat. 8b or 8l (20 mol%)
MeO-C6H4-CO2H (20 mol%)
neat / rt
9
22
23
To be submitted
yield up to 94%
ee up to 96%
Tandem Michael/Elimination/Michael Reaction

Thank you for giving me this chance !!!

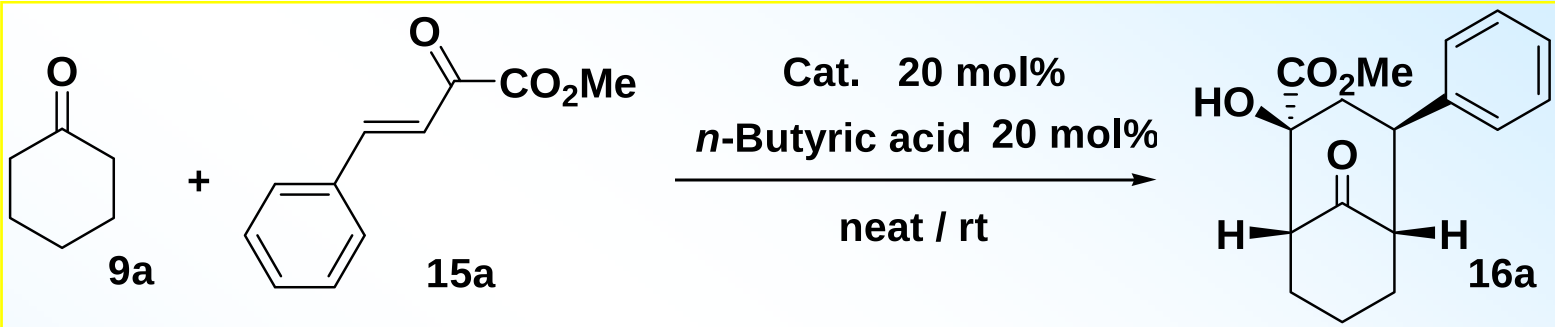
Transition state model:

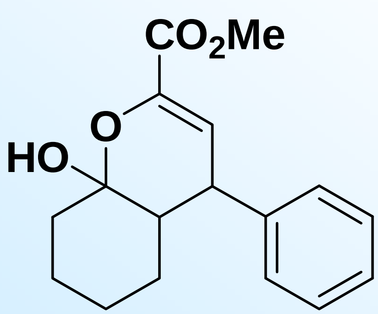


Transition state model:

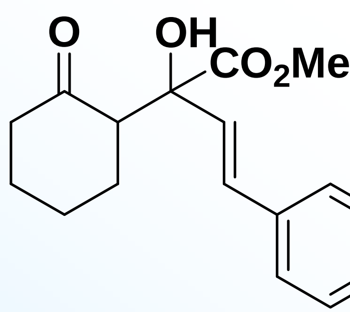


We also isolated the following products in this reaction.

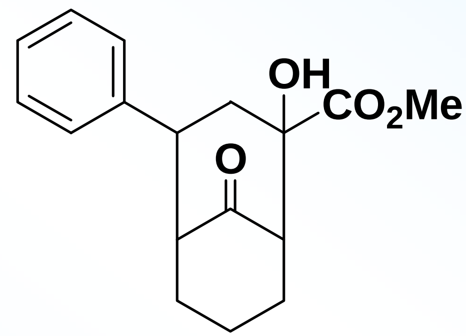




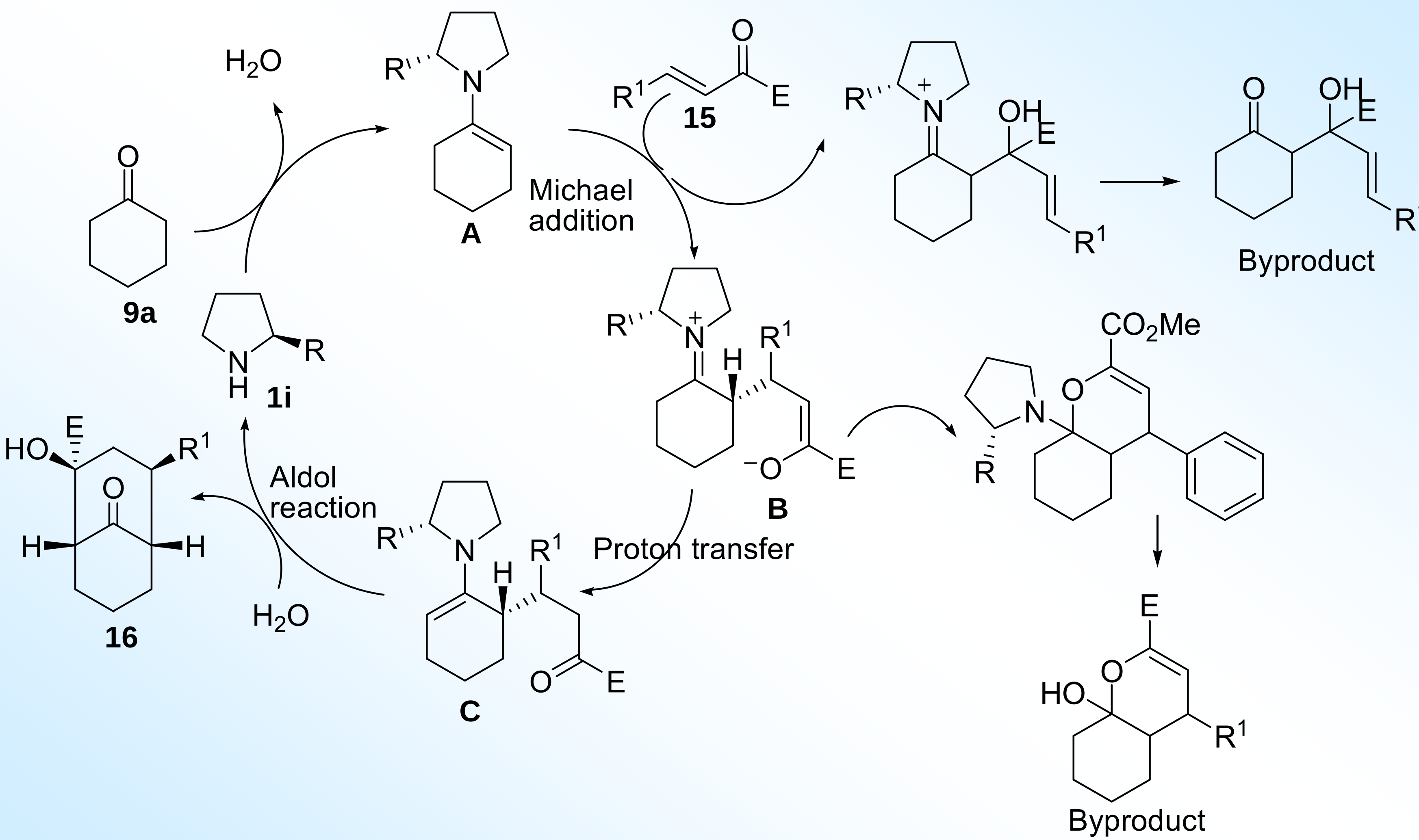
Diels-Alder product

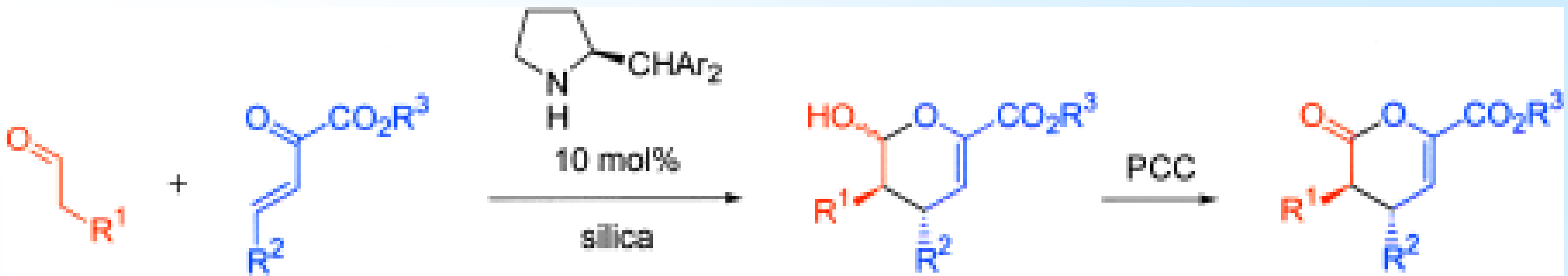


Aldol product

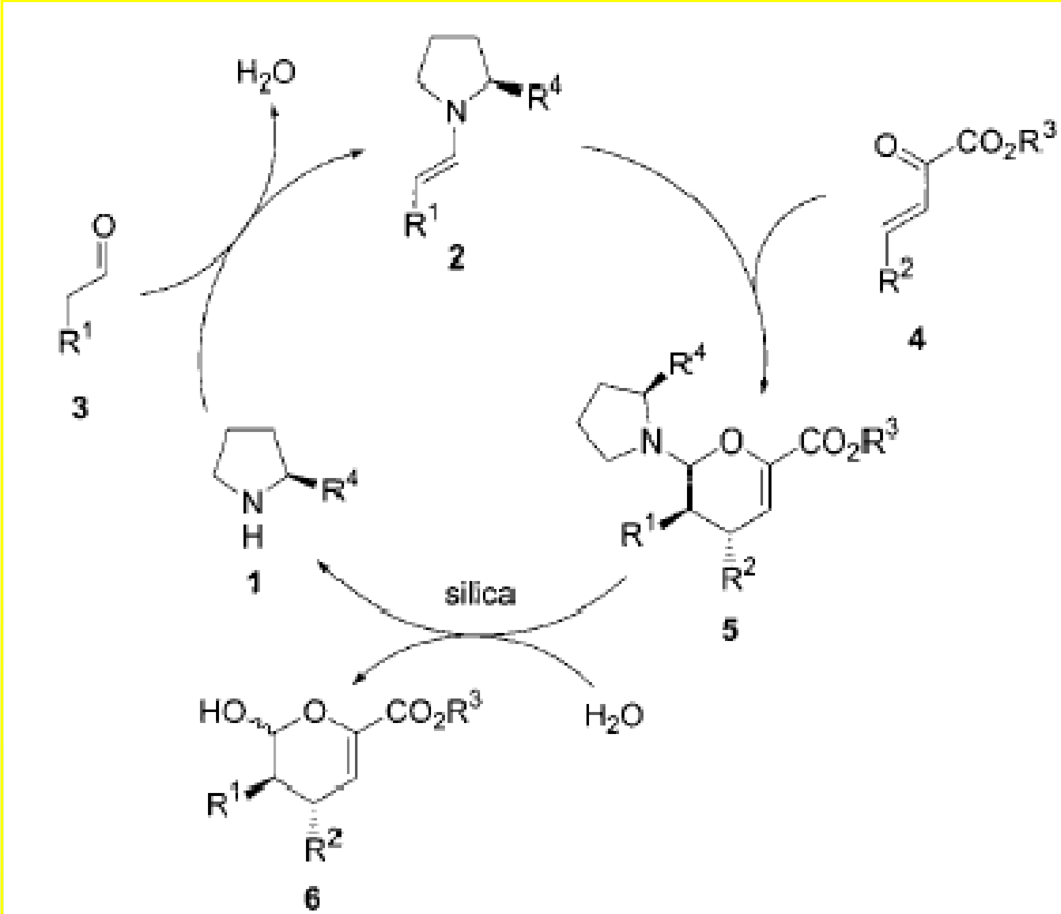


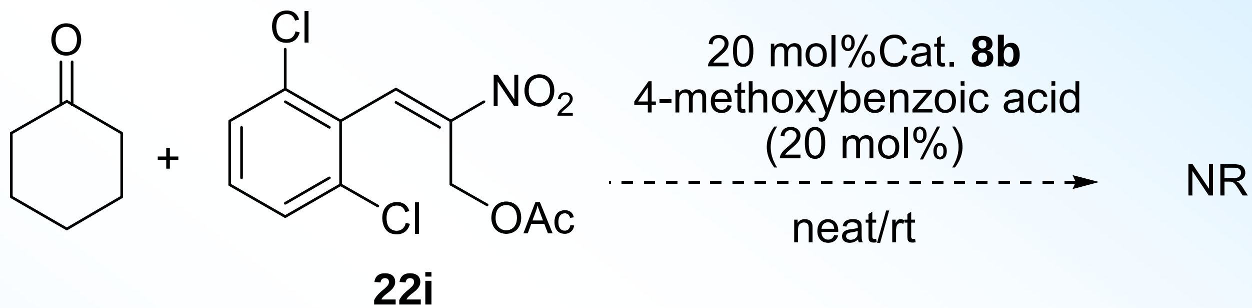
another isomer of
the major product

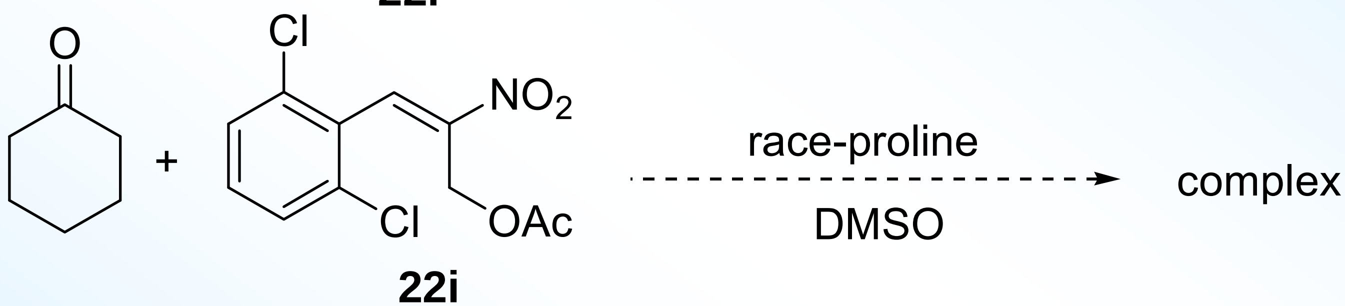

H2O
R1
O
E
15
OH
E
Byproduct
9a
A
Michael addition
1i
B
CO2Me
Aldol reaction
Proton transfer
C
16
H2O
Byproduct

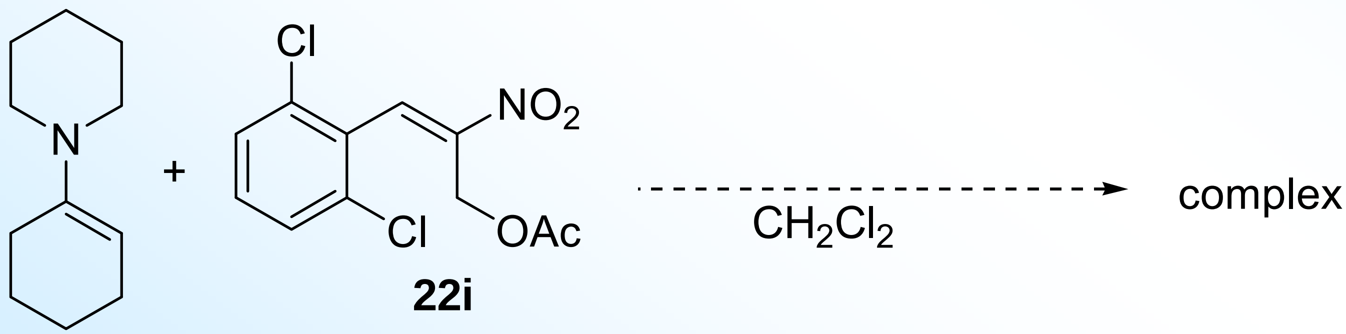


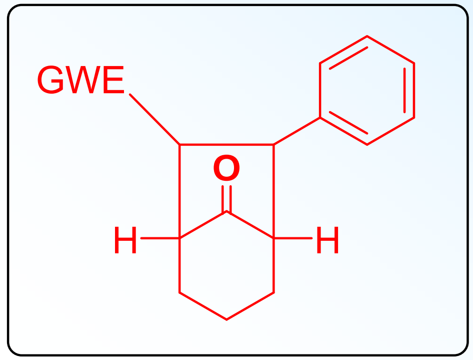
Karl Anker Jørgensen* *Angew. Chem. Int. Ed.* **2003**, *42*, 1498 – 1501

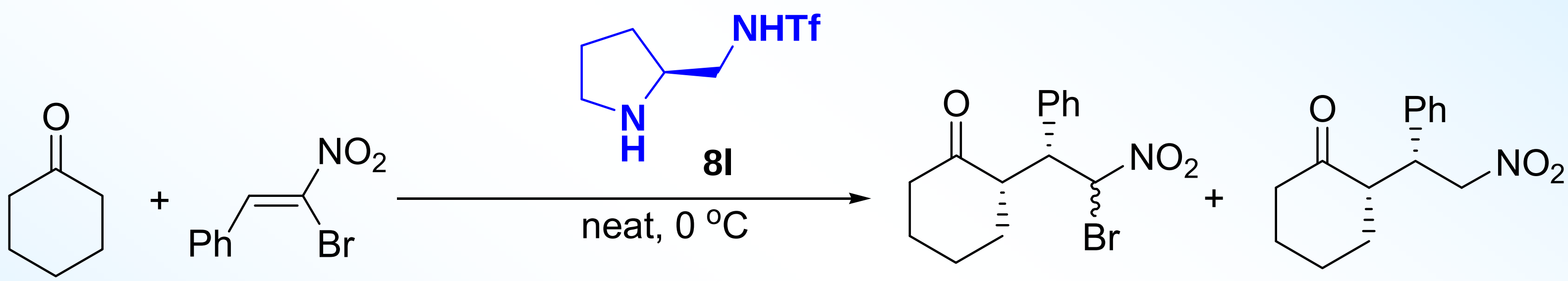


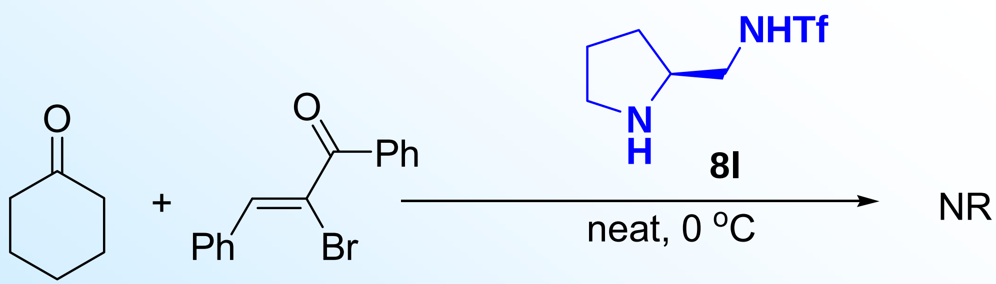

Cl
NO2
Cl
OAc
O
+
22i
20 mol%Cat. 8b
4-methoxybenzoic acid
(20 mol%)
neat/rt
NR
(eq 1)

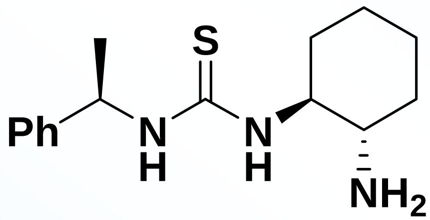

Cl
NO2
Cl
OAc
O
+
22i
race-proline
DMSO
complex
(eq 2)


Cl
NO2
Cl
OAc
N
+
22i
CH2Cl2
complex
(eq 3)

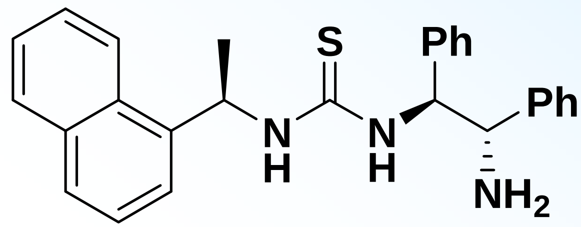

GWE
O
H
H


O
NO2
Ph
Br
NHTf
N
H
8l
neat, 0 oC
O
Ph
NO2
Br
O
Ph
NO2

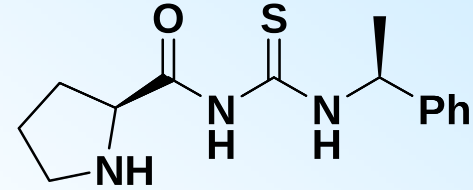

O
O
Ph
Ph
Br
NHTf
N
H
8l
neat, 0 oC
NR



C19

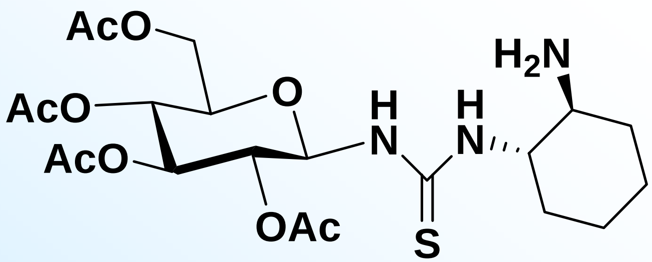


C20



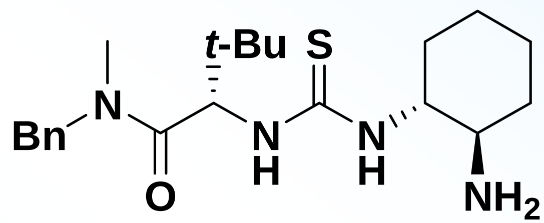
C17

Tsogoeva (2006)



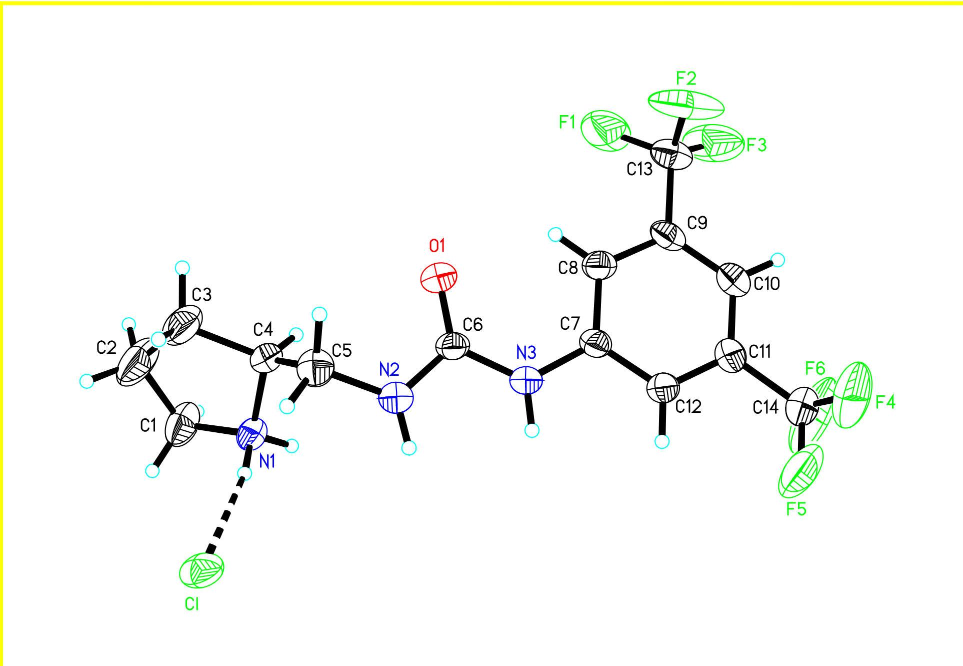
C22

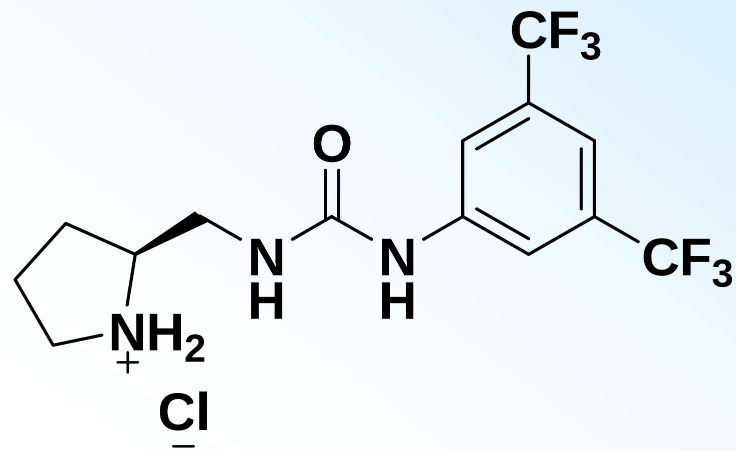
Ma (2007)



C16

Jacobsen (2007)


F2
F1
F3
C13
C9
O1
C8
C10
C3
C4
C6
C7
C2
C5
N3
C11
F6
N2
F4
C1
C12
C14
N1
F5
Cl


CF3
O
N
H
N
H
CF3
NH2
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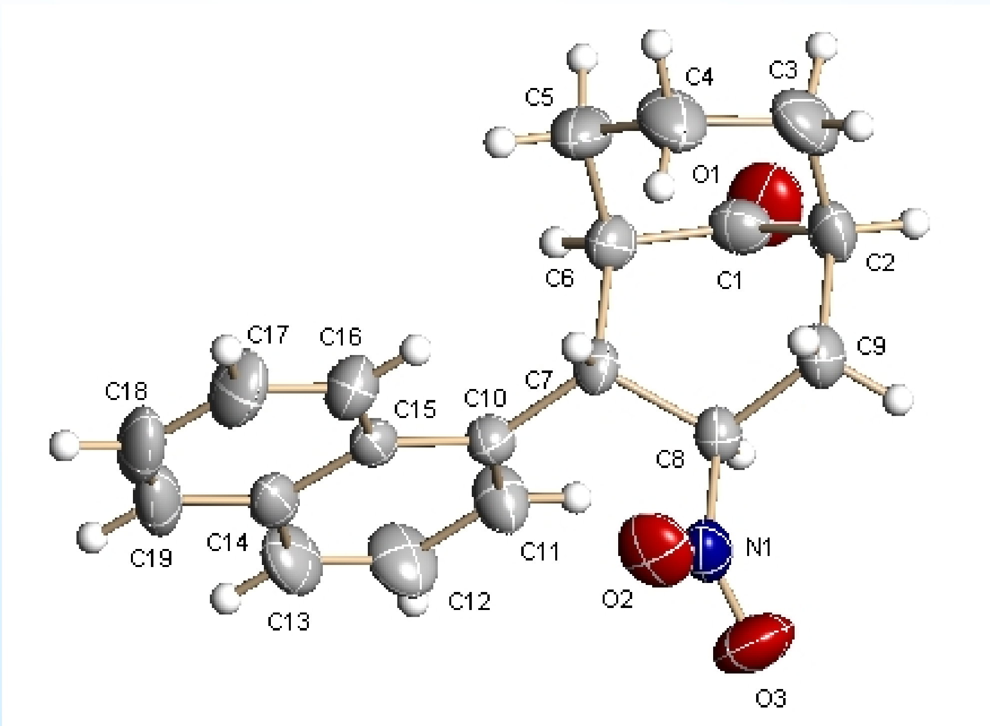
Cl
–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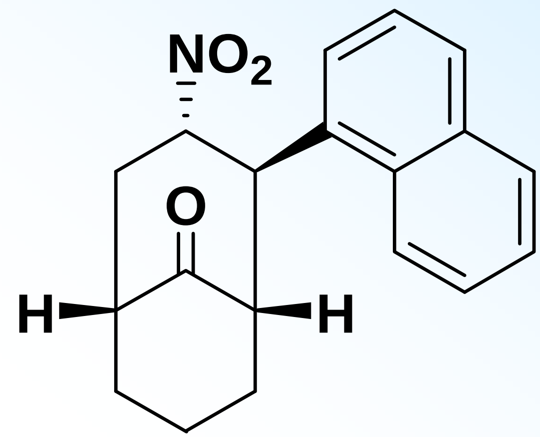
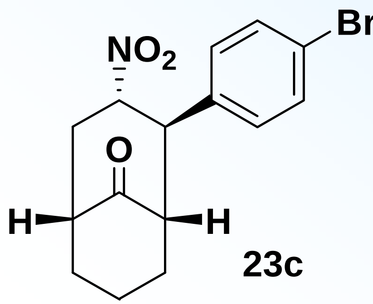
C11
C19
O2
C12
C13
O3


NO2
O
H
H

23g



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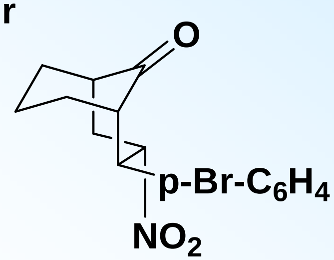

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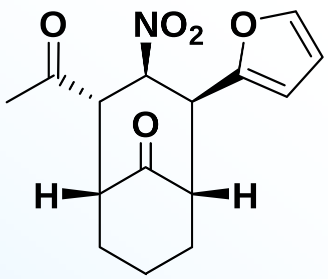

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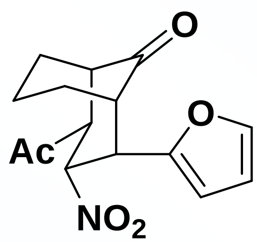

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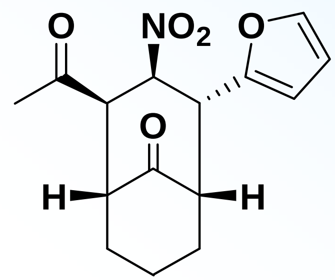

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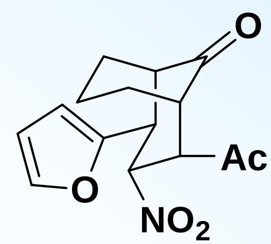

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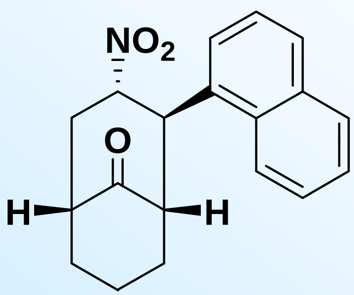

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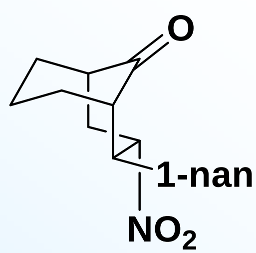

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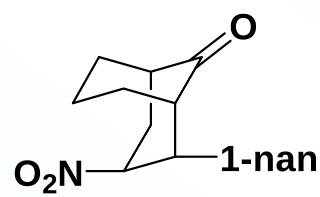

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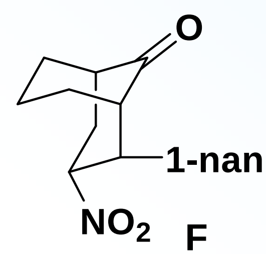

F

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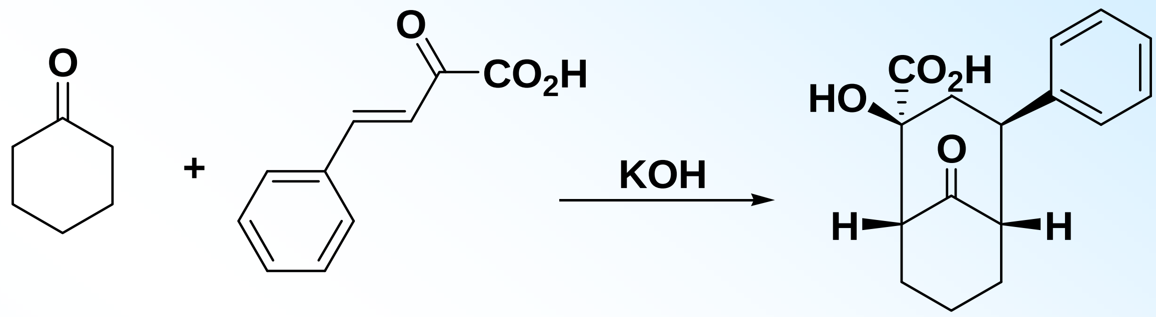

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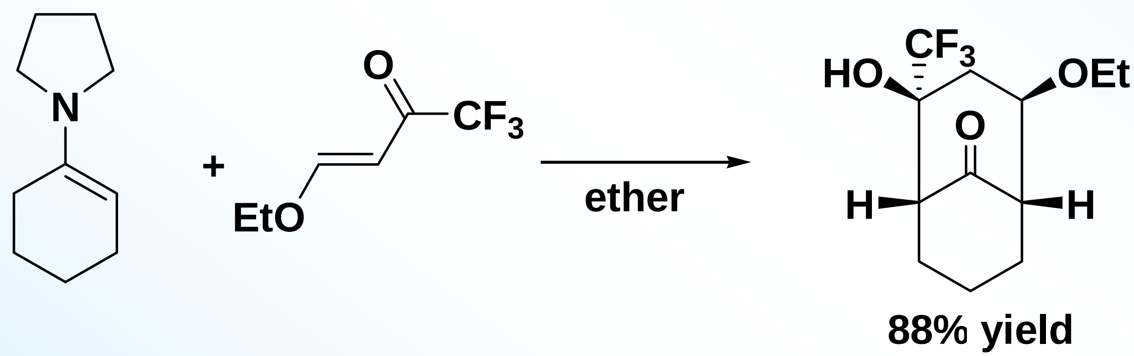

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