Recent advances in spirocyclization of indole derivatives

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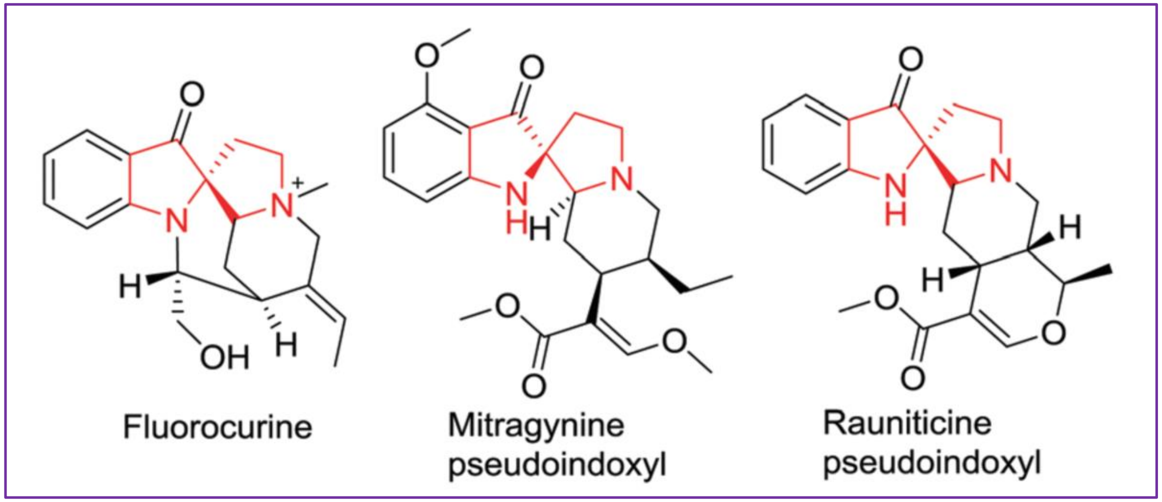
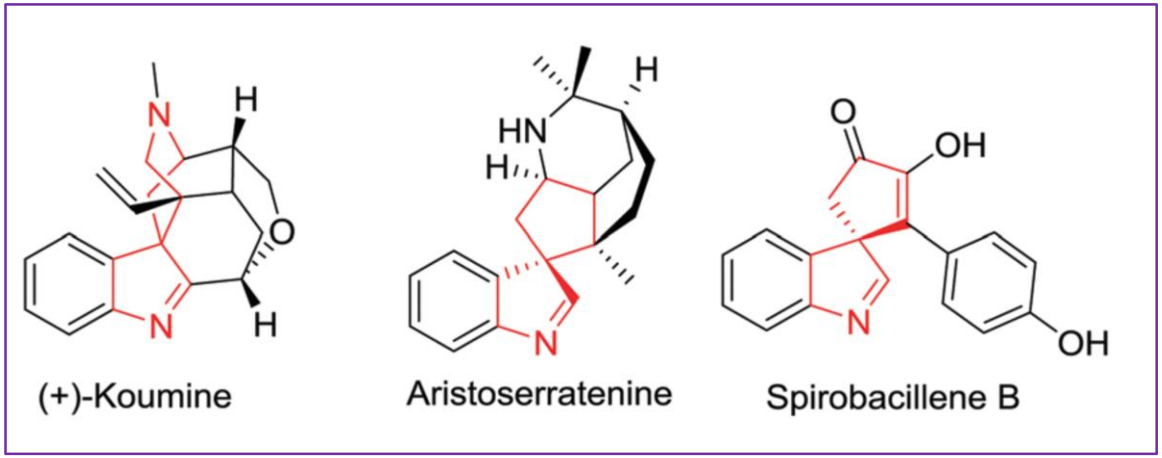
1. Introduction



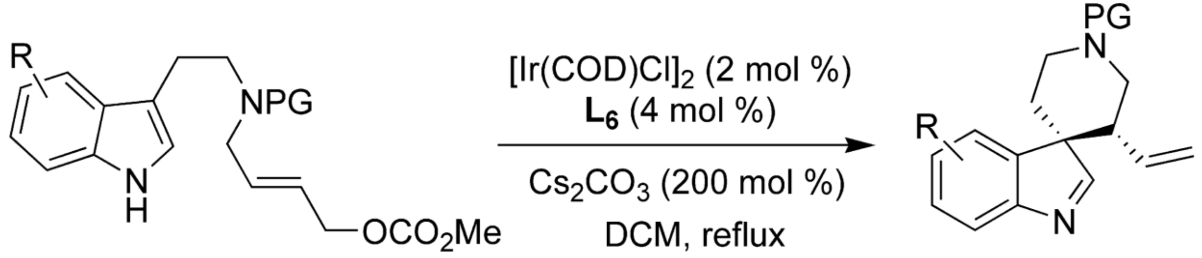
Natural alkaloids containing the C2-spirocyclicindole core structure

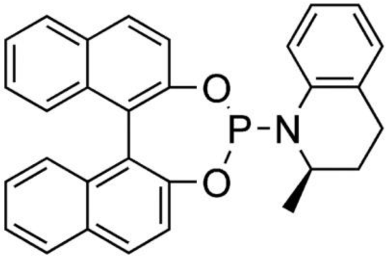


Natural alkaloids containing the C3-spirocyclicindoline core structure

- Rigidity
- Three-dimensional geometries

W. P. Unsworth, *Chem. - Eur. J.* **2016**, *22*, 2856





L₆ (*R*, *R*a)

First successful isolation of a spiroindoline by S. L. You utilizing an Ir catalyst

S. L. You, *J. Am. Chem. Soc.* **2010**, *132*, 11418

2. Spirocyclization of Indoles

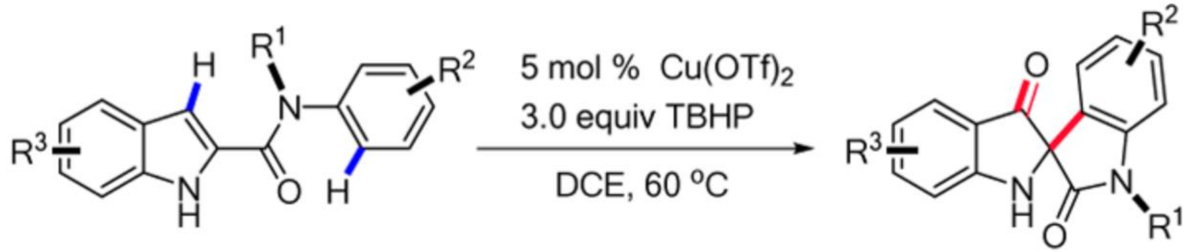
a. Spirocyclization via the 2-position of the indole skeleton

b. Spirocyclization via the 3-position of the indole skeleton

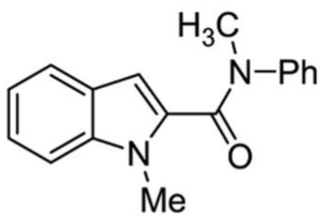
- ✓ *Three membered spiro-cyclic compounds*
- ✓ *Five membered spiro-cyclic compounds*
- ✓ *Six/seven membered spiro-cyclic compounds*

a. Spirocyclization via the 2-position of the indole skeleton

Scheme 1：



Control experiments：



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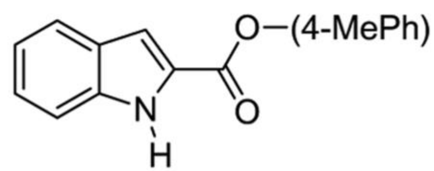

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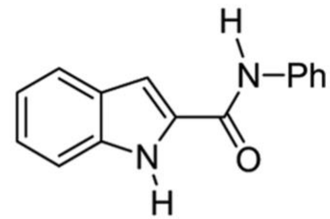

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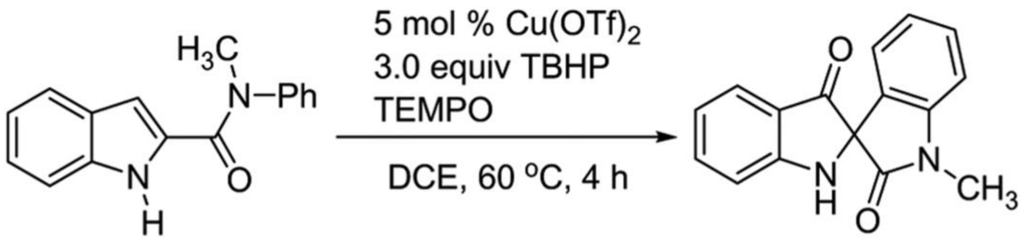
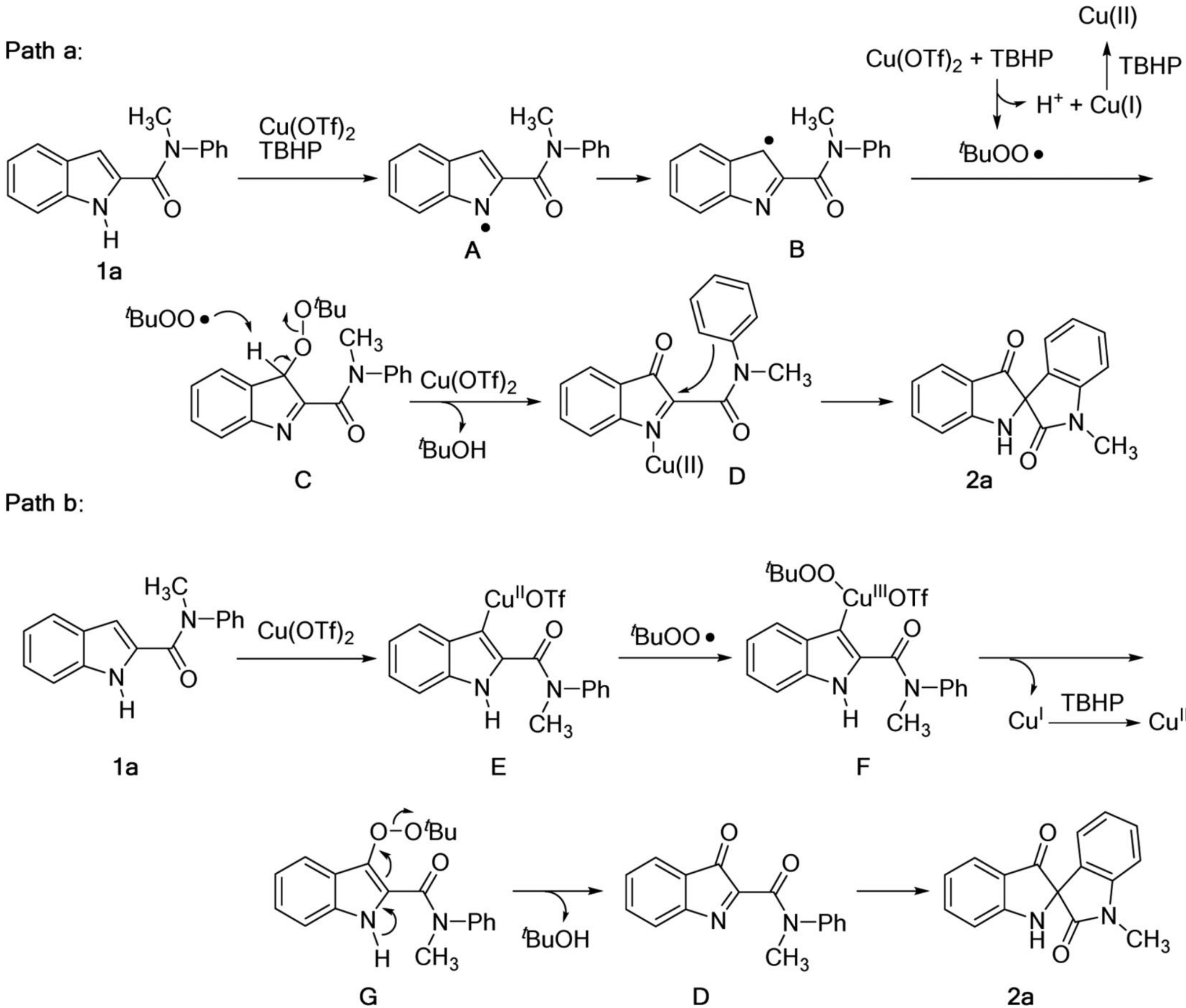


1a

with 2 equiv of TEMPO, 27% **2a**

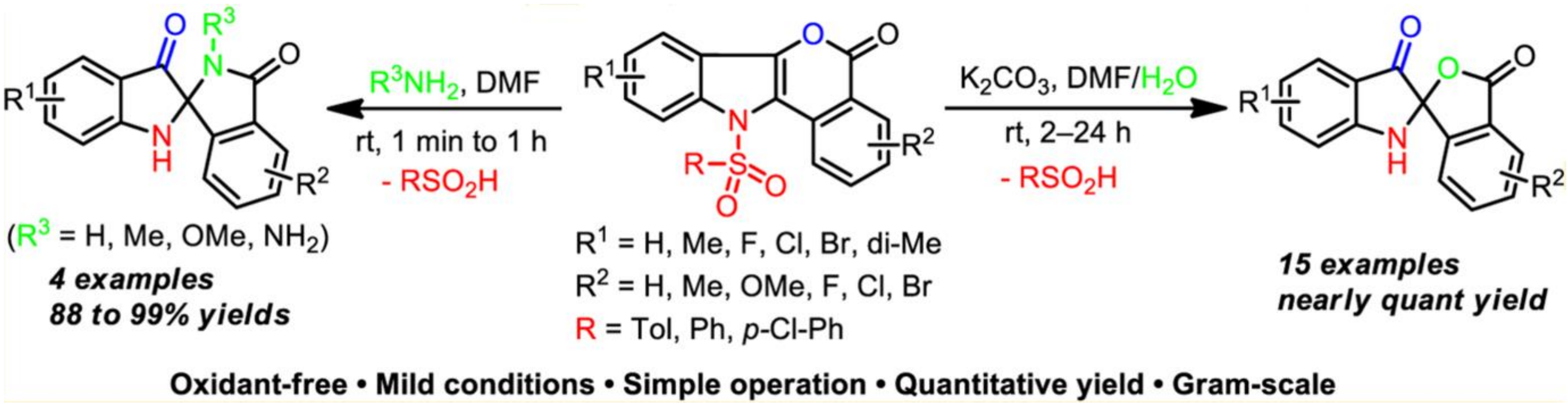
with 4 equiv of TEMPO, trace

Y. Li, *Org. Lett.* **2016**, *18*, 6124

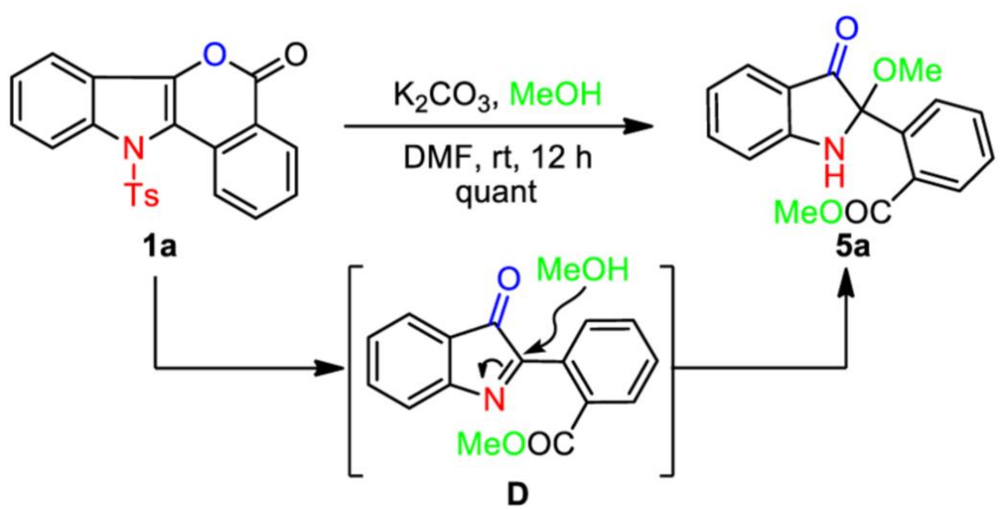


Path a:
Cu(OTf)2 + TBHP
Cu(II)
TBHP
H+ + Cu(I)
tBuOO•
Cu(OTf)2
TBHP
1a
A
B
tBuOO•
Cu(OTf)2
tBuOH
C
D
2a
Cu(II)
Path b:
Cu(OTf)2
CuIIOTf
tBuOO•
tBuOO
CuIIIOTf
CuI
TBHP
CuII
1a
E
F
tBuOH
G
D
2a

Scheme 2：

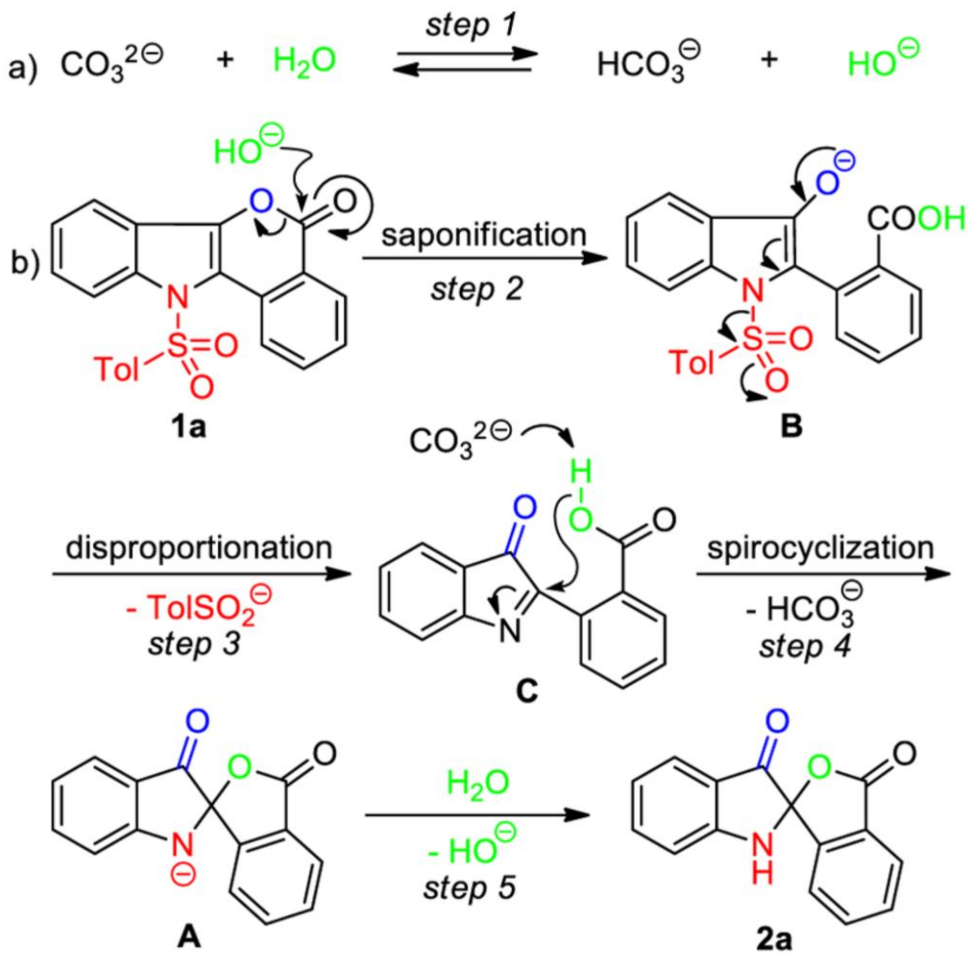


Control experiments：

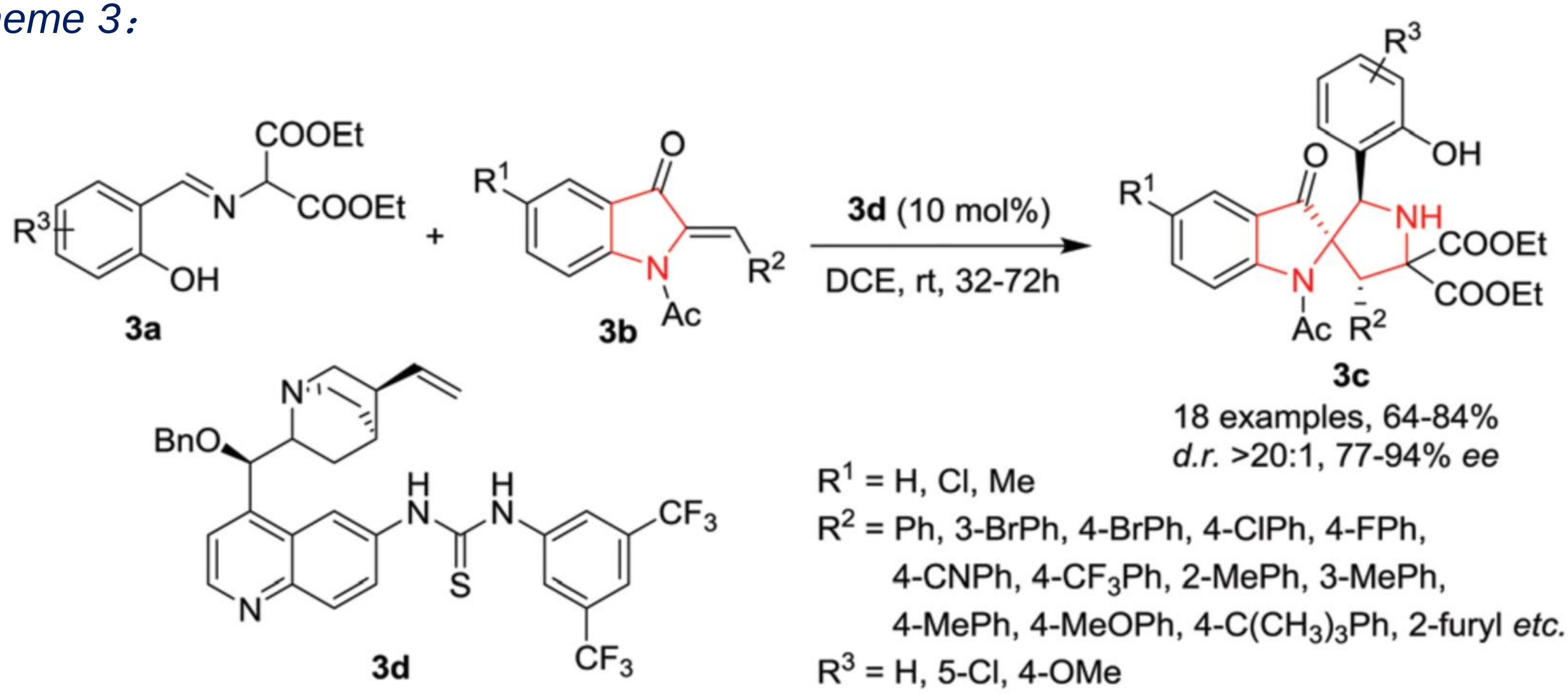


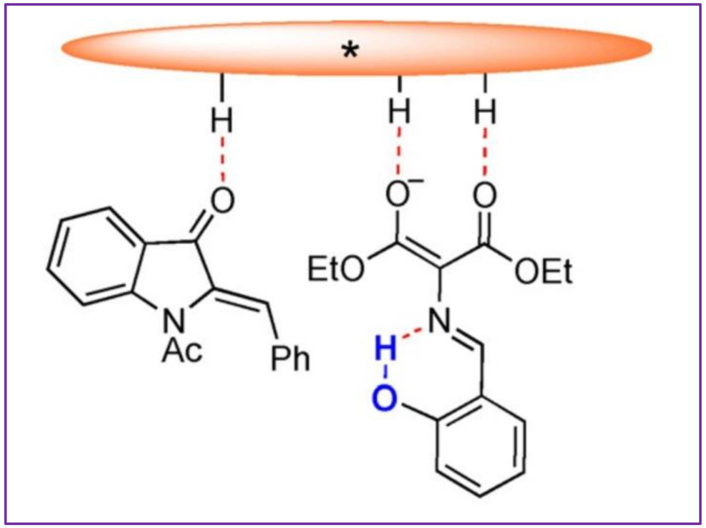
K. Zhao, *J. Org. Chem.* **2016**, *81*, 11397

Proposed Mechanism



Scheme 3:

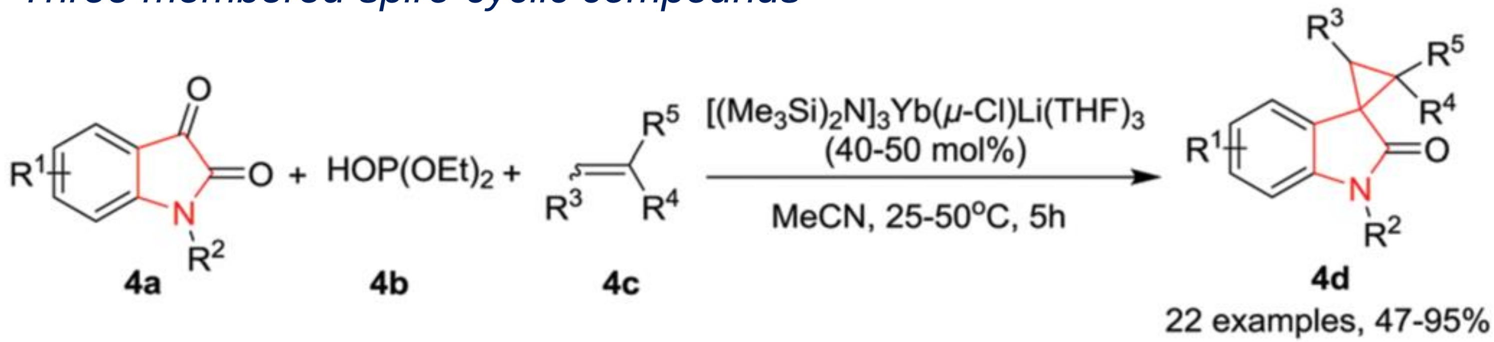


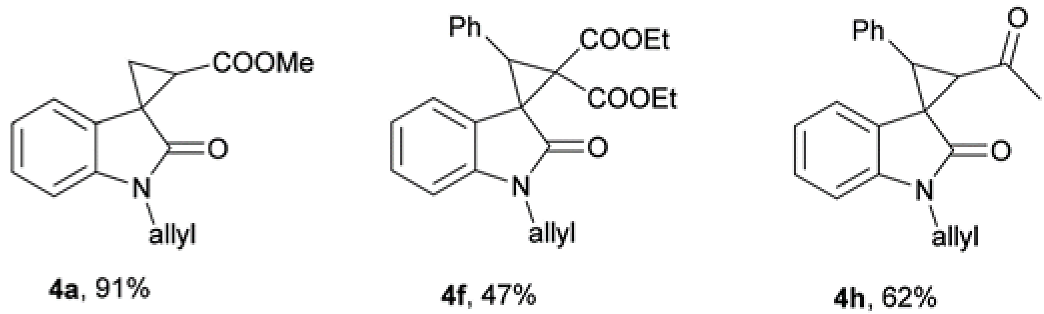


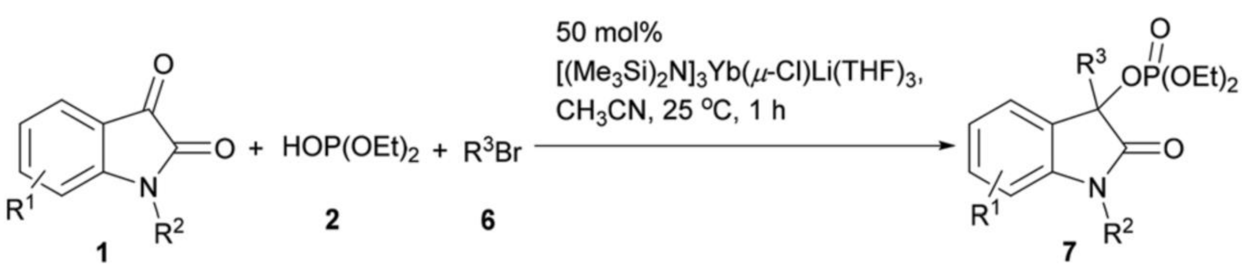
P. Xu, *Chem. Asian J.* **2016**, *11*, 834

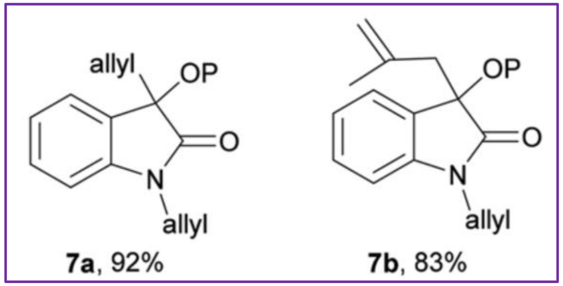
b. Spirocyclization via the 3-position of the indole skeleton

✓ *Three membered spiro-cyclic compounds*



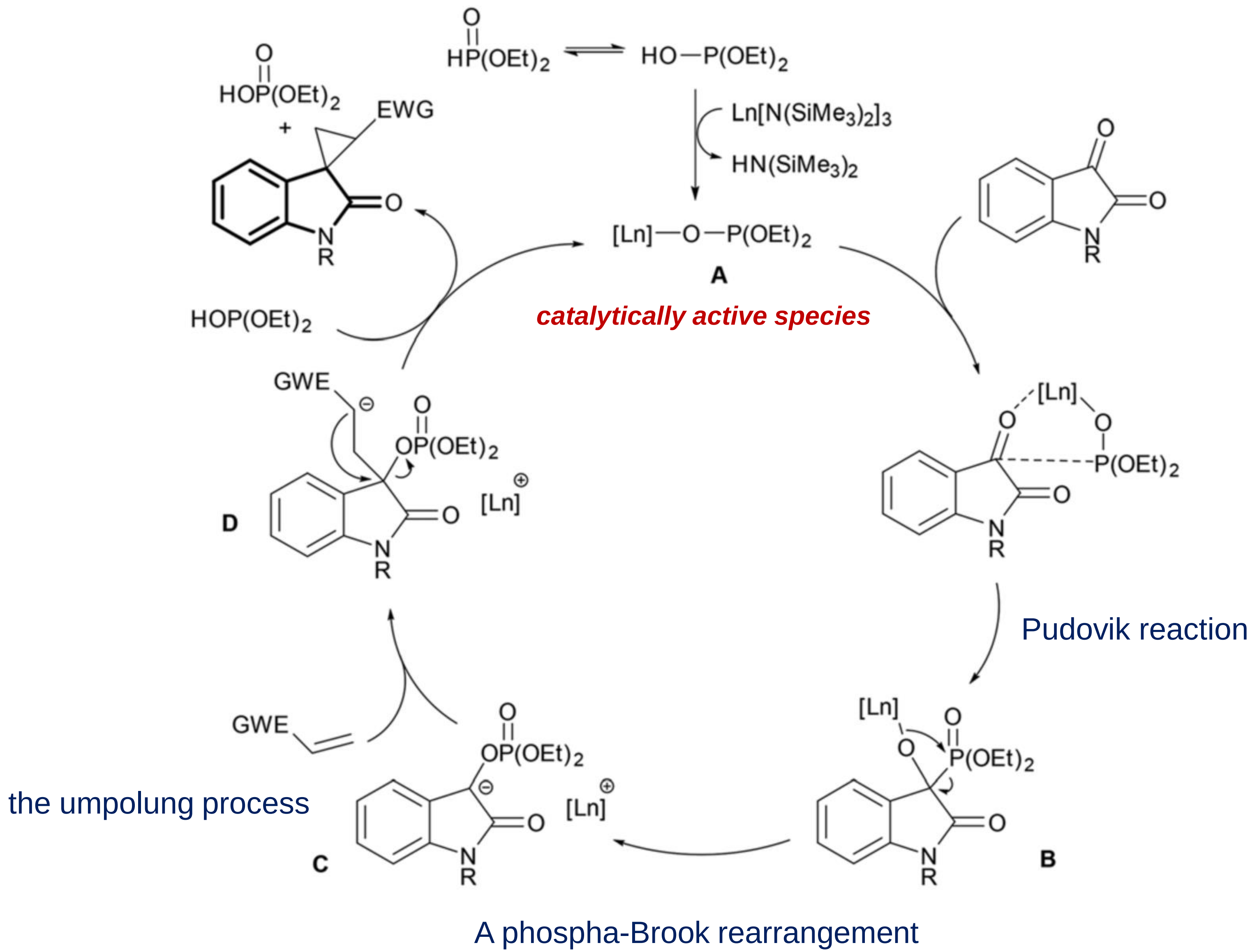




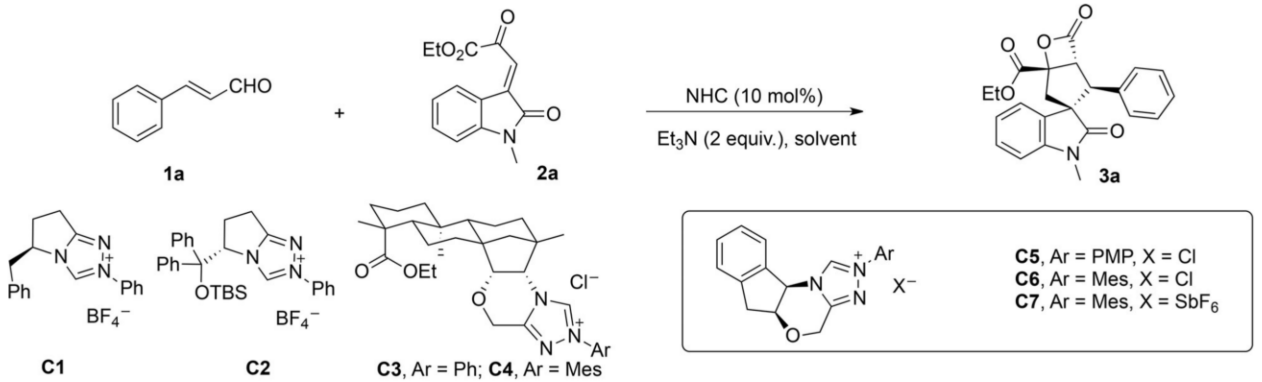


F. Xu, *Org. Biomol. Chem.*, **2017**, *15*, 3968

Proposed Mechanism



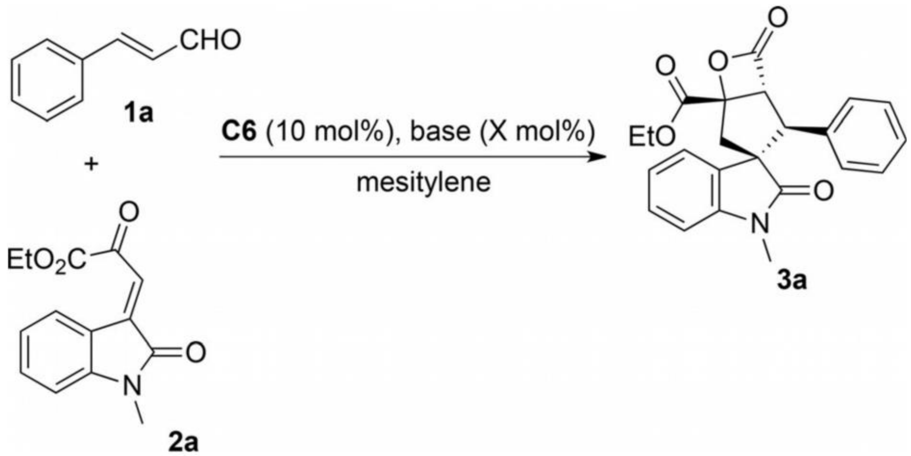
✓ *Five membered spiro-cyclic compounds*



Entry[a]	NHC	Solvent	Time [h]	Yield[b] [%]	*dr*[c]	*ee*[d] [%]
1	**C1**	DCM	120	nr	–	–
2	**C2**	DCM	120	nr	–	–
3	**C3**	DCM	120	nr	–	–
4	**C4**	DCM	120	nr	–	–
5	**C5**	DCM	120	36	>99:1	24
6	**C6**	DCM	24	47	>99:1	34
7	**C7**	DCM	36	33	>99:1	16
8	**C6**	DCE	2	51	>99:1	39
9	**C6**	THF	12	83	>99:1	10
10	**C6**	Et_2O	2	52	>99:1	30
11	**C6**	1,4-dioxane	36	48	>99:1	73
12	**C6**	MTBE	14	44	>99:1	80
13	**C6**	benzene	6	47	>99:1	63
14	**C6**	toluene	12	51	>99:1	71
15	**C6**	ethylbenzene	6	51	>99:1	82
16	**C6**	*o*-xylene	6	49	>99:1	84
17	**C6**	PhF	6	53	>99:1	60
18	**C6**	$PhCF_3$	12	50	>99:1	67
19	**C6**	*p*-xylene	6	48	>99:1	79
20	**C6**	mesitylene	12	52	>99:1	85
21	**C6**	THF/mesitylene (v/v, 4:1)	12	56	>99:1	81
22	**C6**	THF/mesitylene (v/v, 1:1)	6	73	>99:1	47

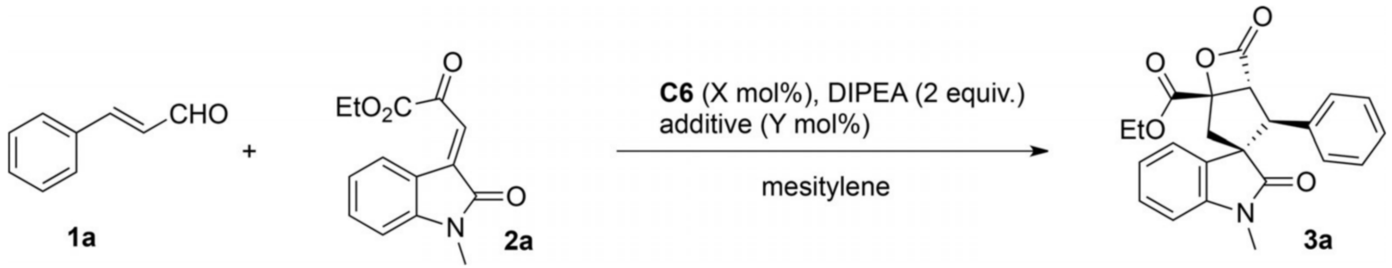
[a] Unless otherwise noted, reactions were carried out with **1a** (0.15 mmol, 1.5 equiv.), **2a** (0.1 mmol), Et_3N (0.2 mmol, 2 equiv.), cat. (10 mol%) in the given solvent (0.5 mL) at 25 °C.
[b] Isolated yield.
[c] Determined by ^1H NMR analysis.
[d] Determined by chiral HPLC.

X. Wang, *Adv. Synth. Catal.* **2017**, *359*, 1541



Entry[a]	Base	X	Time [h]	Yield[b] [%]	*dr*[c]	*ee*[d] [%]
1	DMAP	200	48	trace	–	ND
2	DBU	200	48	trace	–	ND
3	DIPEA	200	12	52	>99:1	85
4	KO-*t*-Bu	200	12	51	>99:1	76
5	K_2CO_3	200	36	trace	–	ND
6	Na_2CO_3	200	36	trace	–	ND
7	LiOAc	200	36	39	>99:1	55
8	KOAc	200	36	38	>99:1	53
9	KSAc	200	36	47	>99:1	67
10	$K_3PO_4 \cdot 3H_2O$	200	6	49	>99:1	75
11	DIPEA	20	12	49	>99:1	59
12	DIPEA	50	12	41	>99:1	52
13	DIPEA	100	12	52	>99:1	81
14	DIPEA	300	16	37	>99:1	79

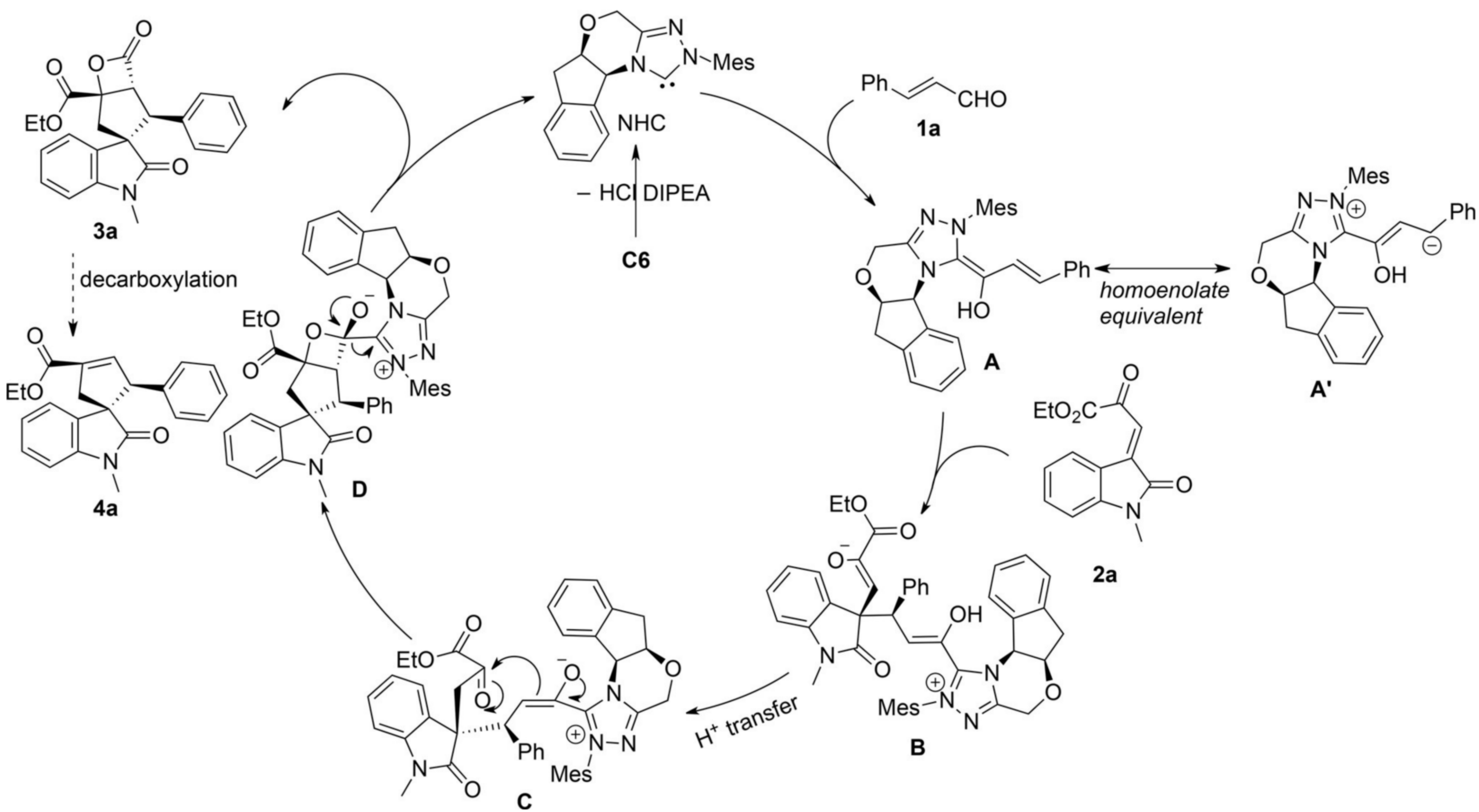
[a] Unless otherwise noted, reactions were carried out with **1a** (0.15 mmol, 1.5 equiv.), **2a** (0.1 mmol), base (X mol%), cat. (10 mol%) in the given solvent (0.5 mL) at 25 °C.
[b] Isolated yield.
[c] Determined by ^{1}H NMR analysis.
[d] Determined by chiral HPLC.



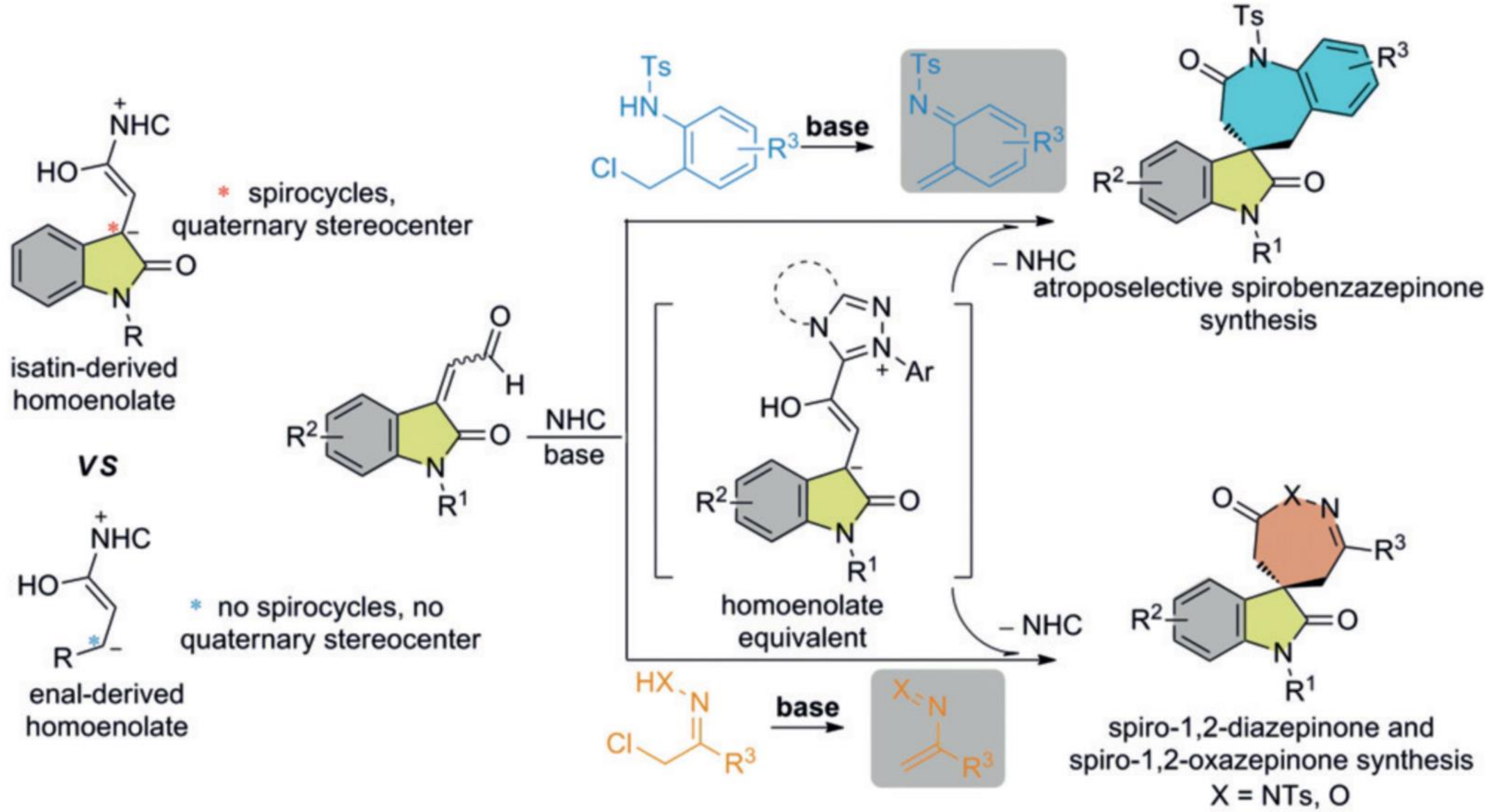
Entry[a]	X	Temp. [°C]	Additive	Time [h]	Y [%]	Yield[c] [%]	*dr*[b]	*ee*[d] [%]
1	10	r.t.	PhCOOH	36	50	33	>99:1	71
2	10	r.t.	$Sc(OTf)_3$	48	50	trace	–	–
3	10	r.t.	$Cu(OTf)_2$	48	50	trace	–	–
4	10	r.t.	Ti(O-*i*-Pr)$_4$	12	50	49	>99:1	81
5	10	r.t.	PPh_3	18	50	45	>99:1	90
6	10	r.t.	3 Å MS	18	50 mg	43	>99:1	90
7	10	r.t.	5 Å MS	36	50 mg	50	>99:1	51
8	10	r.t.	13X MS	48	50 mg	46	>99:1	71
9	10	r.t.	4 Å MS	72	50 mg	48	>99:1	90
10	10	rt	4 Å MS	24	10 mg	52	>99:1	90
11	5	r.t.	4 Å MS	72	10 mg	39	>99:1	90
12	20	r.t.	4 Å MS	19	10 mg	52	>99:1	90
13	10	0	4 Å MS	30	10 mg	52	>99:1	91
14	10	−10	4 Å MS	39	10 mg	48	>99:1	91
15	10	−20	4 Å MS	72	10 mg	31	>99:1	91

[a] Unless otherwise noted, reactions were carried out with **1a** (0.15 mmol, 1.5 equiv.), **2a** (0.1 mmol), DIPEA (0.2 mmol), additive (Y mol%), cat. (10 mol%) in the corresponding solvent (0.5 mL) at 25 °C.
[b] Determined by ^{1}H NMR analysis.
[c] Isolated yield.
[d] Determined by chiral HPLC.

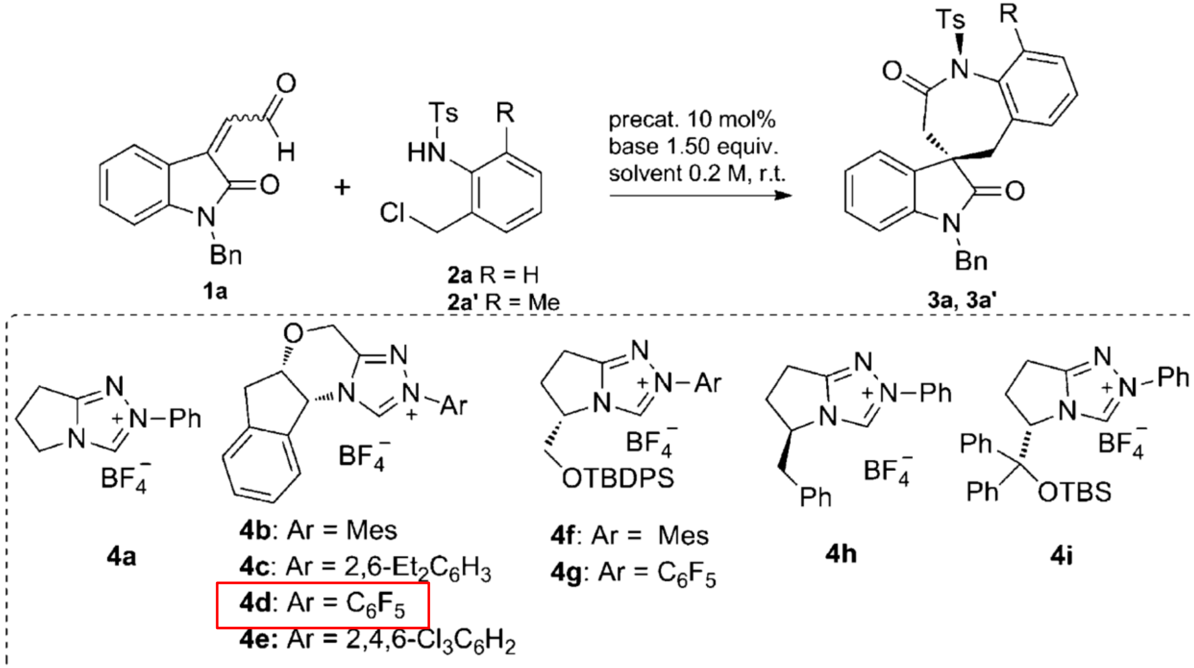
Proposed Mechanism



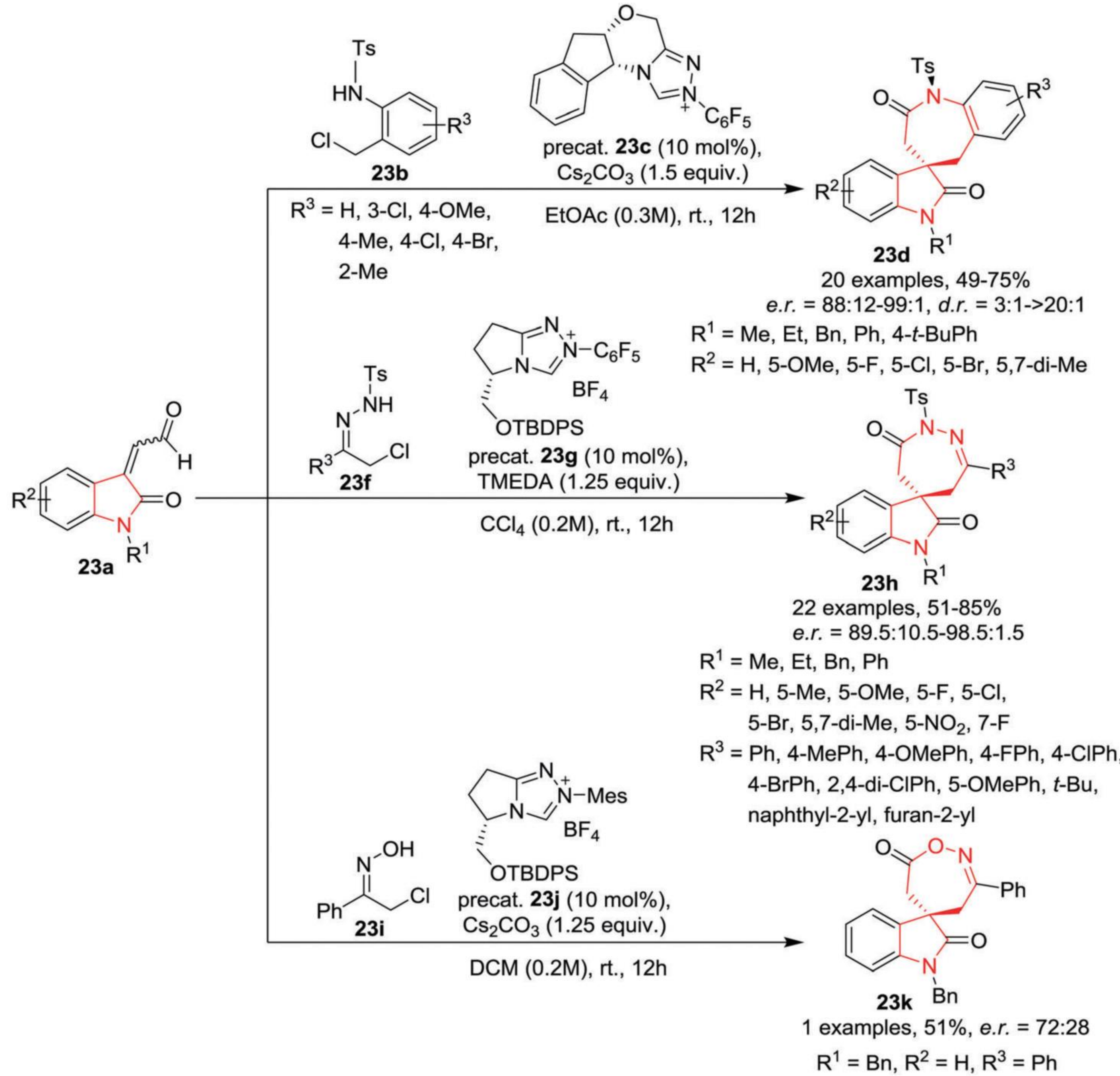
✓ *Six/seven membered spiro-cyclic compounds*



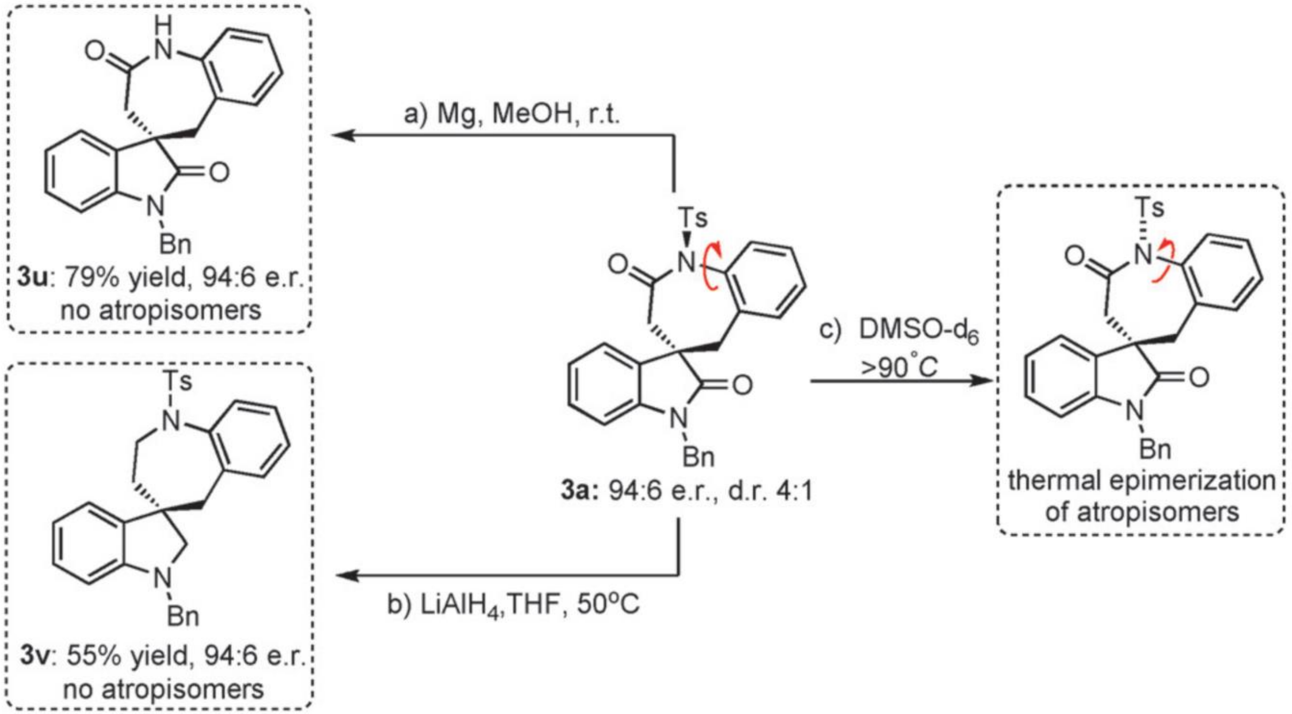
D. Enders, *Angew. Chem. Int. Ed.* **2016**, *55*, 11110



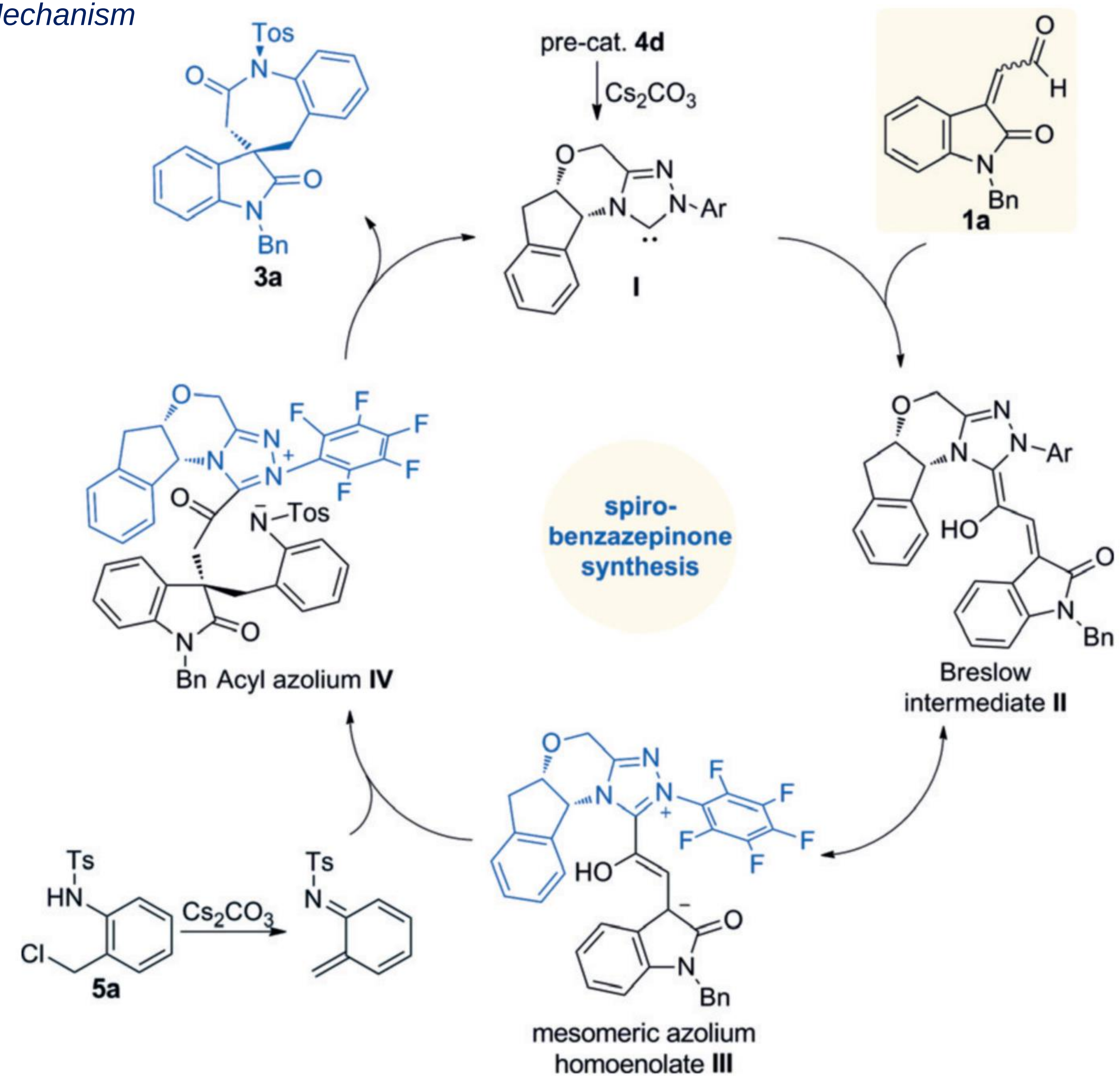
Entry	4	Solvent	Base	Yield [%][b]	d.r.[c]	e.r. [%][d]
1	**4a**	CH_2Cl_2	K_3PO_4	55	–	–
2	**4b**	CH_2Cl_2	K_3PO_4	58	4:1	72:28
3	**4c**	CH_2Cl_2	K_3PO_4	56	4:1	77:23
4	**4d**	CH_2Cl_2	K_3PO_4	71	5:1	79:21
5	**4e**	CH_2Cl_2	K_3PO_4	67	5:1	73:27
6	**4f**	CH_2Cl_2	K_3PO_4	55	3:1	62:38
7	**4g**	CH_2Cl_2	K_3PO_4	68	4:1	59:41
8	**4h**	CH_2Cl_2	K_3PO_4	63	4:1	74:26
9	**4i**	CH_2Cl_2	K_3PO_4	n.r.	–	–
10	**4d**	**EtOAc**	**Cs_2CO_3**	**68**	**4:1**	**93:7**
11[e]	**4d**	EtOAc	Cs_2CO_3	58	>20:1	90:10


Ts
HN
Cl
R3
23b
R3 = H, 3-Cl, 4-OMe,
4-Me, 4-Cl, 4-Br,
2-Me
O
N
N
N
+
C6F5
precat. 23c (10 mol%),
Cs2CO3 (1.5 equiv.)
EtOAc (0.3M), rt., 12h
Ts
O
N
R3
R2
O
N
R1
23d
20 examples, 49-75%
e.r. = 88:12-99:1, d.r. = 3:1->20:1
R1 = Me, Et, Bn, Ph, 4-t-BuPh
R2 = H, 5-OMe, 5-F, 5-Cl, 5-Br, 5,7-di-Me
O
H
R2
O
N
R1
23a
Ts
NH
N
R3
Cl
23f
N
N
+
N−C6F5
BF4
OTBDPS
precat. 23g (10 mol%),
TMEDA (1.25 equiv.)
CCl4 (0.2M), rt., 12h
Ts
O
N
N
R3
R2
O
N
R1
23h
22 examples, 51-85%
e.r. = 89.5:10.5-98.5:1.5
R1 = Me, Et, Bn, Ph
R2 = H, 5-Me, 5-OMe, 5-F, 5-Cl,
5-Br, 5,7-di-Me, 5-NO2, 7-F
R3 = Ph, 4-MePh, 4-OMePh, 4-FPh, 4-ClPh,
4-BrPh, 2,4-di-ClPh, 5-OMePh, t-Bu,
naphthyl-2-yl, furan-2-yl
OH
N
Ph
Cl
23i
N
N
+
N−Mes
BF4
OTBDPS
precat. 23j (10 mol%),
Cs2CO3 (1.25 equiv.)
DCM (0.2M), rt., 12h
O
O
N
Ph
O
N
Bn
23k
1 examples, 51%, e.r. = 72:28
R1 = Bn, R2 = H, R3 = Ph

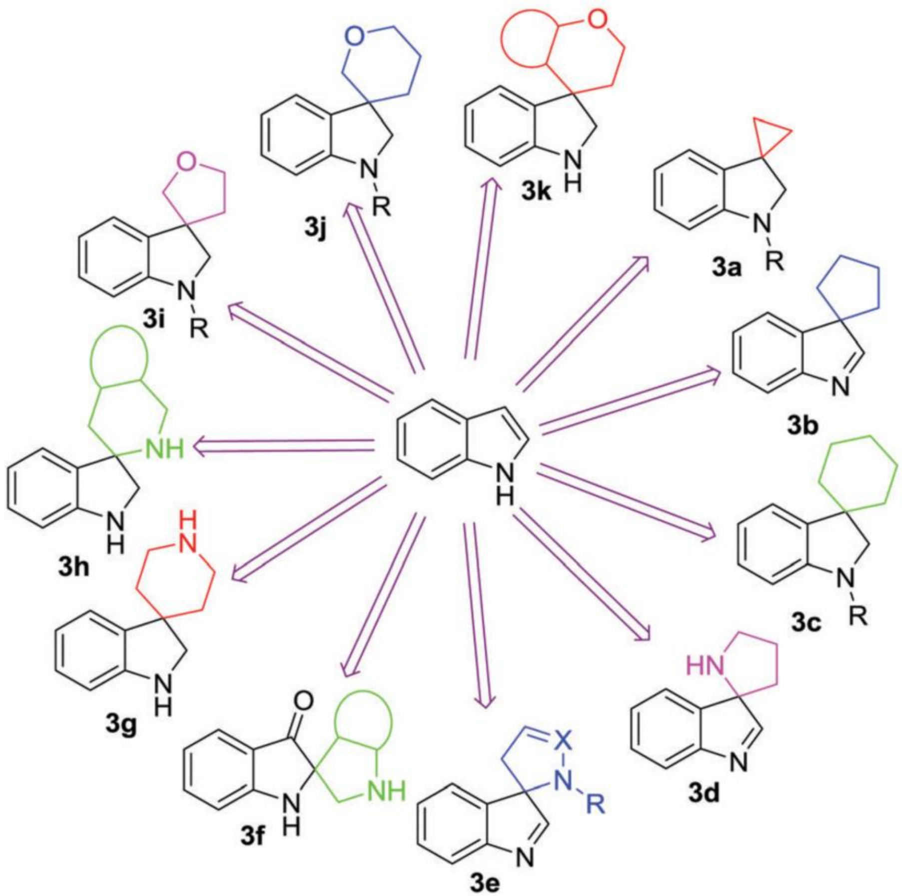
Thermal epimerization and loss of atropisomerism study



Proposed Mechanism



3. Conclusion



- This review will provide a good introduction to the field of spirocyclization reactions of indoles and will serve as a springboard for further reading.
- This review highlights the recent and significant advances in the construction of spiroindolines and spiroindoles.
- It highlights the recently used ligands and catalysts to achieve diastereoselective and enantioselective synthesis of spiroindolenines.

4. Acknowledgement

- **Prof. Huang**
- **Mr. Chen**
- **All members here**

Thanks for your attention!