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N-Heterocyclic Carbene Catalysis via Azolium Dienolates: An Efficient Strategy for Enantioselective Remote Functionalizations

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2018/04/02

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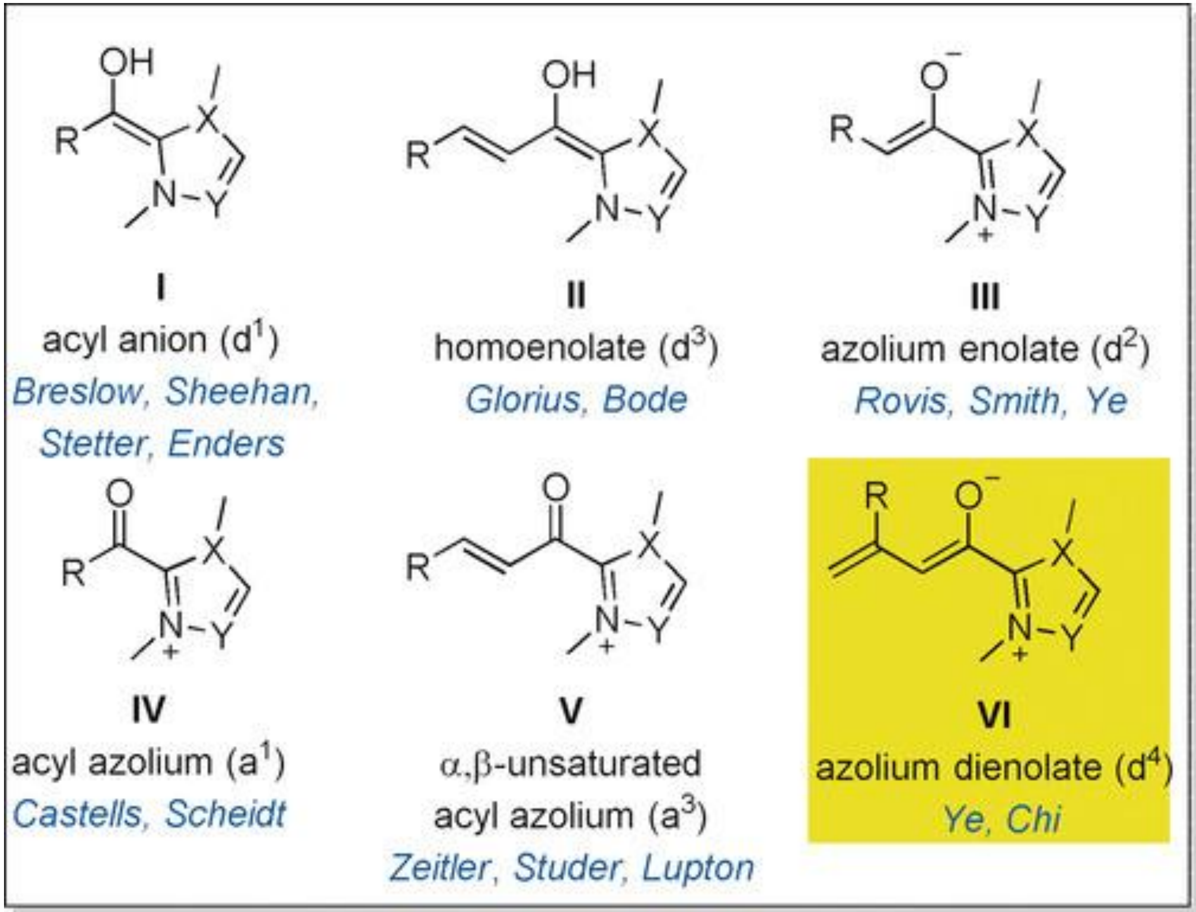
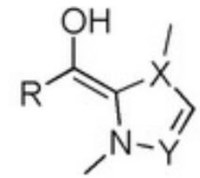
NHC generated reactive intermediates

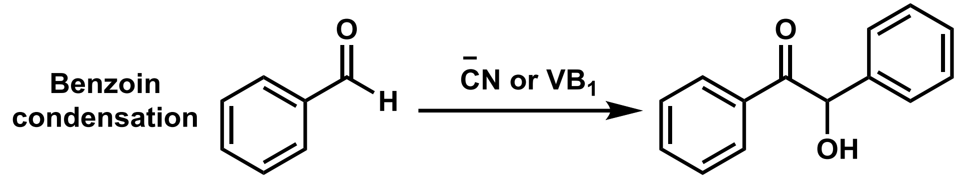


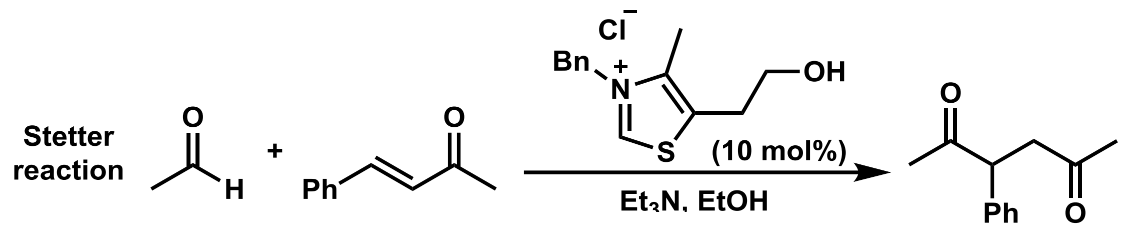


I

acyl anion (d[1])

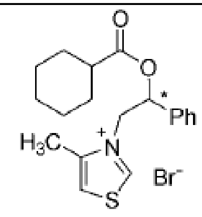
Breslow, Sheehan, Stetter, Enders





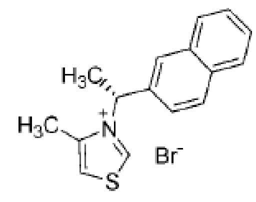
1966： Sheenhan and Hunneman

First asymmetric benzoin (NHCs):



8

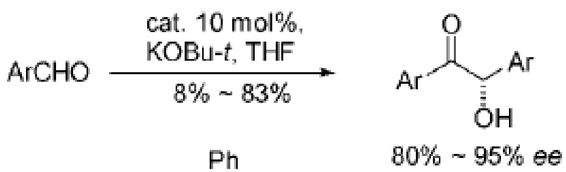
2% ee

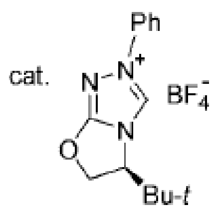


9

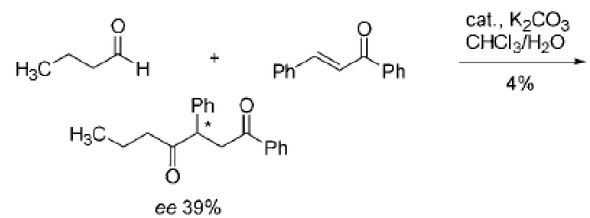
52% ee, 2% yield

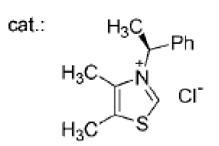
2002: Enders



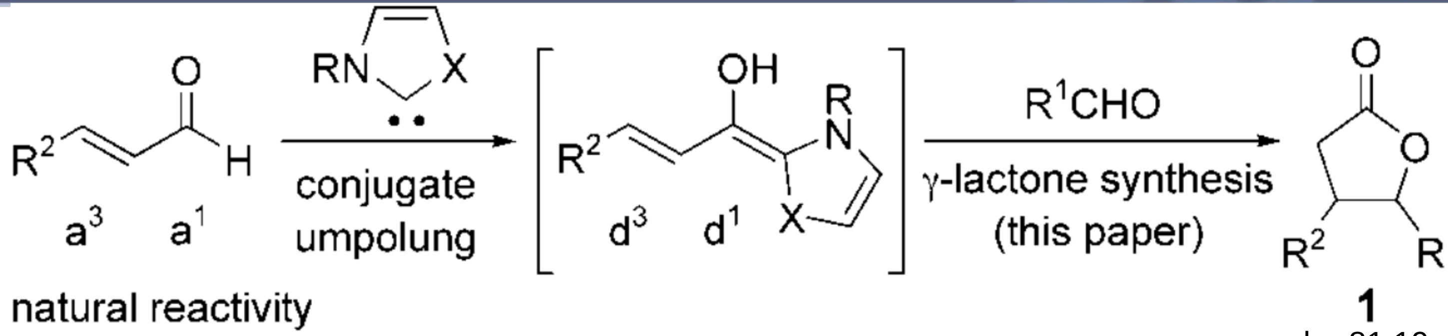


13



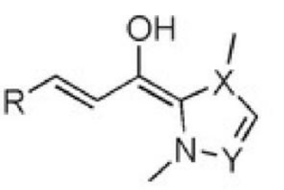


Glorius



1

dr= 81:19

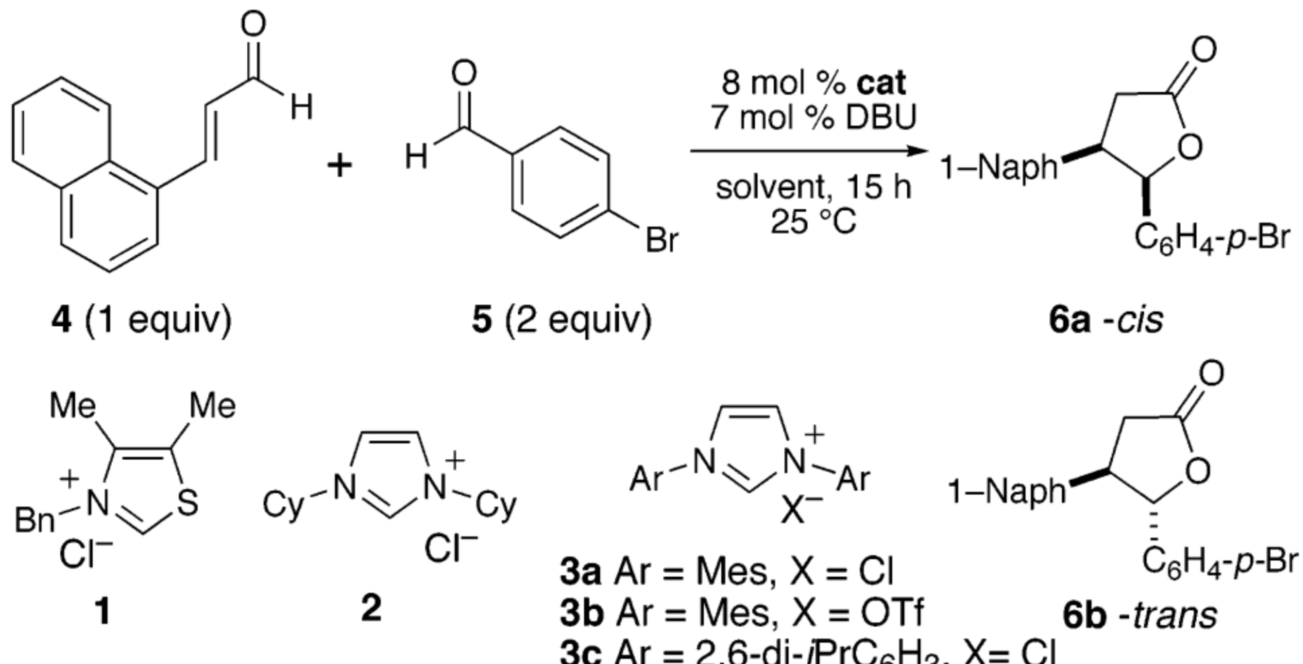


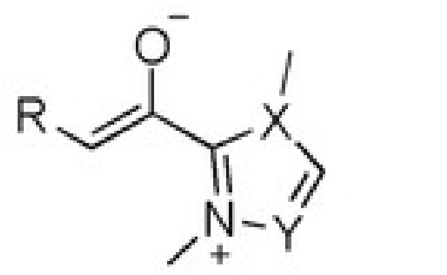
II

homoenolate (d^3)

Glorius, Bode

Bode

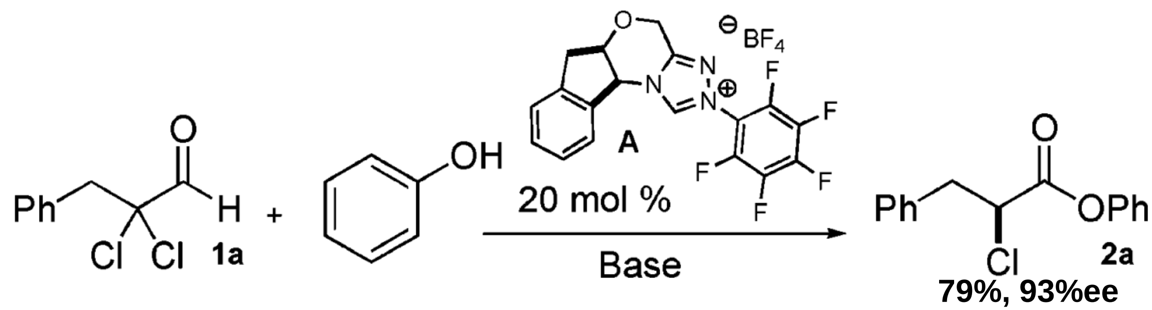


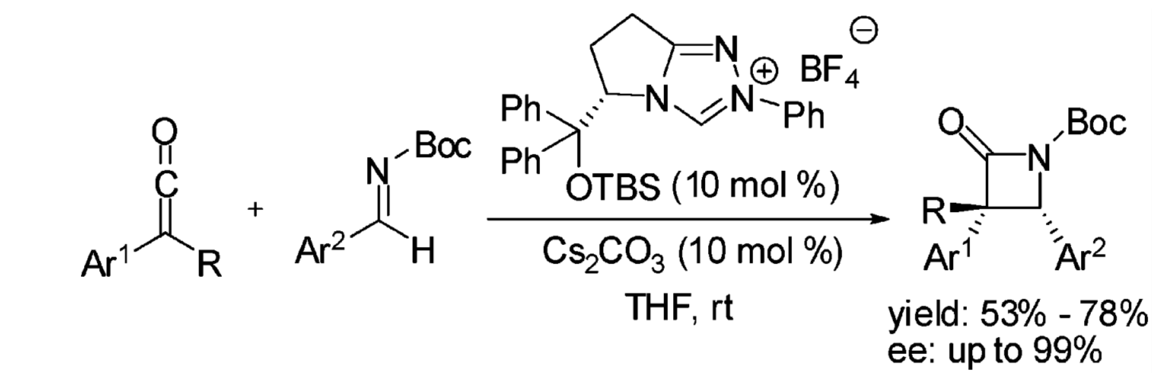


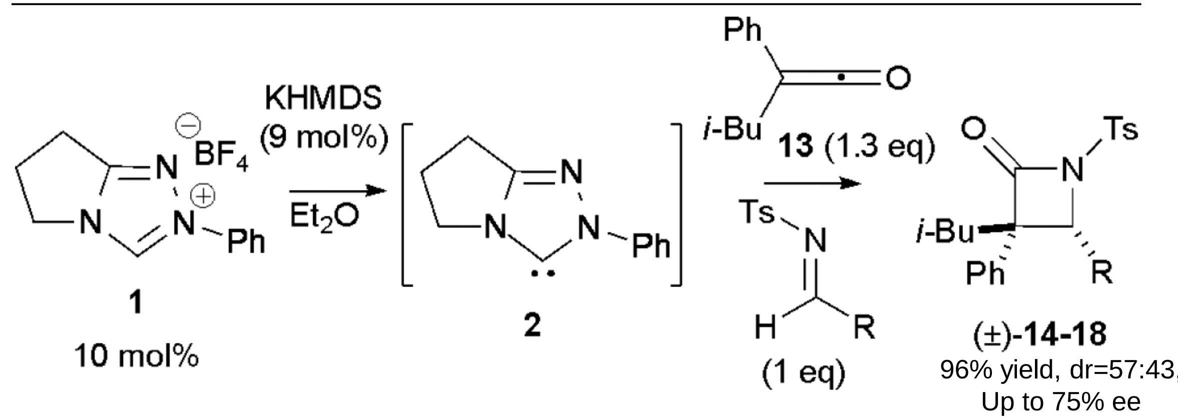
III

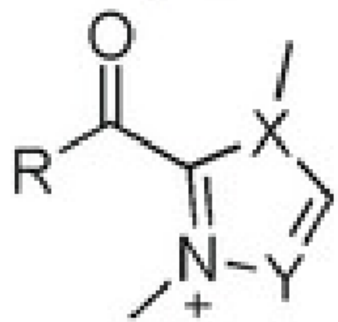
azolium enolate (d^2)

Rovis, Smith, Ye





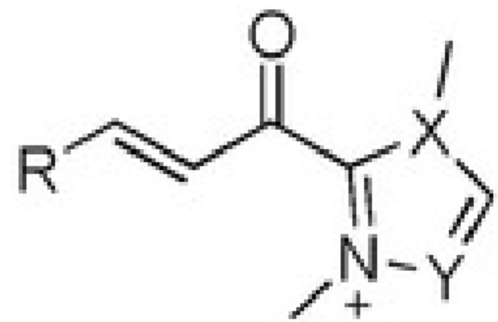




IV

acyl azolium (a^1)

Castells, Scheidt

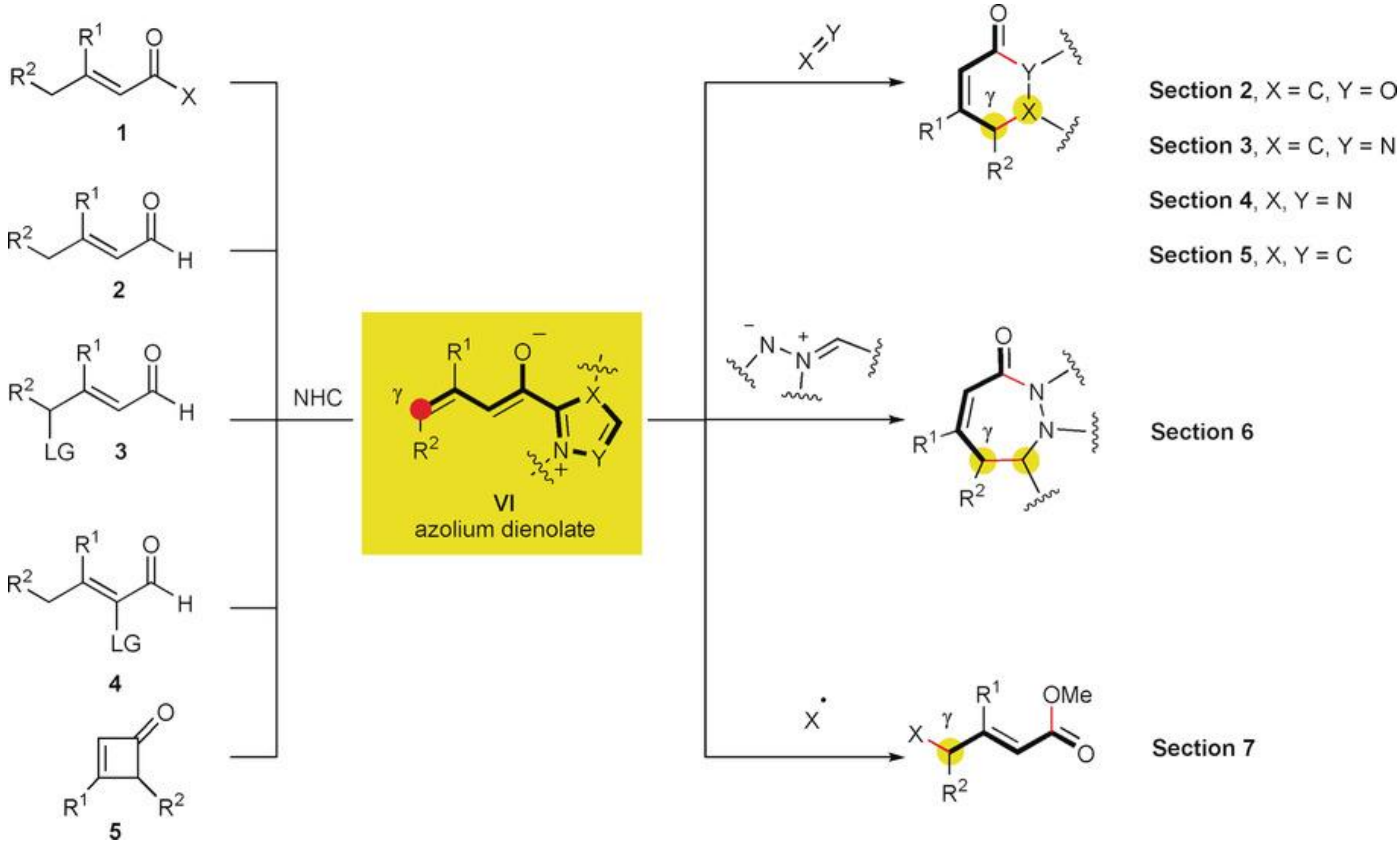


V

α,β-unsaturated acyl azolium (a^3)

Zeitler, Studer, Lupton

ACS Catal. **2017**, *7*, 2583; *Tetrahedron Lett.* **1977**, *18*, 205; *Org. Lett.* **2007**, *9*,371.



R1
O
R2
X
1
H
2
LG
3
4
5
NHC
γ
R2
VI
azolium dienolate
X=Y
Y
X
Section 2, X = C, Y = O
Section 3, X = C, Y = N
Section 4, X, Y = N
Section 5, X, Y = C
N
Section 6
X
OMe
Section 7

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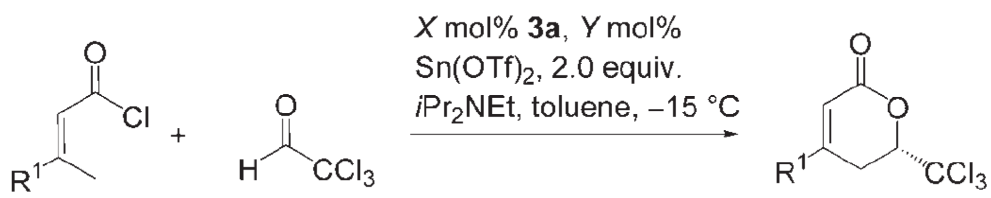
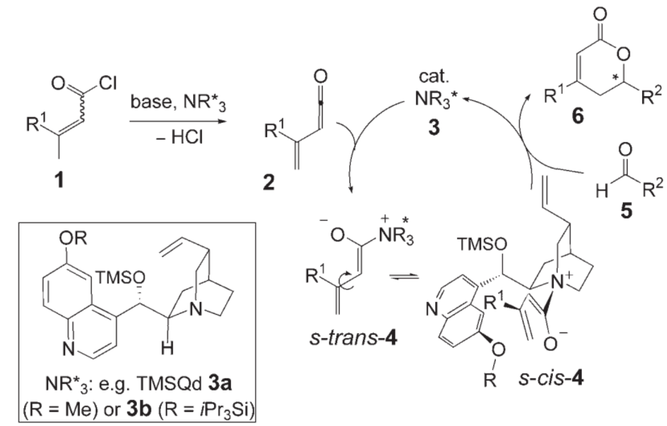
Contents

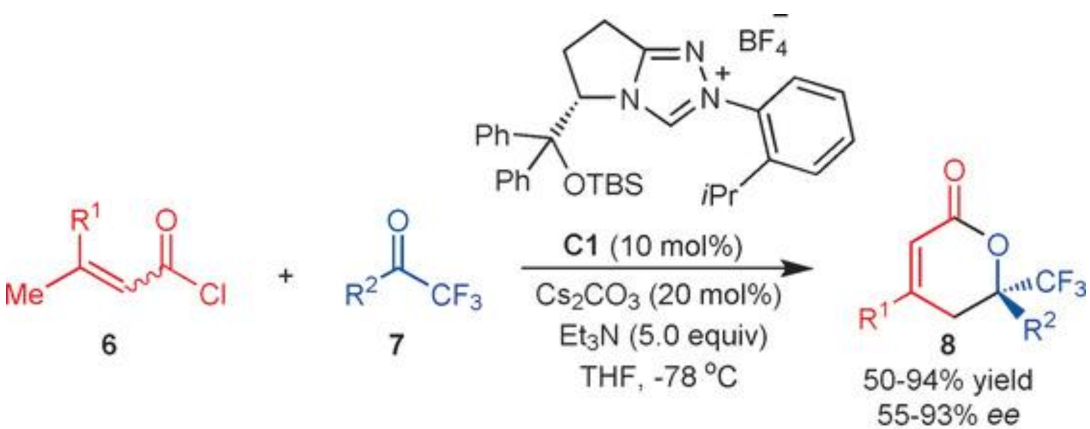
2.1.1 Azolium Dienolates Generated from α,β-Unsaturated Acid Chlorides

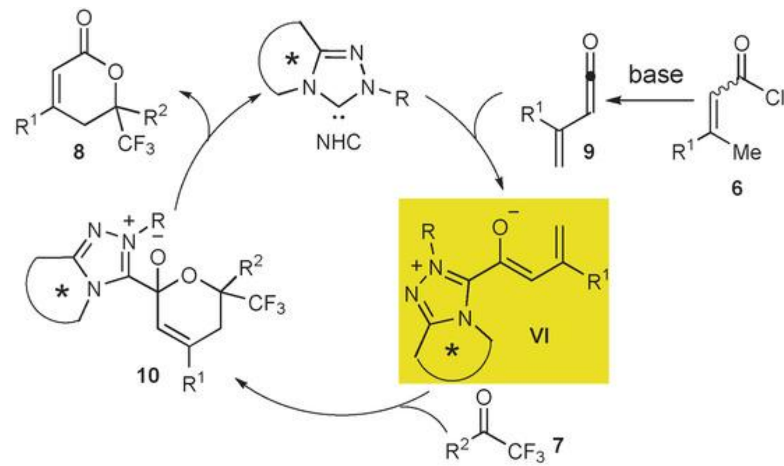


2007 Peters



Ye

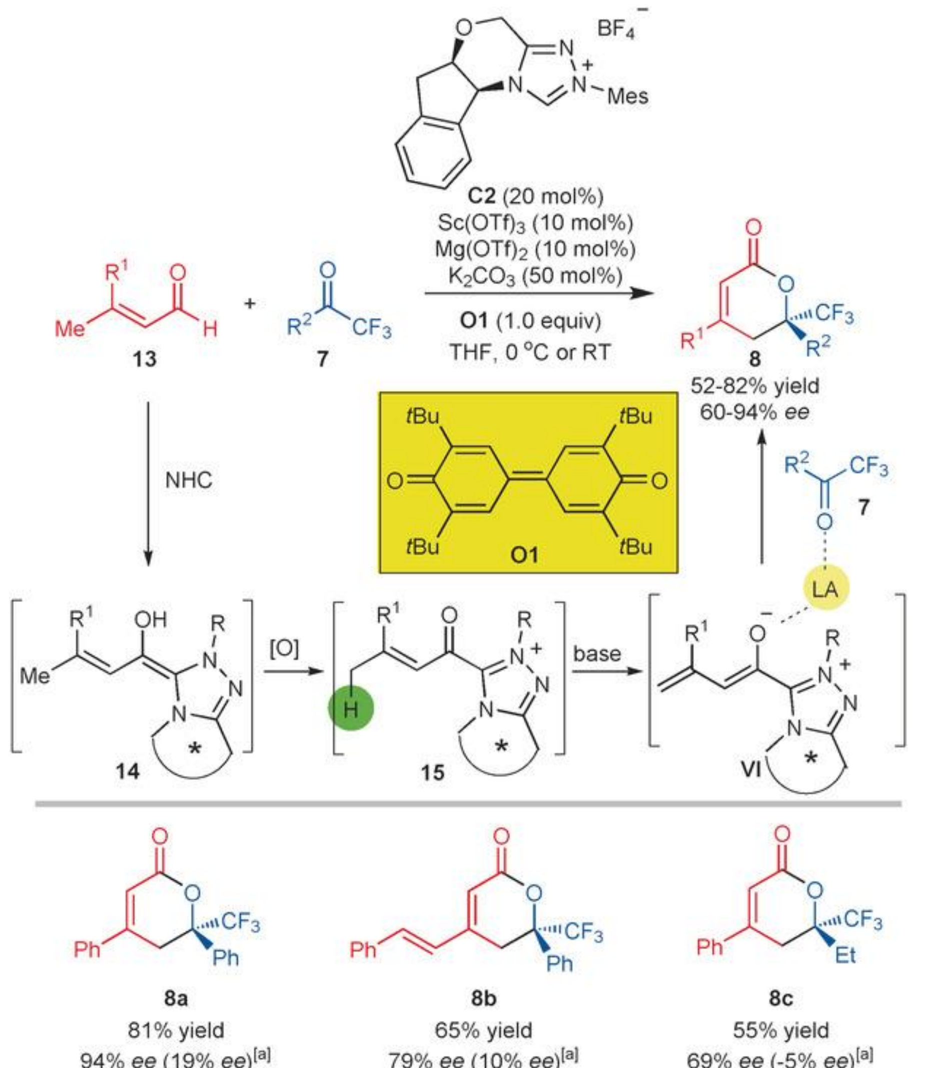




first use of NHC-catalyzed [4+2] cycloaddition of α,β -unsaturated acid chlorides with trifluoromethyl ketones.

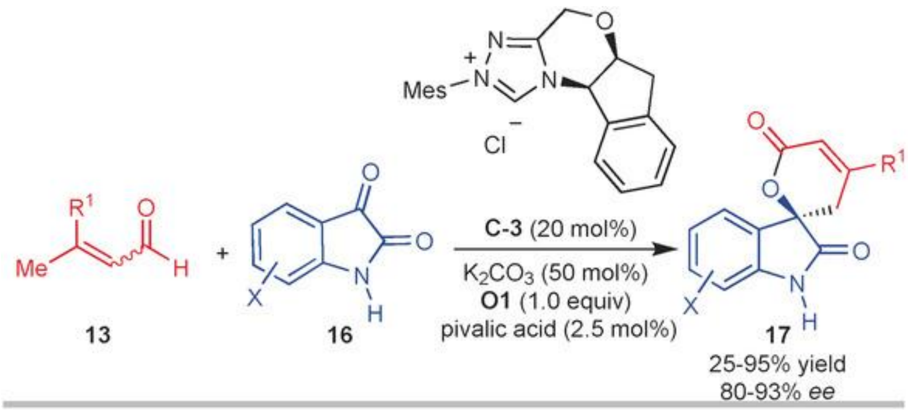
R1
O
Me
Cl
6
+
O
O
N
X
R2
11
C1 (10 mol%)
Cs2CO3 (20 mol%)
Et3N (5 equiv)
THF, -40 °C
O
O
R1
O
N
X
R2
12
55-83% yield
77-95% ee

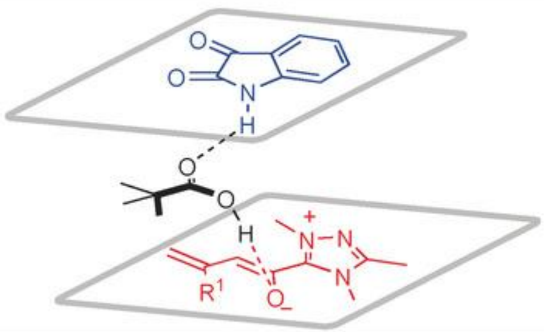
Chi and co-workers

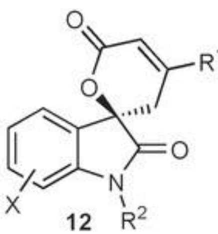


[a] The ee for the reaction without the addition of the Lewis acid is given in parentheses

Zhong and co-workers

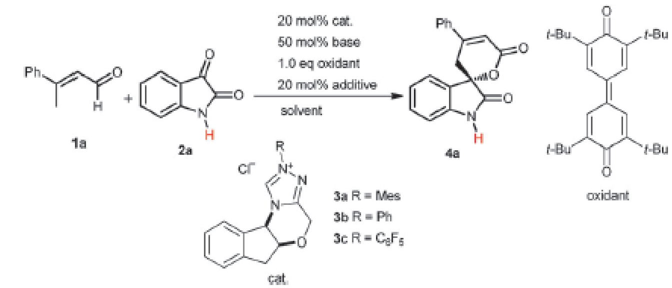






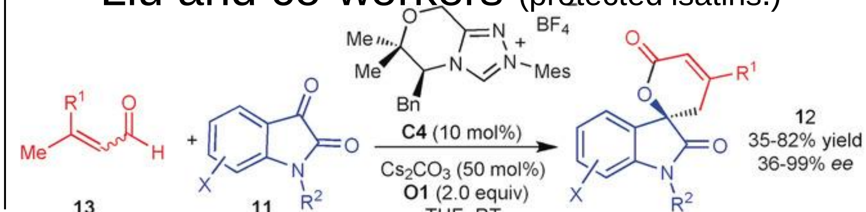
Entry	R^2	Yield [%]	*ee* [%]
1	$COCH_3$	25	40
2	Me	80	29
3	Bn	87	19

NHC-catalyzed oxidative [4+2] cycloaddition of enals with unprotected isatins.

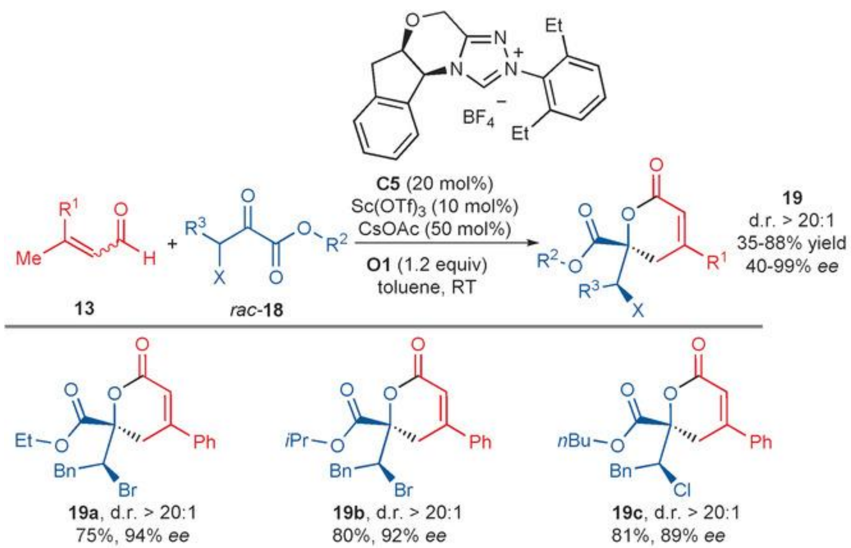


Entry	Cat.	Solvent	Base	Additive	Yield[b] (%)	ee[c] (%)
1	3a	THF	K_2CO_3	—	50	44
2	3b	THF	K_2CO_3	—	25	35
3	3c	THF	K_2CO_3	—	Trace	n.d
4	3a	THF	K_2CO_3	$Sc(OTF)_3$	23	34
5	3a	THF	K_2CO_3	$Mg(OTF)_2$	35	24
6	3a	THF	K_2CO_3	LiOTF	40	46
7	3a	THF	K_2CO_3	$LiBF_4$	26	10
8	3a	THF	K_2CO_3	LiCl	25	20
9	3a	THF	K_2CO_3	AcOH	63	60
10	3a	THF	K_2CO_3	Propanoic acid	67	74
11	3a	THF	K_2CO_3	Pivalic acid	68	76
12	3a	THF	K_2CO_3	Pivalic acid	65	80
13	3a	Ether	K_2CO_3	Pivalic acid	25	82
14	3a	MTBE	K_2CO_3	Pivalic acid	46	74
15	3a	Toluene	K_2CO_3	Pivalic acid	59	68
16	3a	CH_2Cl_2	K_2CO_3	Pivalic acid	45	34
17[d]	**3a**	**THF/ether 1 : 1**	**K_2CO_3**	**Pivalic acid**	**85**	**83**
18	3a	THF/ether 1 : 1	Cs_2CO_3	Pivalic acid	40	70
19	3a	THF/ether 1 : 1	Et_3N	Pivalic acid	75	72
20	3a	THF/ether 1 : 1	DIPEA	Pivalic acid	82	76
21	3a	THF/ether 1 : 1	NaOAc	Pivalic acid	85	70
22	3a	THF/ether 1 : 1	DMAP	Pivalic acid	70	76

Liu and co-workers (protected isatins.)

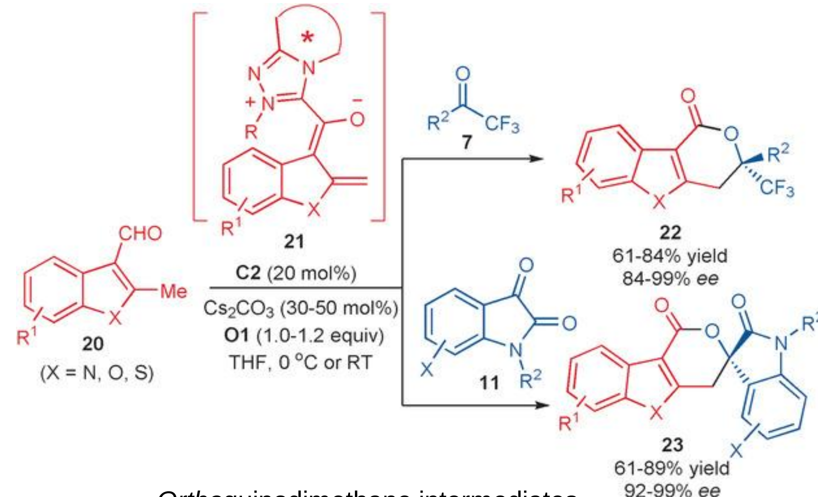


J. Wang.



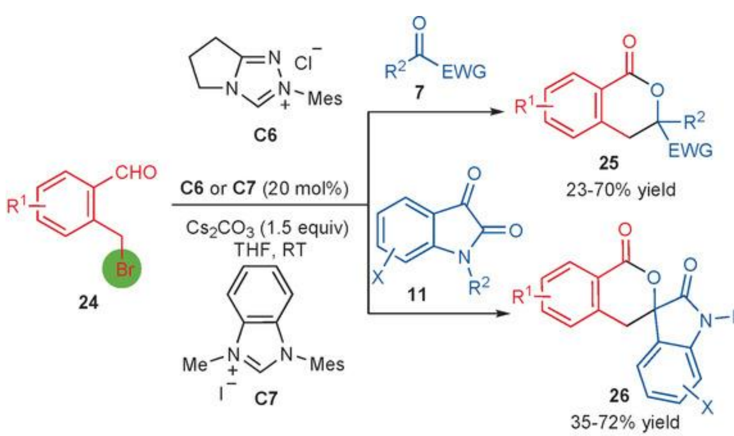
an intermolecular dynamic kinetic resolution of α -ketoesters.

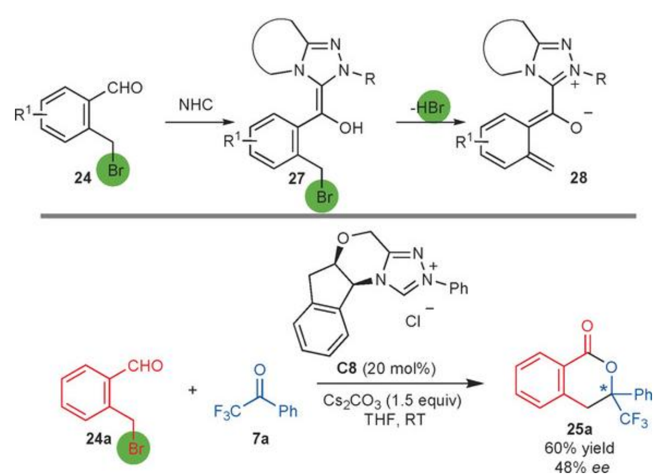
Chi and co-workers



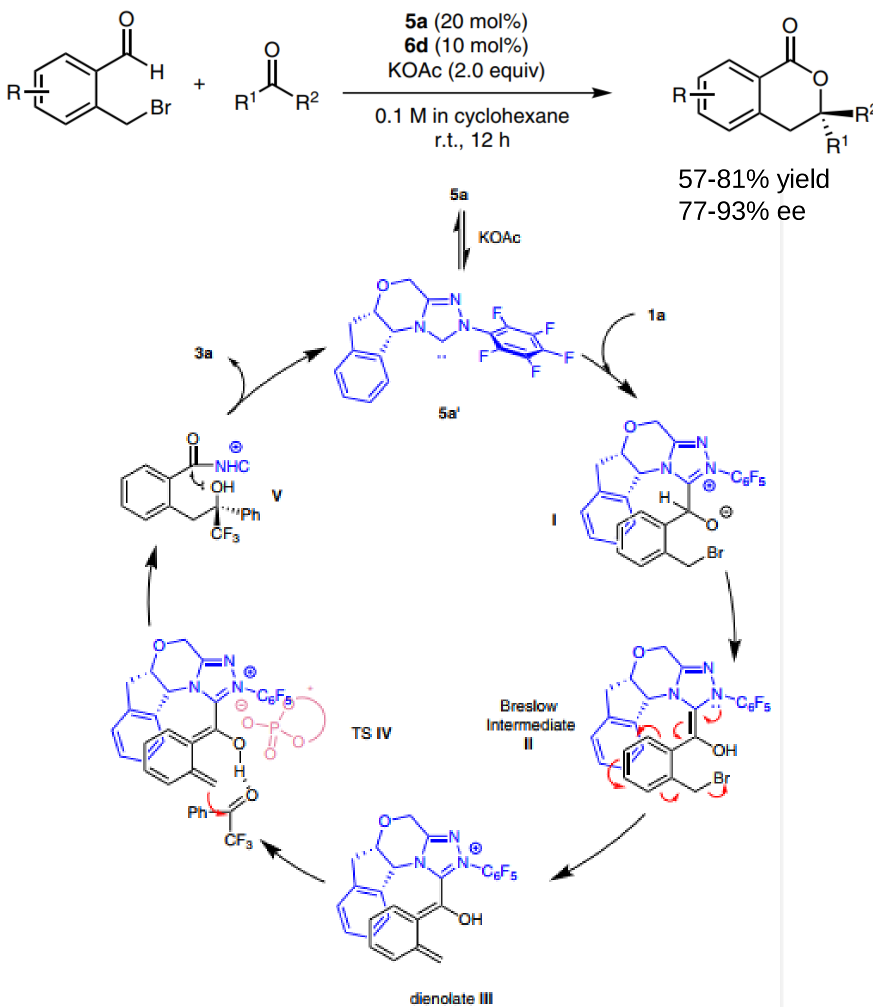
*Ortho*quinodimethane intermediates.

Glorius

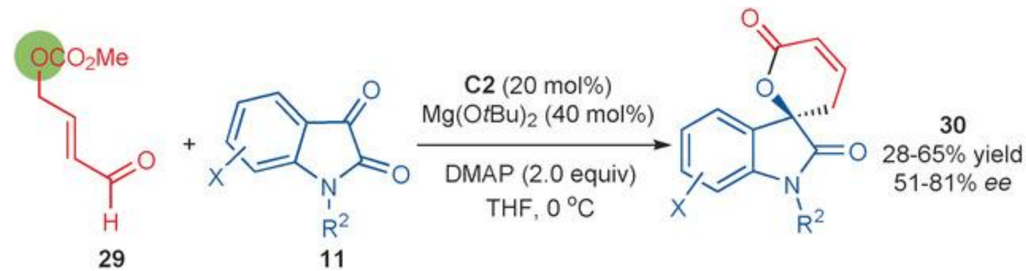




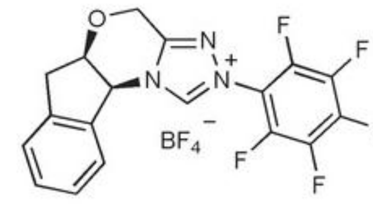
Rovis and co-workers



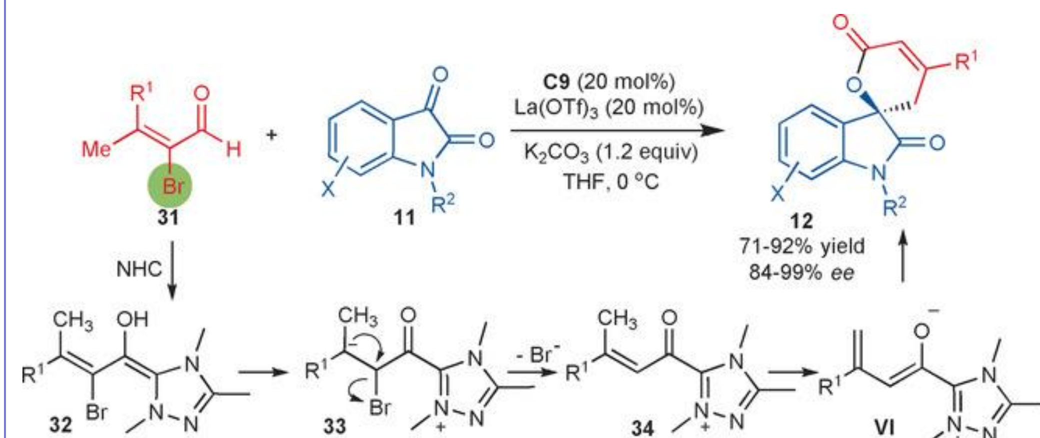
Ye and co-workers



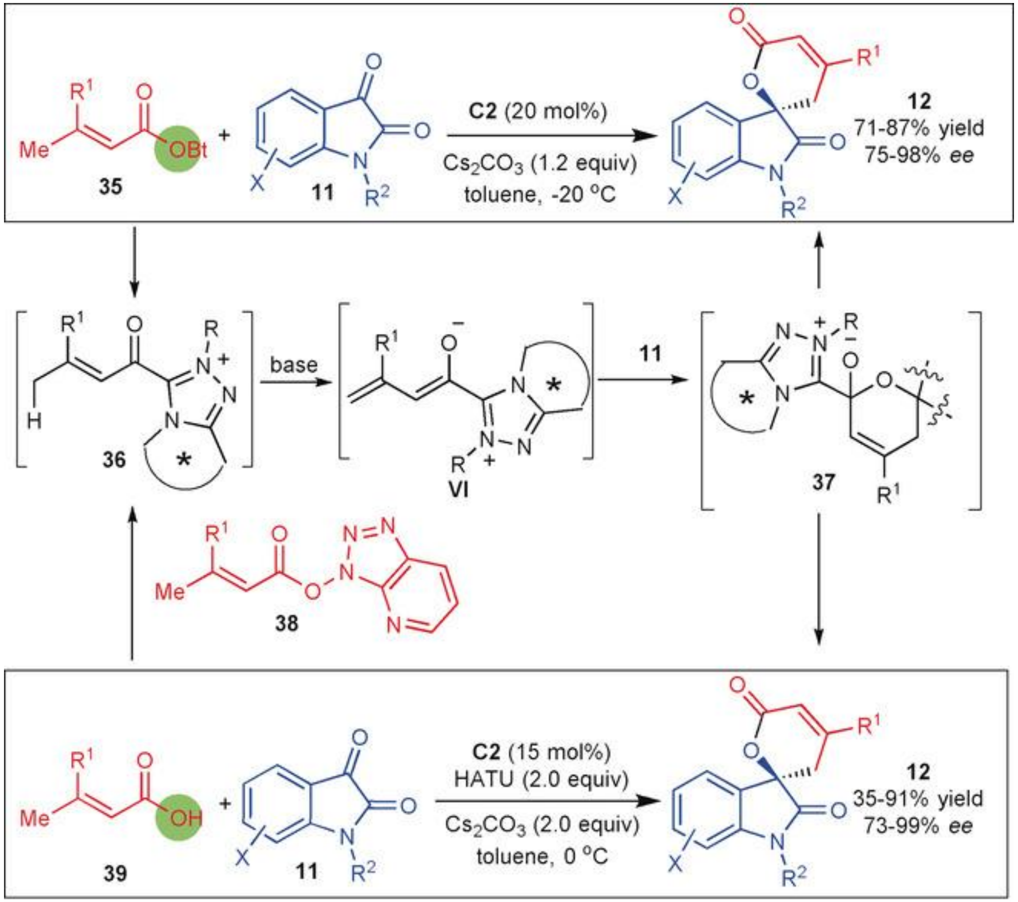
Yao and co-workers



C9



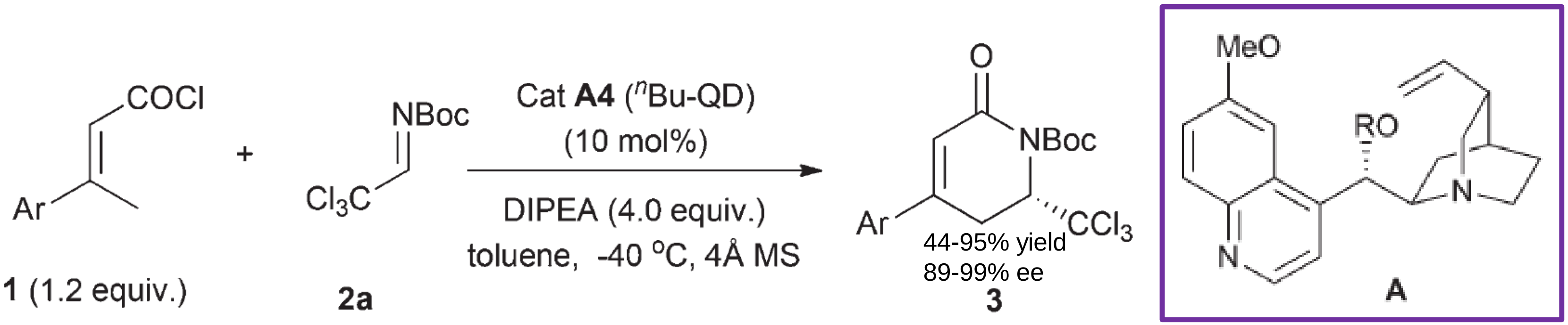
2015: Yao and co-workers



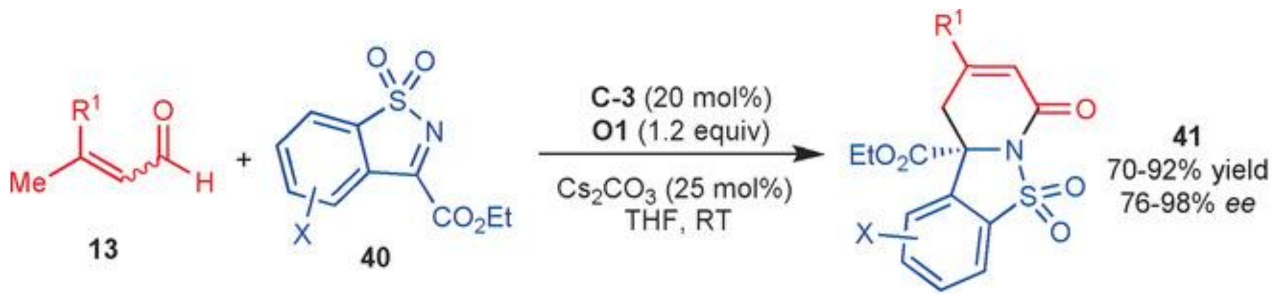
2.2. [4+2] cycloadditions with azomethine compounds

2.2.1. Azolium Dienolates Generated from α,β -Unsaturated Aldehydes

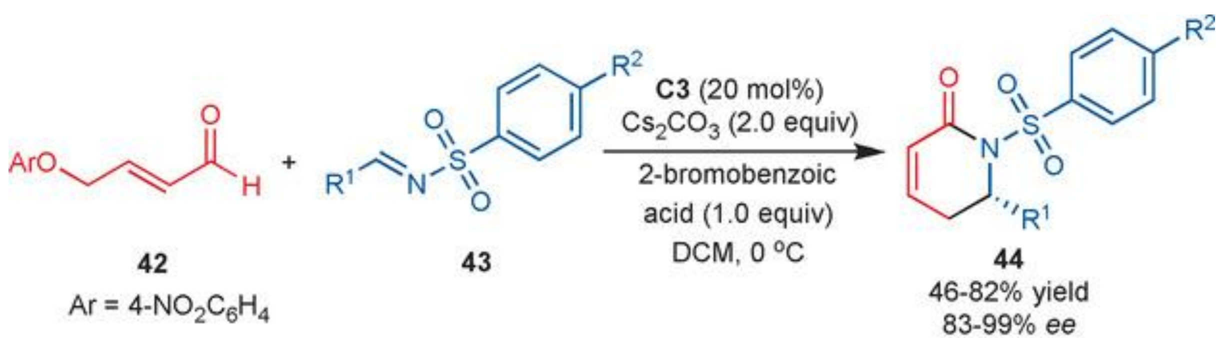
Ye



Chi

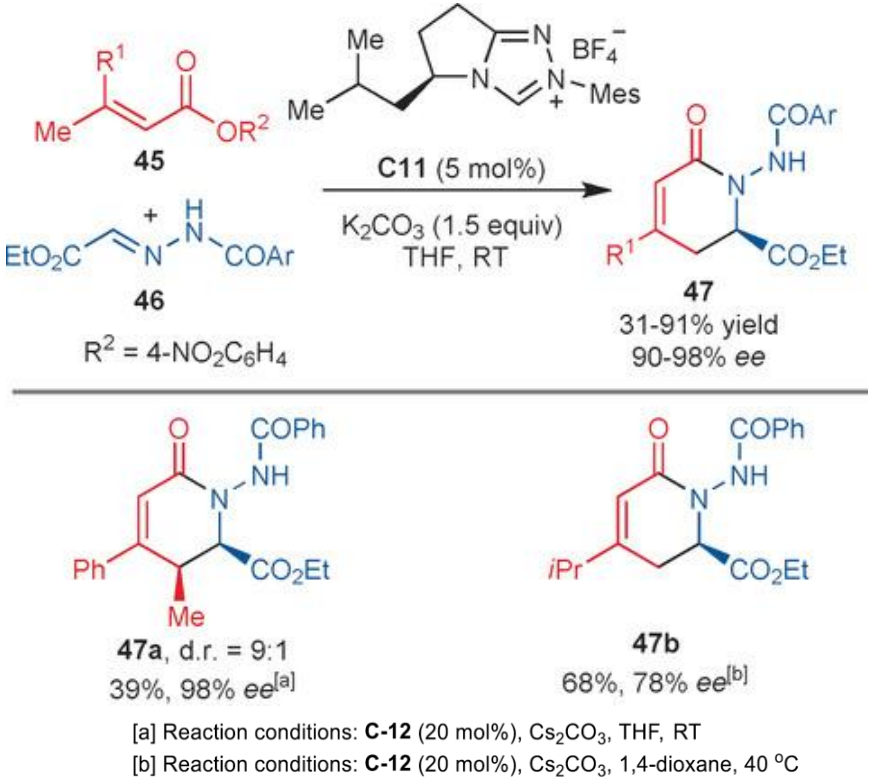


Liu

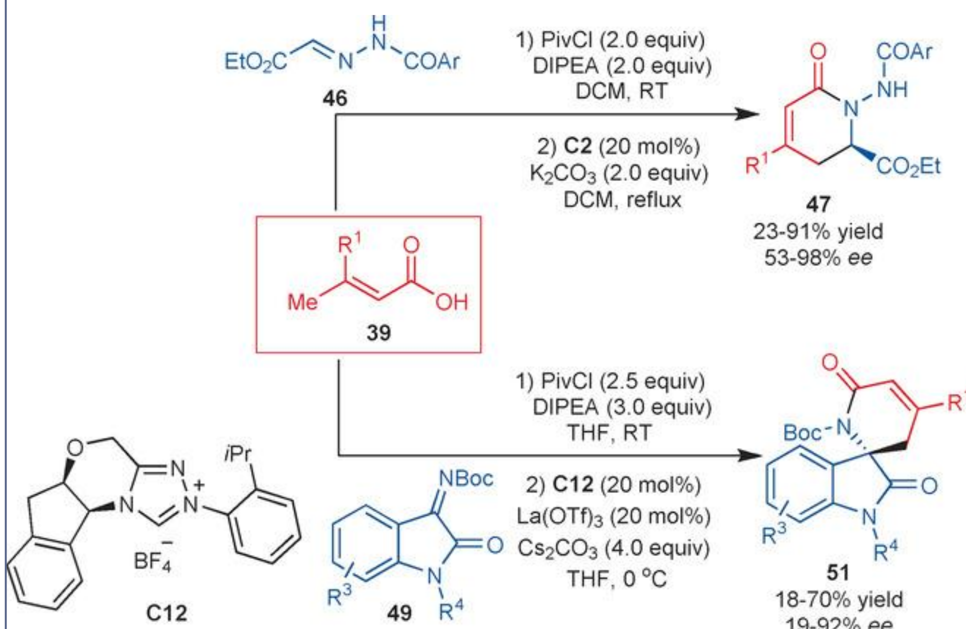


2.2.2. Azolium Dienolates Generated from α,β -Unsaturated Carboxylic Acid Derivatives

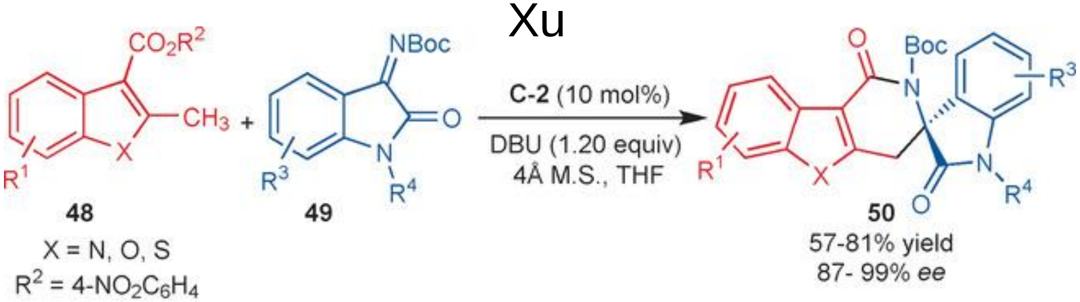
Chi



Ye

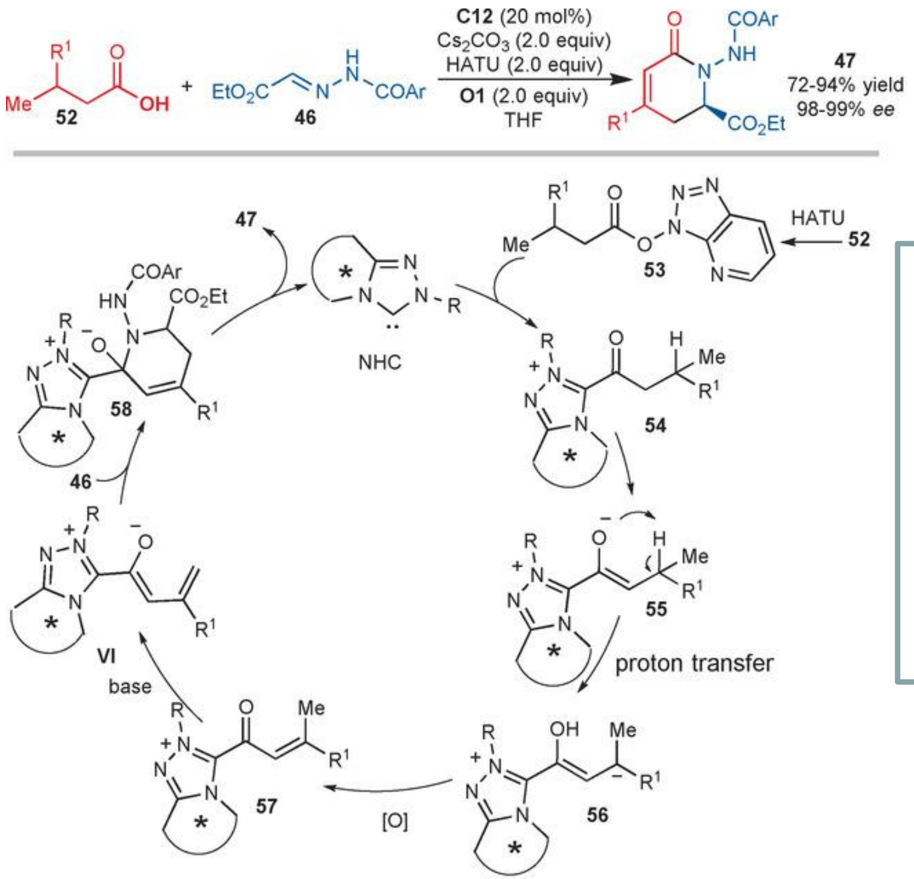


Xu

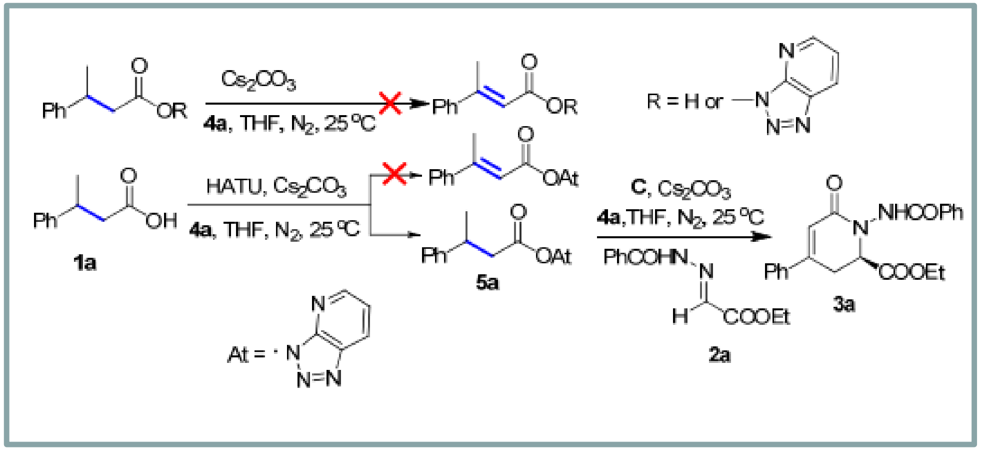


2.2.3. Azolium Dienolates Generated from Saturated Carboxylic Acids

Yao

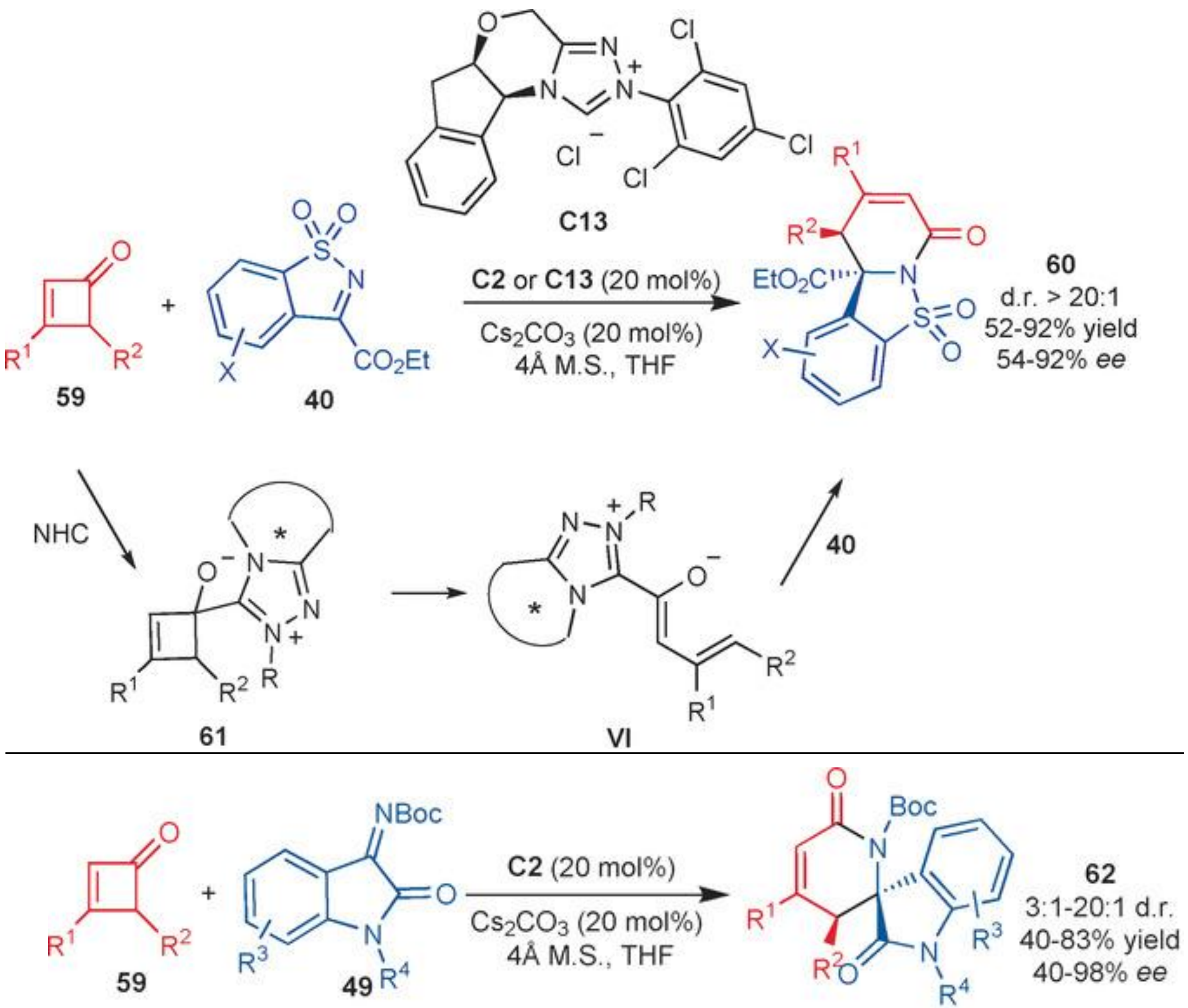


Mechanism Experiment

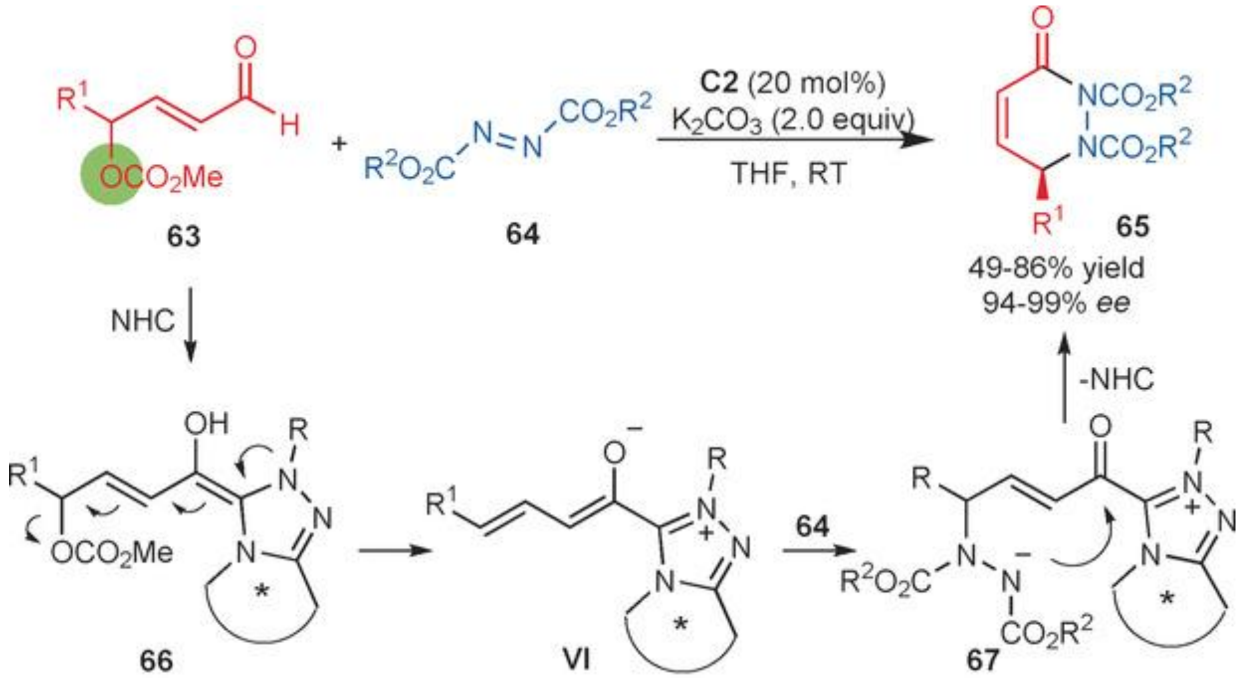


4a=O1, C=NHC

Chi


C13
C2 or C13 (20 mol%)
Cs2CO3 (20 mol%)
4Å M.S., THF
59
40
60
d.r. > 20:1
52-92% yield
54-92% ee
NHC
61
VI
40
C2 (20 mol%)
Cs2CO3 (20 mol%)
4Å M.S., THF
59
49
62
3:1-20:1 d.r.
40-83% yield
40-98% ee

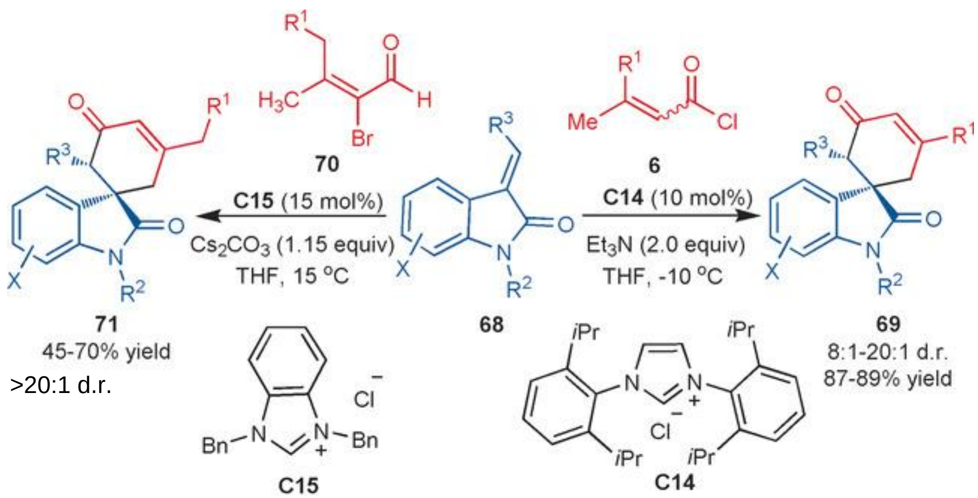
2.3. [4+2] Cycloadditions of Azodicarboxylates



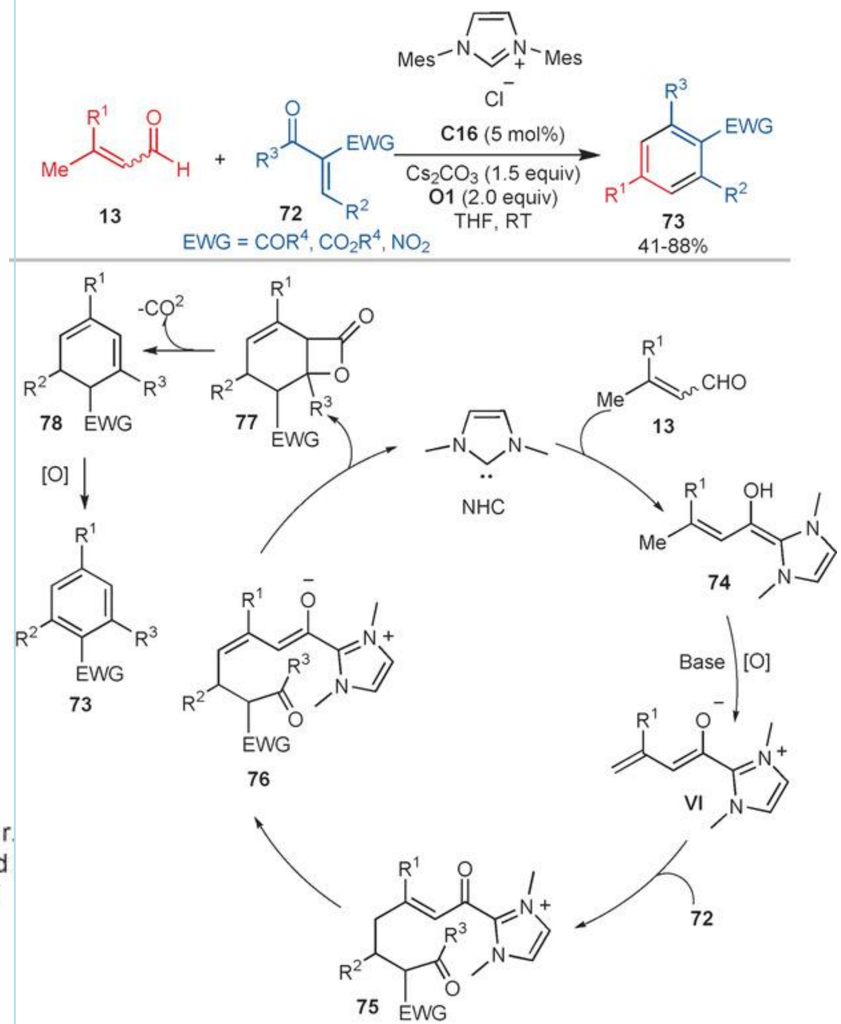
2.4. [4+2] Cycloadditions of Michael Acceptors

Yao

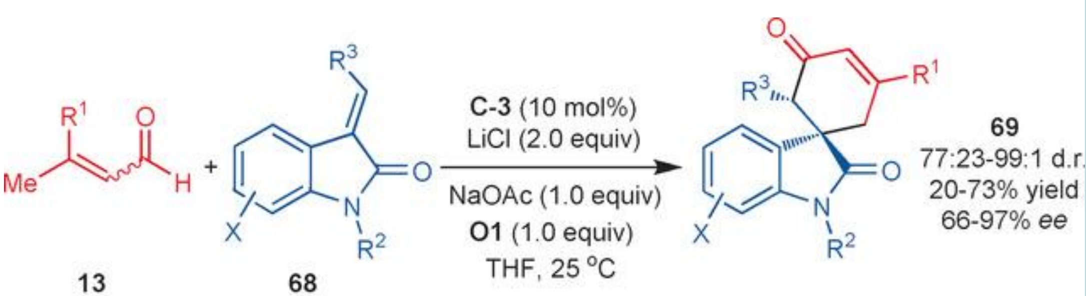
Ye



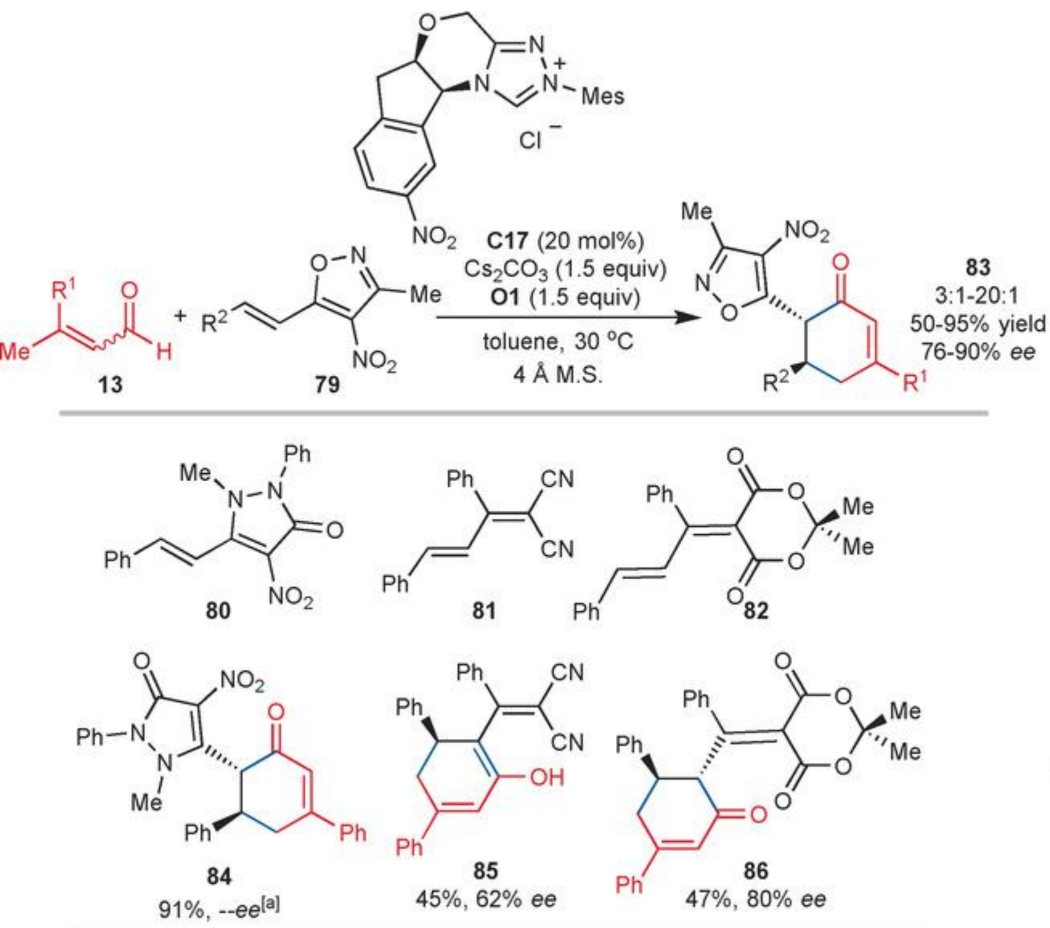
Chi



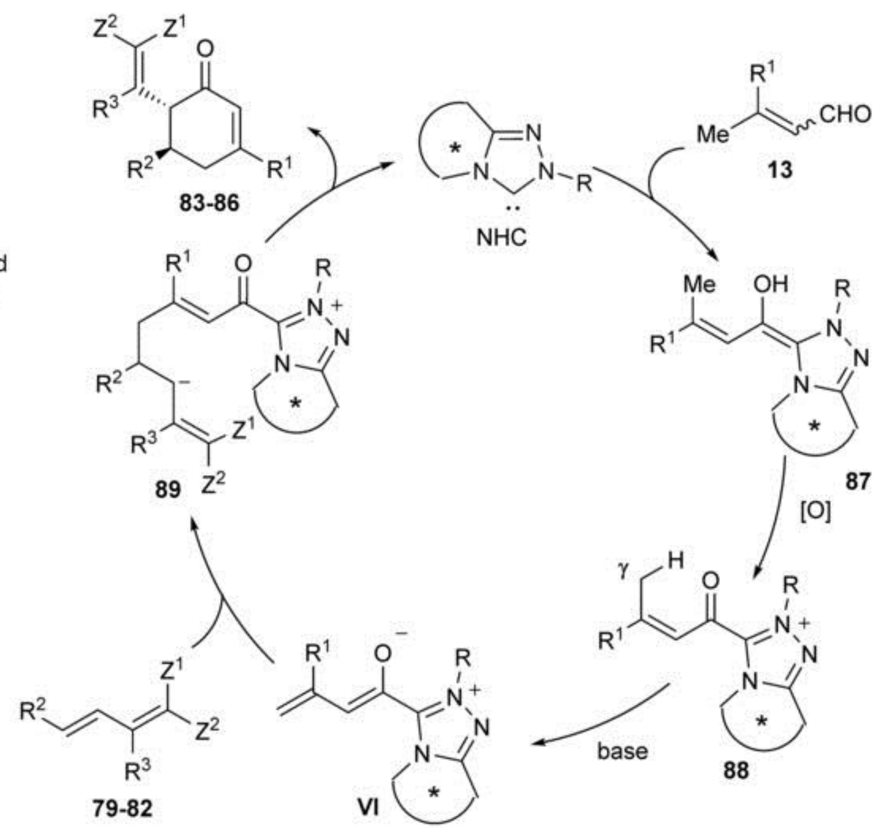
Liu



Enders



Mechanism

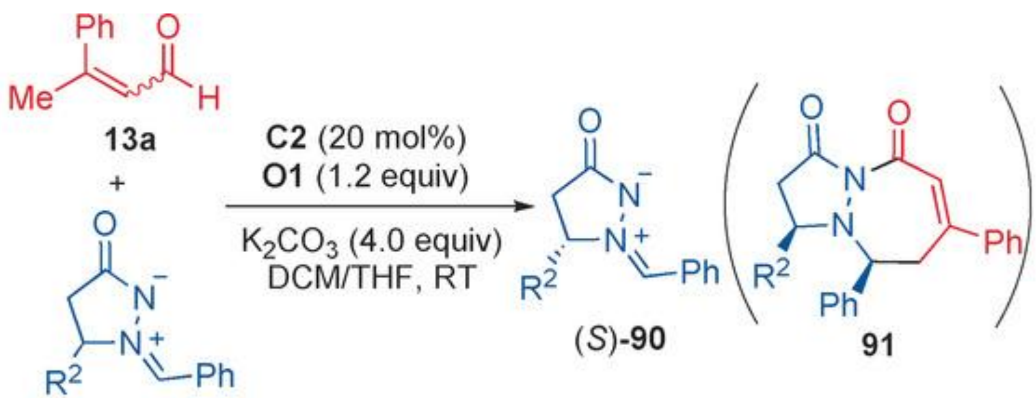


Synthesis of diaryl cyclohexenones via 1,6-addition of azolium dienolates to electron-deficient 2,4-dienes.

13 *rac*-**90** (2.2 equiv) **91**

d.r. > 20:1
52-81% yield
84-99% *ee*

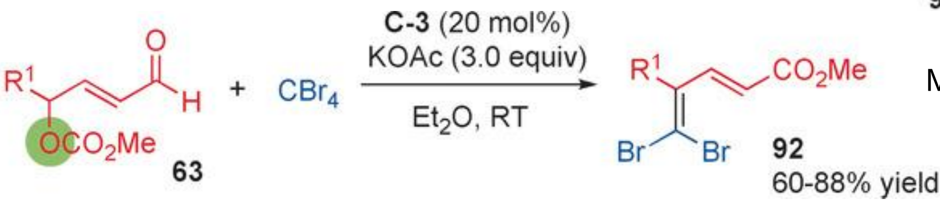
Chi



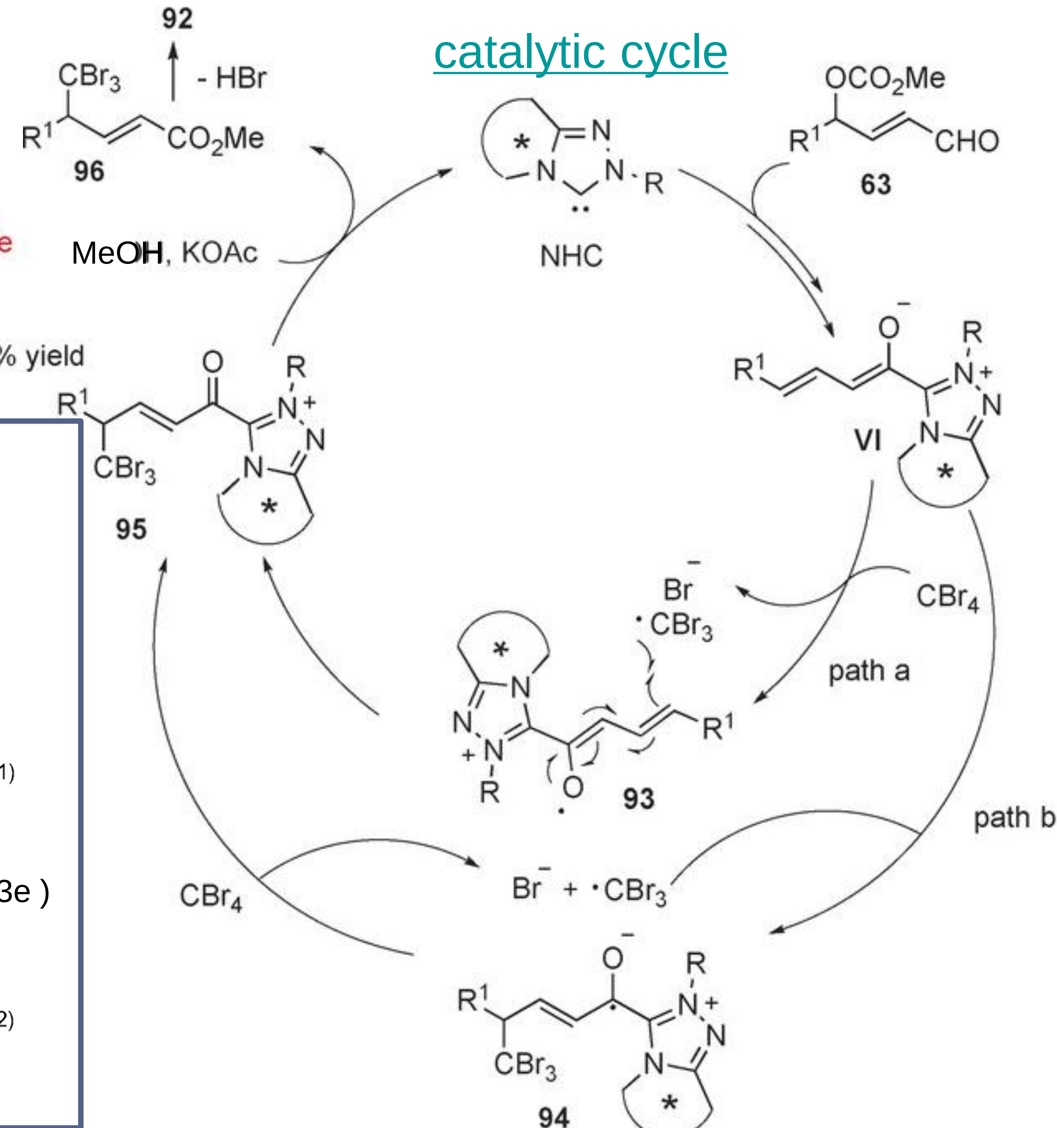
Entry	R^2	(*S*)-**90** yield [%]	(*S*)-**90** *ee* [%]	**91** yield [%]	**91** *ee* [%]	*S*
1	Ph	38	93	41	96	168
2	*i*Pr	51	53	26	99	339

2.6. Miscellaneous

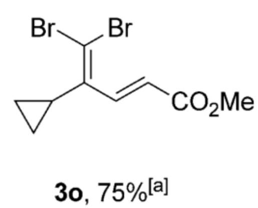
Sun

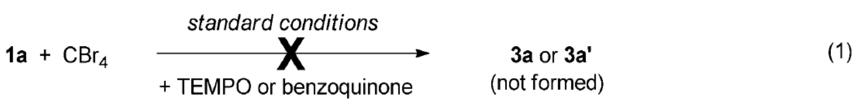


catalytic cycle

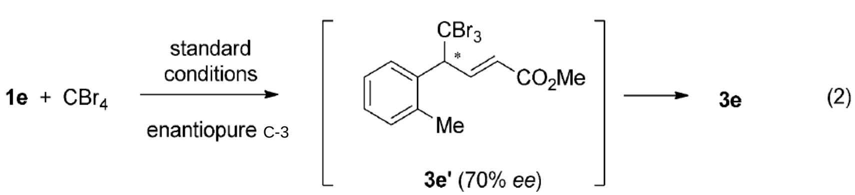


Mechanism experiments





R^1=Ph (3a)
2-MeC_6H_4 (3e)



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Contents

3. Summary and Outlook

1. The synthetic applications of azolium dienolate intermediates, readily generated from α,β-unsaturated aldehydes, functionalized enals, α,β-unsaturated acid derivatives and cyclobutenones

2. Remote functionalizations allowing the asymmetric synthesis of valuable molecules, such as δ-lactones, δ-lactams, γ-amino acids, cyclohexenones and sevenmembered dinitrogen-fused heterocyclic derivatives.

3. The limition of the dienophilic partners to activated ketones and imines.

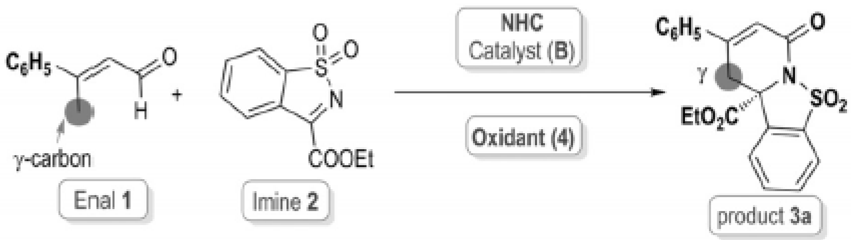
4. The recent findings on mering azolium dienolates with single-electron chemistry and the development of asymmetric methods under remote stereocontrol by combining azolium dienolates with the various radicals

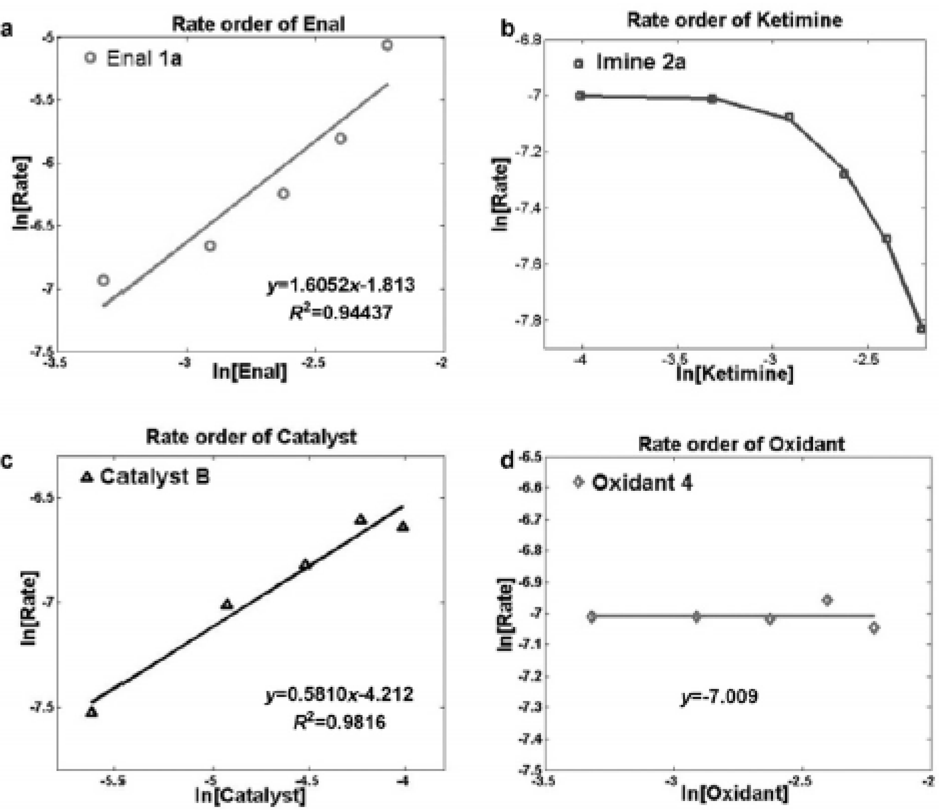
4. Acknowledgement

Thank *Prof.* Yong Huang;

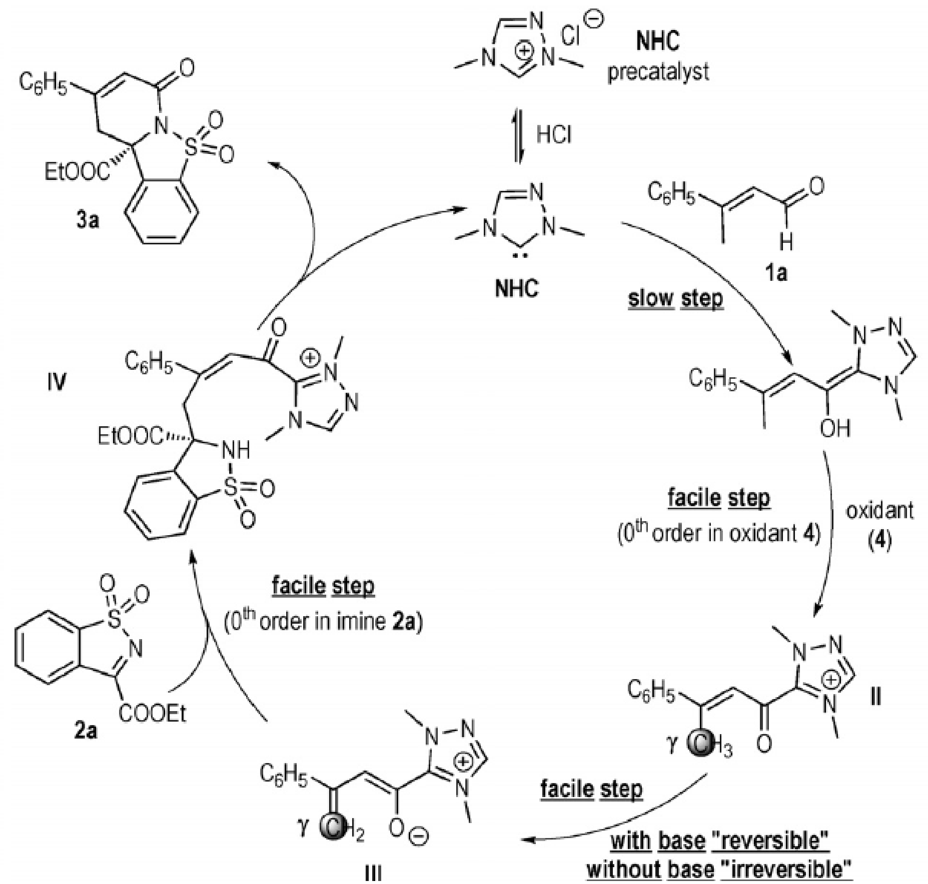
Thank *Dr.* Chen, Zhen Wang, Xinhang Zhang;

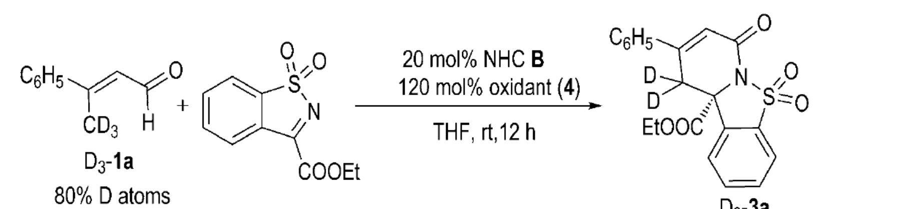
Thank all of you being here.





$K_{obs} = 3.1701\ s^{-1}$

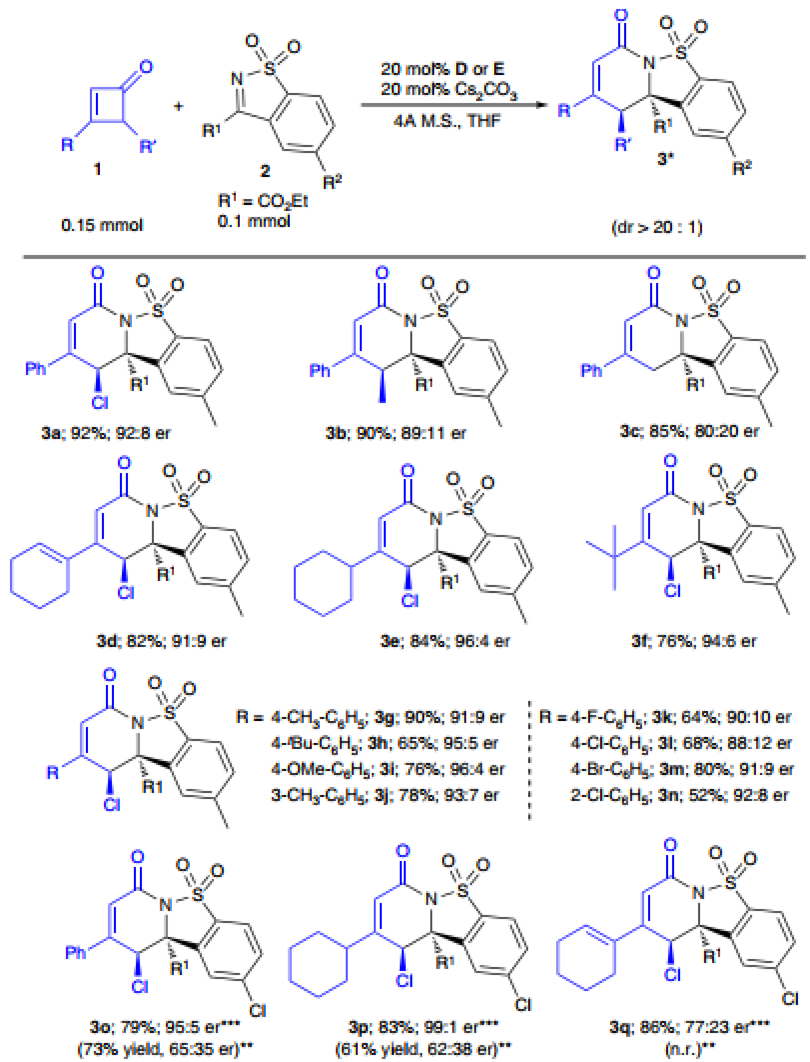




$K_h/K_d = 1.2$

without base: 77% yield, 97:3 e.r., **80% D atoms**

with base: 78% yield, 97:3 e.r., 50% D atoms



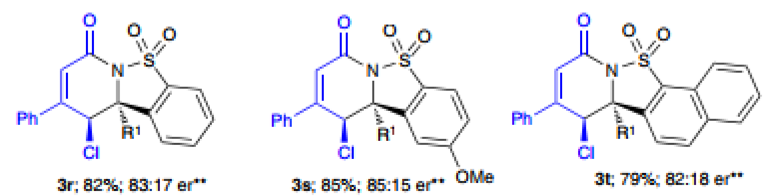
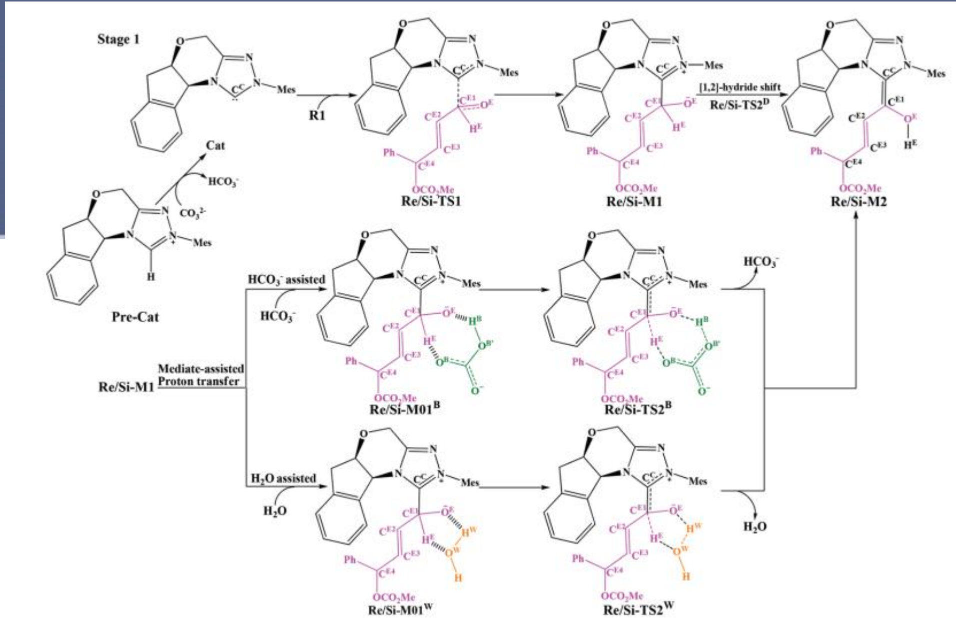
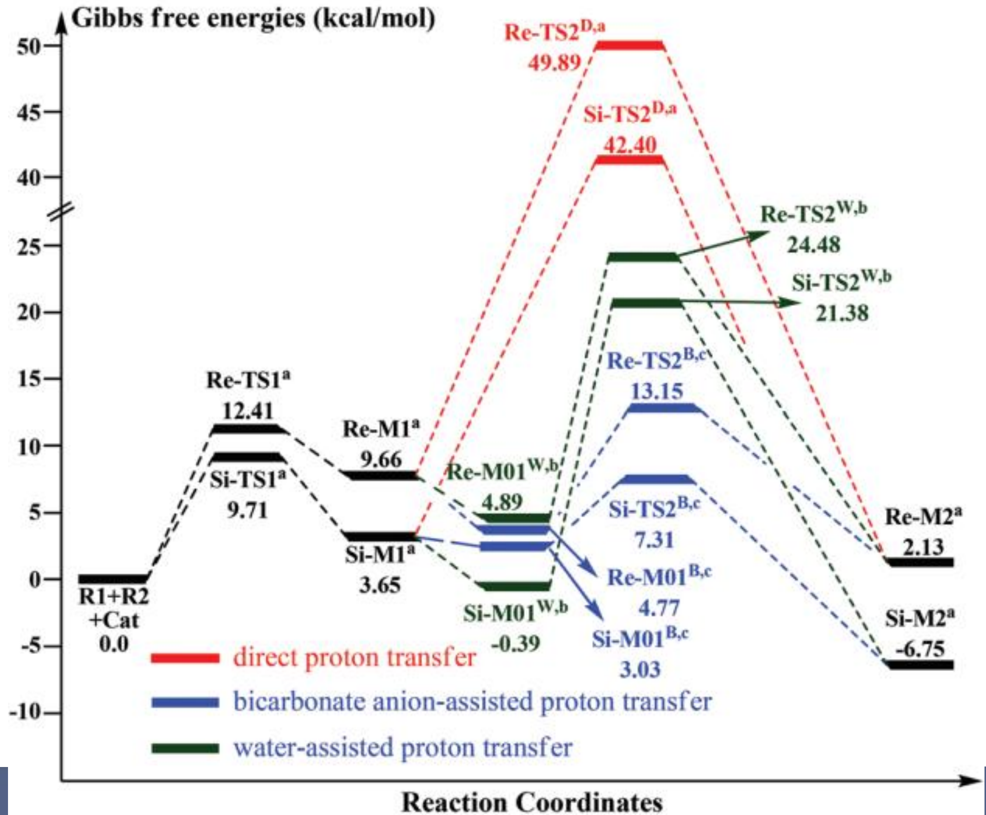
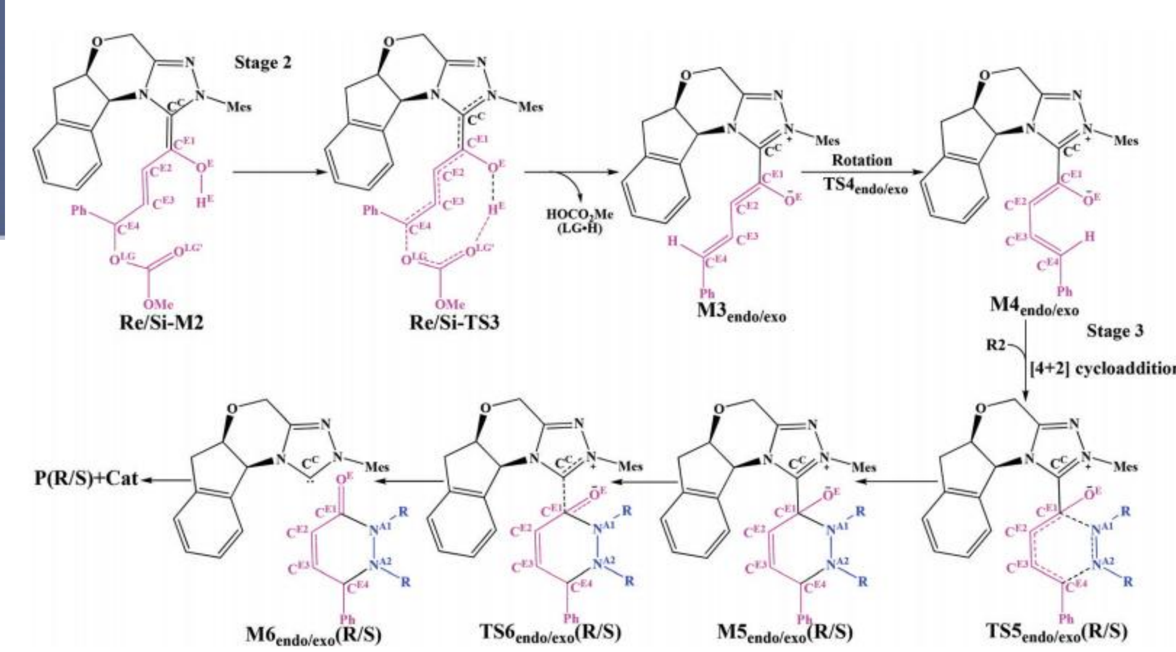


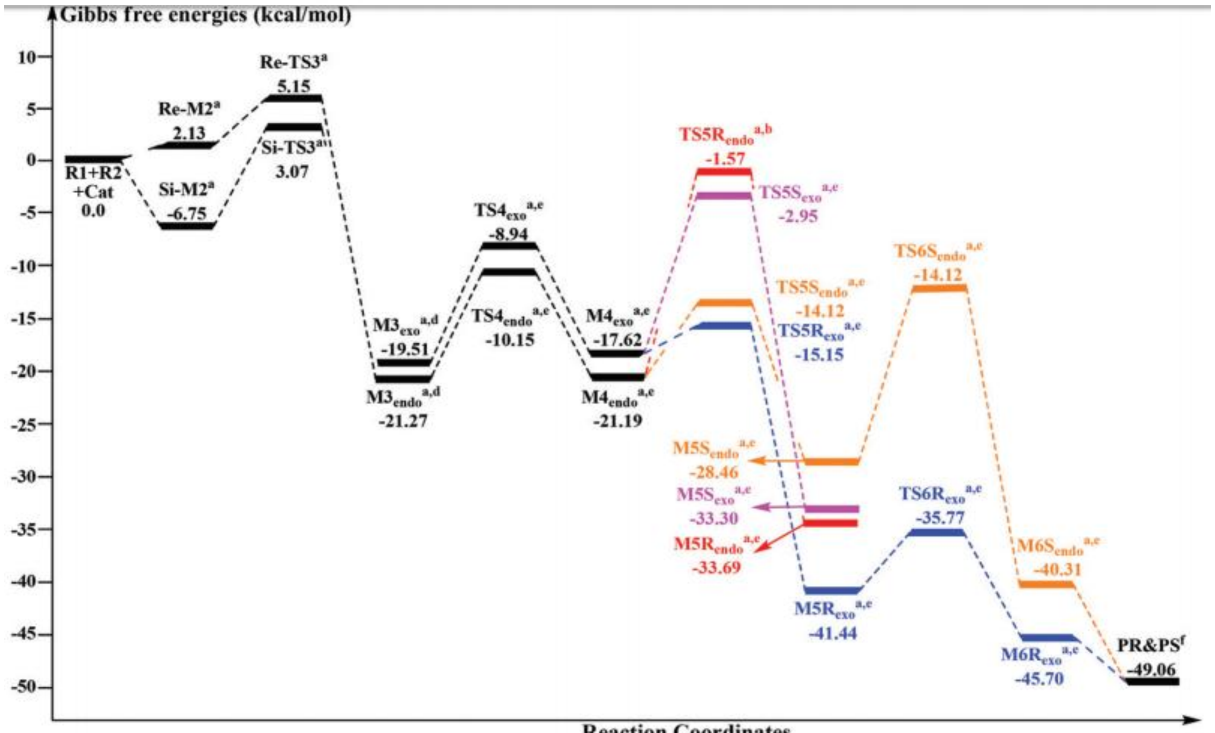
Figure 2 | Reaction scope. *The scope of this catalytic transformation was evaluated under standard conditions (Table 1, entry 7). Substrate scope includes γ- (**3a–3c**) and β-substituents (**3d–3n**) cyclobutenones (using **2a** as the optimal imine), and various imines (**3o–3t**, using **1a** as the optimal substrate). Reported yields were isolated yields of **3** based on imine **2**. Diastereoselective ratio (dr of **3** was determined via ^{1}H NMR analysis of the unpurified reaction mixture. Relative configuration of the major diastereoisomer was assigned based on X-ray structure of **3b** and **3m** (CCDC 988901, CCDC 988902, see Supplementary Information for more details). **The reactions were performed at 25 °C for 36 h. ***The reactions were performed using pre-catalyst **E** at 25 °C for 36 h (the reaction temperature was 0 °C for **3p**).


Stage 1
R1
[1,2]-hydride shift
Re/Si-TS2^D
Re/Si-TS1
Re/Si-M1
Re/Si-M2
Cat
Pre-Cat
HCO3- assisted
H2O assisted
Mediate-assisted
Proton transfer
Re/Si-M1
Re/Si-M01^B
Re/Si-TS2^B
Re/Si-M01^W
Re/Si-TS2^W


Gibbs free energies (kcal/mol)
Re-TS2^D,a
49.89
Si-TS2^D,a
42.40
Re-TS2^W,b
24.48
Si-TS2^W,b
21.38
Re-TS2^B,c
13.15
Re-TS1^a
12.41
Si-TS1^a
9.71
Re-M1^a
9.66
Si-M1^a
3.65
Re-M01^W,b
4.89
Si-M01^W,b
-0.39
Si-TS2^B,c
7.31
Re-M01^B,c
4.77
Si-M01^B,c
3.03
Re-M2^a
2.13
Si-M2^a
-6.75
R1+R2
+Cat
0.0
direct proton transfer
bicarbonate anion-assisted proton transfer
water-assisted proton transfer
Reaction Coordinates



Stage 2
Re/Si-M2
Re/Si-TS3
HOCO2Me (LG•H)
M3endo/exo
Rotation
TS4endo/exo
M4endo/exo
Stage 3
R2
[4+2] cycloaddition
TS5endo/exo(R/S)
M5endo/exo(R/S)
TS6endo/exo(R/S)
M6endo/exo(R/S)
P(R/S)+Cat



Gibbs free energies (kcal/mol)
Reaction Coordinates
R1+R2 +Cat 0.0
Re-M2a 2.13
Si-M2a -6.75
Re-TS3a 5.15
Si-TS3a 3.07
M3exo a,d -19.51
M3endo a,d -21.27
TS4exo a,e -8.94
TS4endo a,e -10.15
M4exo a,e -17.62
M4endo a,e -21.19
TS5Rendo a,b -1.57
TS5Sexo a,e -2.95
TS5Sendo a,e -14.12
TS5Rexo a,e -15.15
TS6Sendo a,e -14.12
M5Sendo a,e -28.46
M5Sexo a,e -33.30
M5Rendo a,e -33.69
M5Rexo a,e -41.44
TS6Rexo a,e -35.77
M6Sendo a,e -40.31
M6Rexo a,e -45.70
PR&PSf -49.06