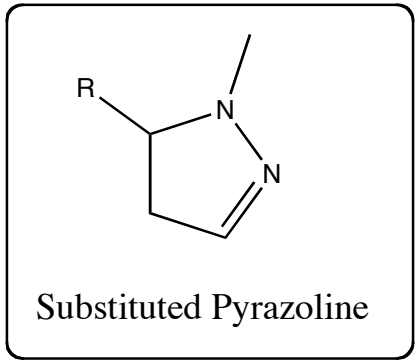
Literature Presentation

Wynter Gilson
Dec. 4, 2009

Pyrazolines: Biological Activity



Substituted Pyrazoline

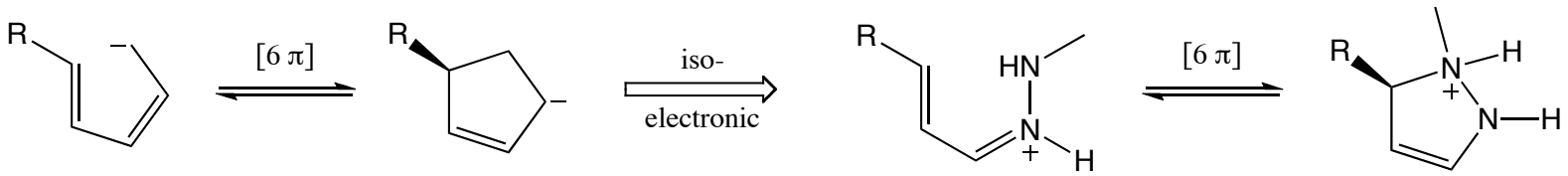
Biological Activity

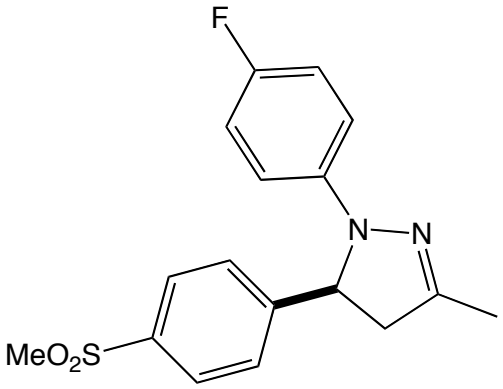
- Antidepressant
- Anticancer
- Anti-inflammatroy
- Antibacterial
- Antiviral

Müller, Steffen; List, B. *Angew Chem* **2009**, ASAP.

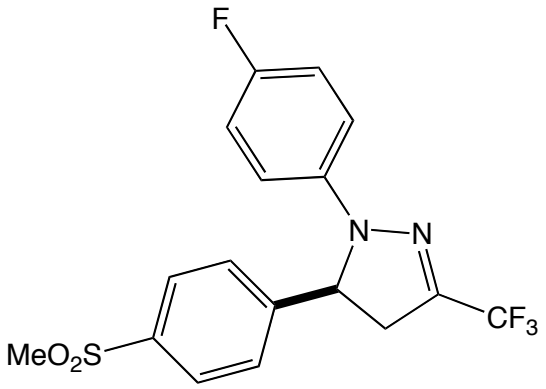
6 π electrocyclization

6 π electrocyclization:





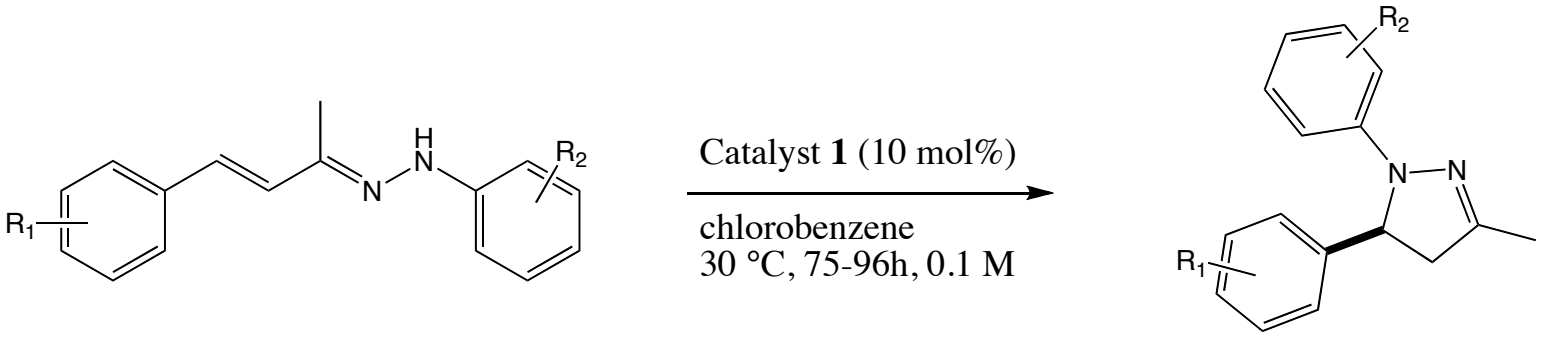
COX-2 inhibitor

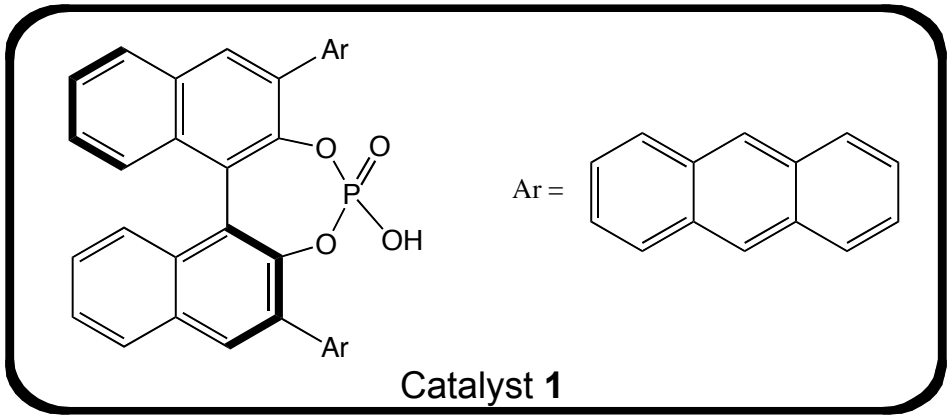


COX-2 inhibitor (S)-(-)-E-6244

Müller, Steffen; List, B. *Angew Chem* **2009**, ASAP.

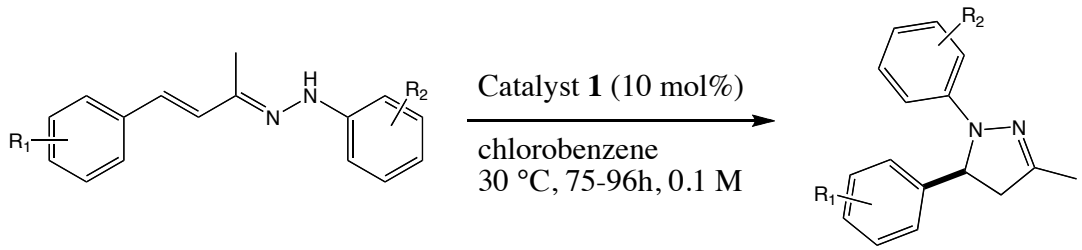
1st Catalytic Asymmetric 6 π Electrocyclization

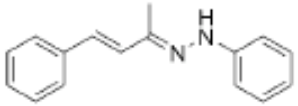
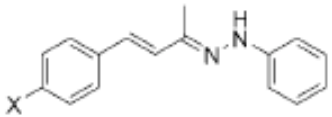
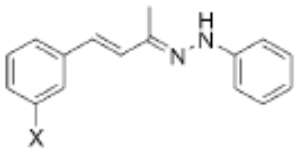


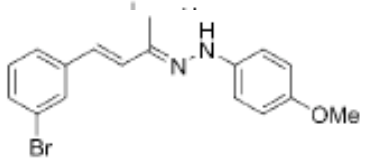
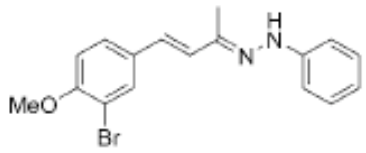
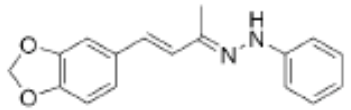
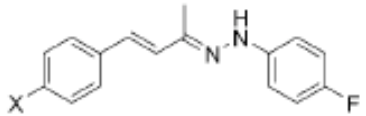


Müller, Steffen; List, B. *Angew Chem* **2009**, ASAP.

Substrate Scope



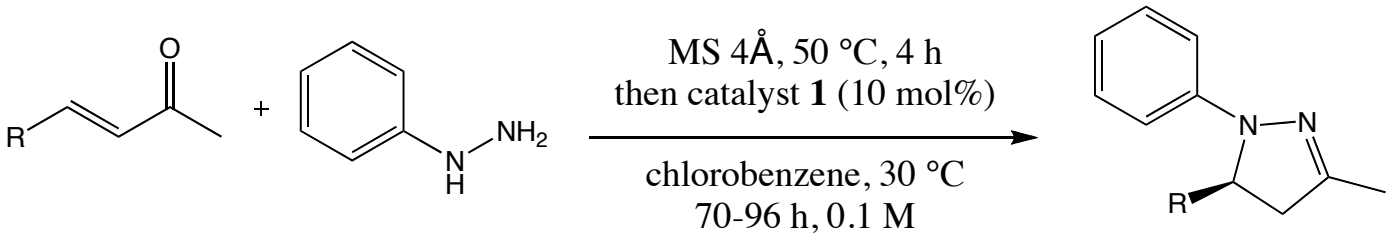
Entry	Substrate 1		Yield [%][b]	e.r.[c]
1		1a	92	88:12
2		1b: X = F	94	94:6
3		1c: X = Cl	96	95:5
4		1d: X = Br	95	95:5
5[d]		1e: X = NO_2	93	96:4
6[e]		1f: X = CF_3	88	96:4
7		1g: X = F	91	94:6
8		1h: X = Cl	96	96:4
9[f]		1i: X = Br	95	96:4
10[d,g]		1j: X = NO_2	99	98:2

Entry	Substrate 1		Yield [%][b]	e.r.[c]
11[h]		1k	91	92:8
12		1l	93	95:5
13[i]		1m	85	93:7
14[j]		1n: X = SO_2Me	88	88:12

a) Ar atmosphere with hydrazones **1a-n** (0.10 mmol) and phosphoric acid **3** (10 mol%) in chlorobenzene (1.0 mL) at 30 C. b) yield isolated product. c) Determined by HPLC on chiral stationary phase (absolute config. Of **2i** determined by X-ray structure analysis. d) reaction was run at 40 C. e) 9 d. f) 109 h. g) 60h. h) 36 h. i) rxn at 20 C. j) rxn 50 C.

Müller, Steffen; List, B. *Angew Chem* **2009**, ASAP.

Enones Substrate Scope

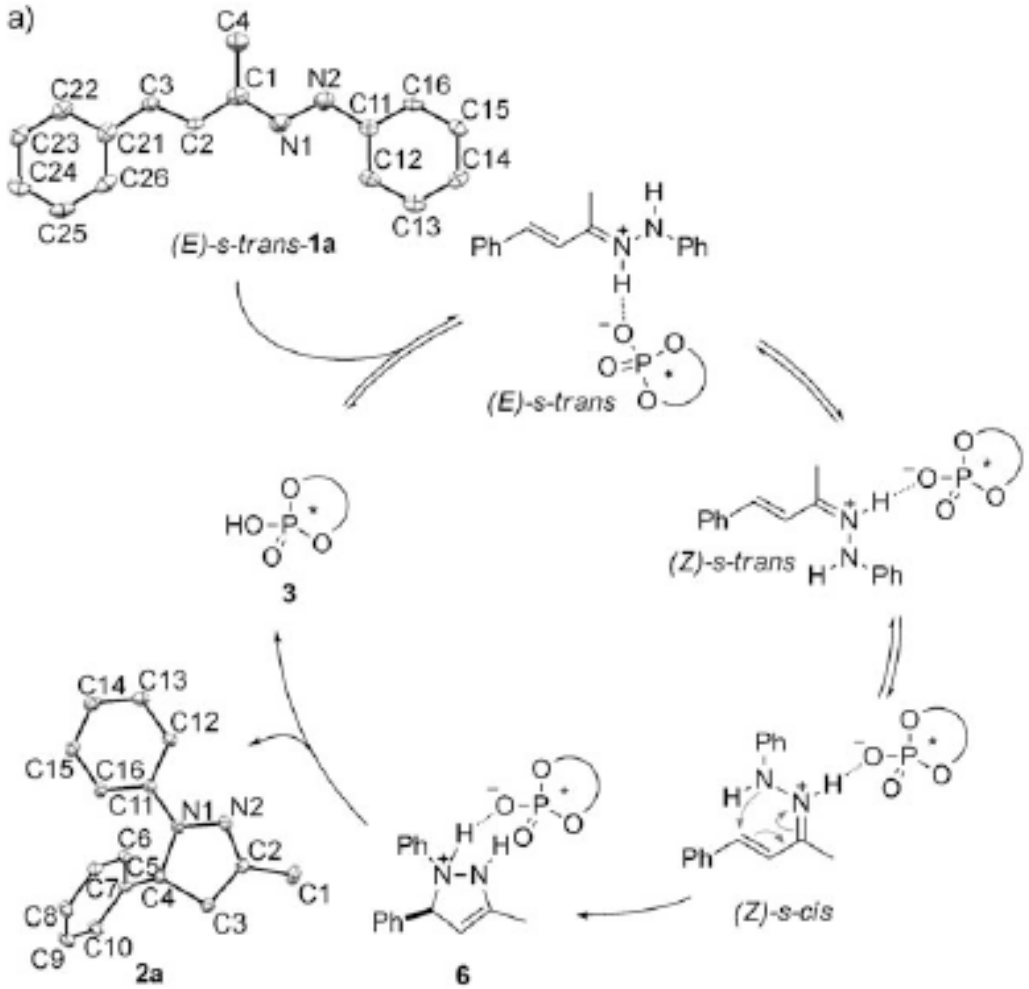


Entry	Product	R	Yield [%][b]	e.r.[c]
1	**2c**	R = 4-Cl-C_6H_4	97	94:6
2	**2i**	R = 3-Br-C_6H_4	90	95:5
3[d]	**2j**	R = 3-NO_2-C_6H_4	99	96:4
4	**2o**	R = 3-I-C_6H_4	89	95:5
5[e]	**2p**	R = *n*-C_5H_{11}	18	35:65
6[f]	**2p**	R = *n*-C_5H_{11}	40	75:25

a)Ar atmosphere with enones (0.105 mmol), phenylhydrazine (0.10 mmol) and phosphoric acid **3** (10 mol%) in chlorobenzene (1.0 mL) at 30 C. b) yield isolated product. c) Determined by HPLC on chiral stationary phase d) reaction was run at 40 C. e) rxn run for 24 h at 100 C with 0.11 mmol enone and **1** (20 mol%). f) rxn run 24 h at 50 C with 0.11 mmol enone and N-triflyl-phosphoramide of **1** (20 mol%) as catalyst.

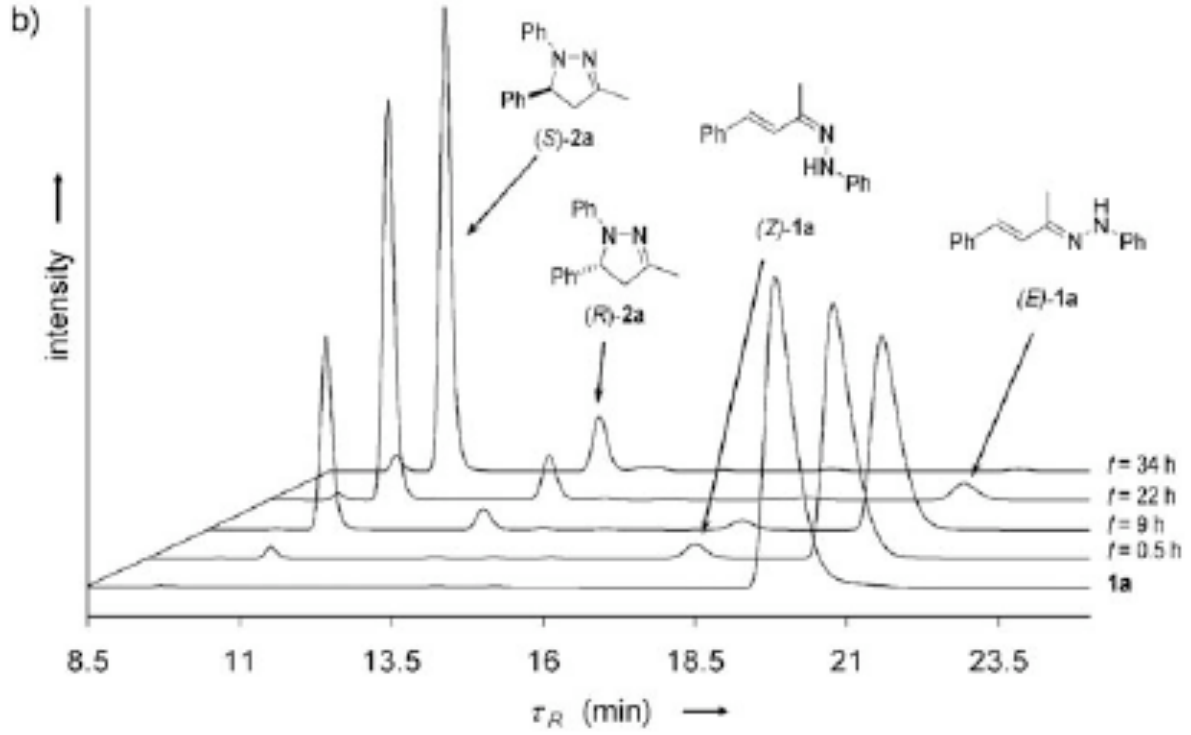
Müller, Steffen; List, B. *Angew Chem* **2009**, ASAP.

Catalytic Cycle



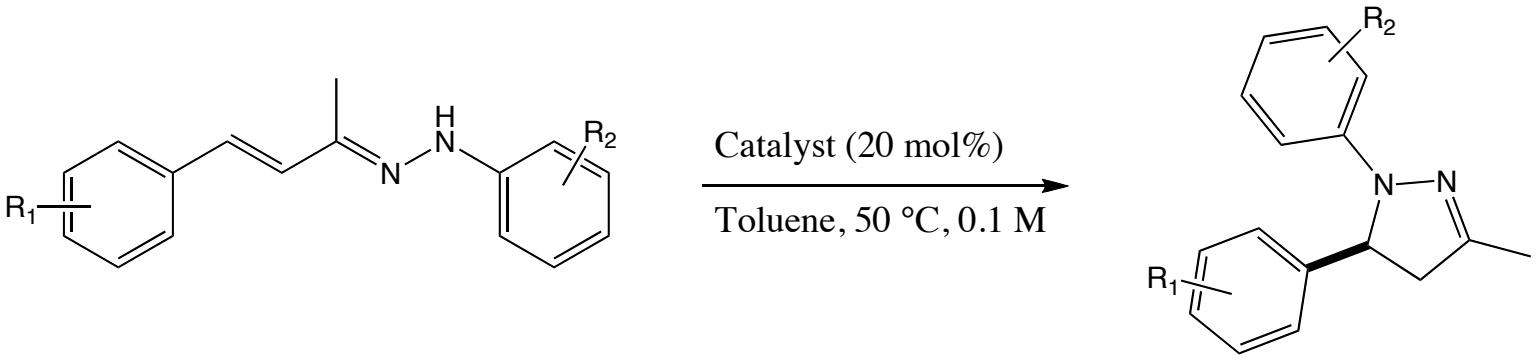
Müller, Steffen; List, B. *Angew Chem* **2009**, ASAP.

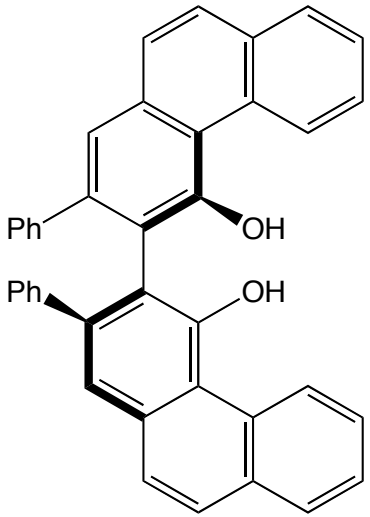
HPLC Analysis



Müller, Steffen; List, B. *Angew Chem* **2009**, ASAP.

Supporting Information

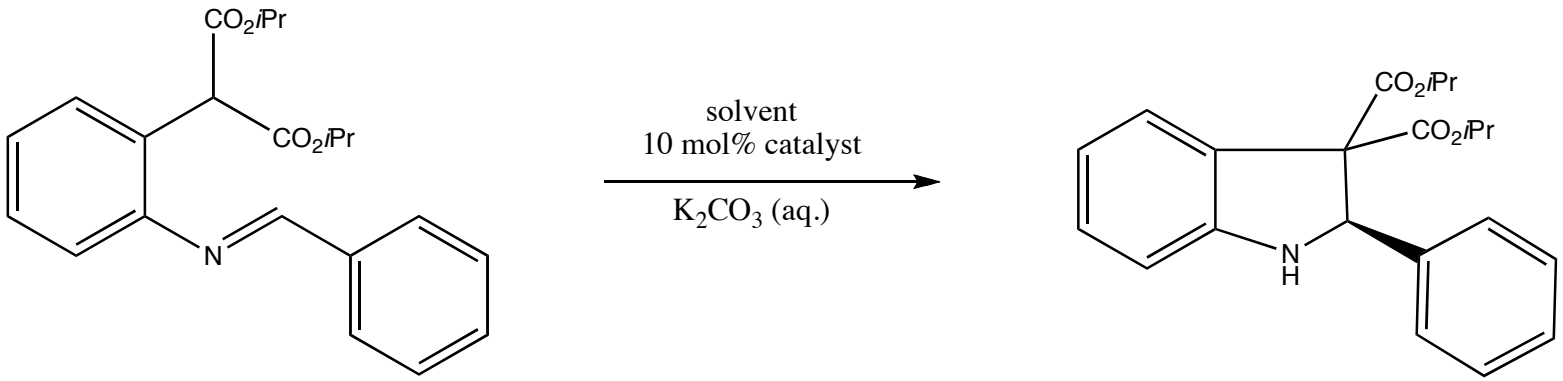




e.r. = 45:55

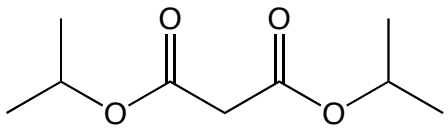
Two Weeks Earlier...

Catalytic Asymmetric 6 π Electrocyclization : Enantioselective Synthesis of Functionalized Indolines



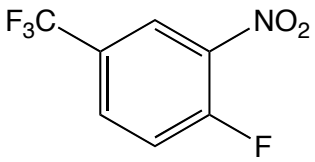
Maciver, E. E.; Thompson, S.; Smith, M. D. *Angew. Chem.* **2009** ASAP.

Preparation of Imine



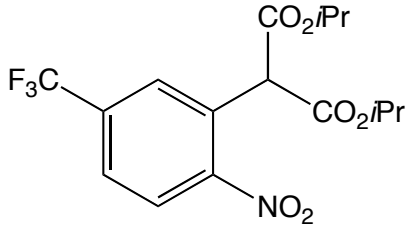
1) K_2CO_3, DMF, 90 C, 10 min

2) 90 C, 2h



1) Cooled

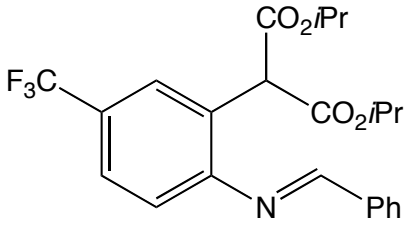
2) 5% HCL dilution



Recyrstallized: 84% yield

1) Pd/C, H_2, MeOH 24 h, rt

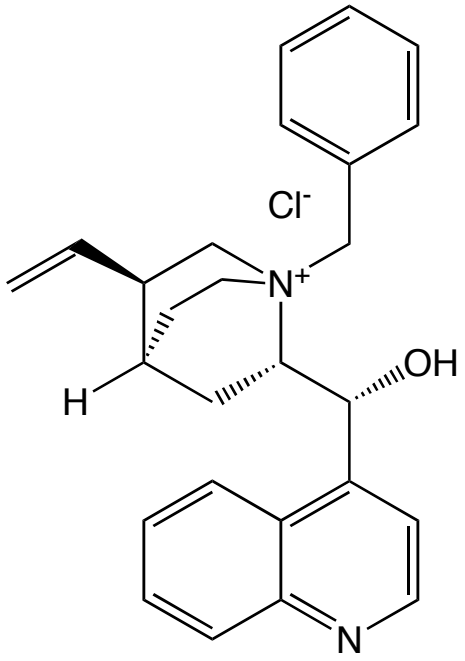
2) PhCHO, Toluene, 24 h $MgSO_4$, rt



Imine purified *via* flash chromatography to yield 73%

Maciver, E. E.; Thompson, S.; Smith, M. D. *Angew. Chem.* **2009** ASAP.

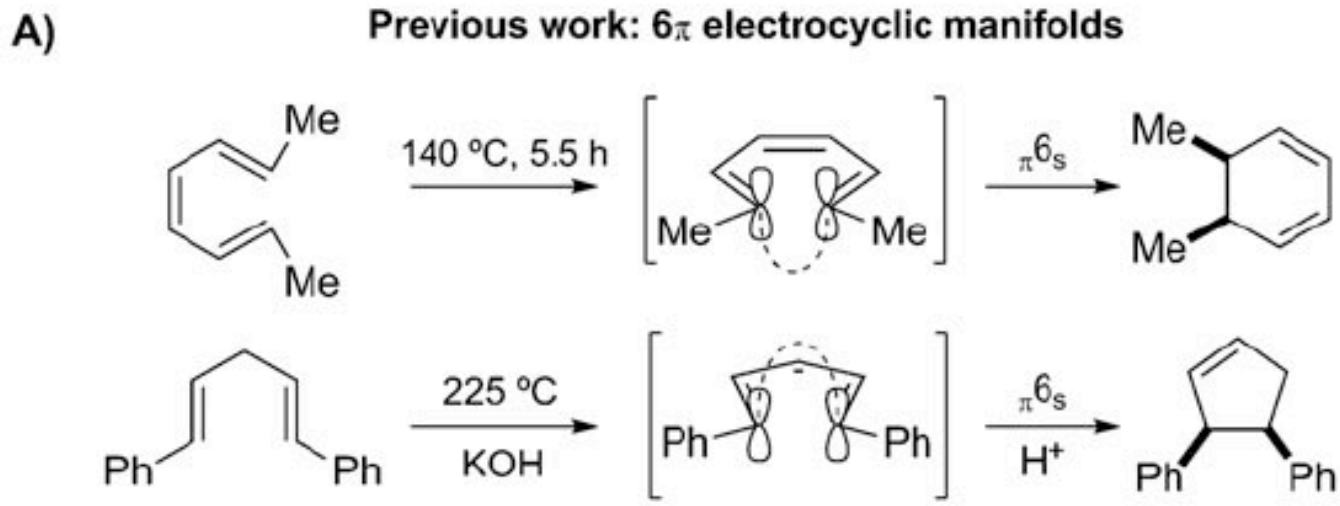
Catalyst

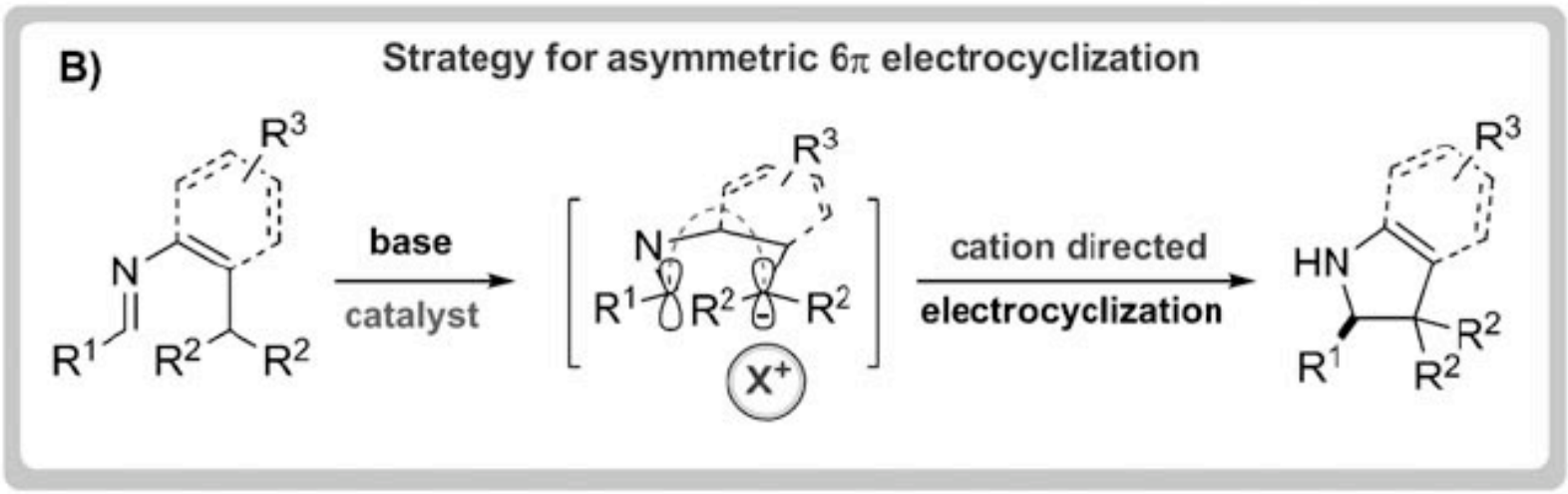


Sigma Aldrich
10 g = $95.50

http://www.sigmaaldrich.com/united-states.html

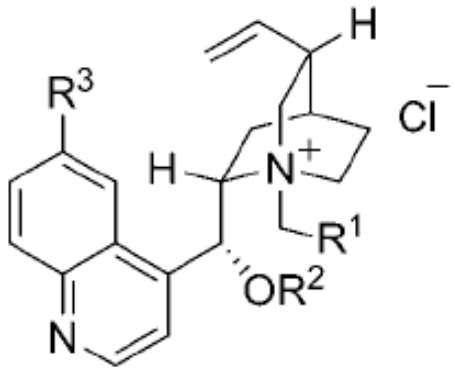
Strategic Approach to Asymmetric Electrocyclization



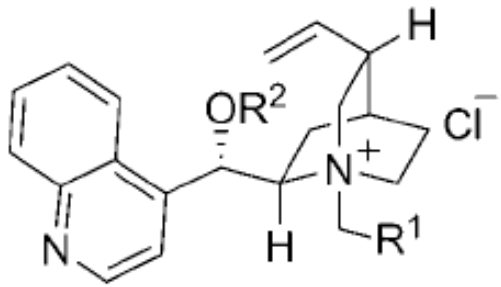


Maciver, E. E.; Thompson, S.; Smith, M. D. *Angew. Chem.* **2009** ASAP.

Catalysts Scope



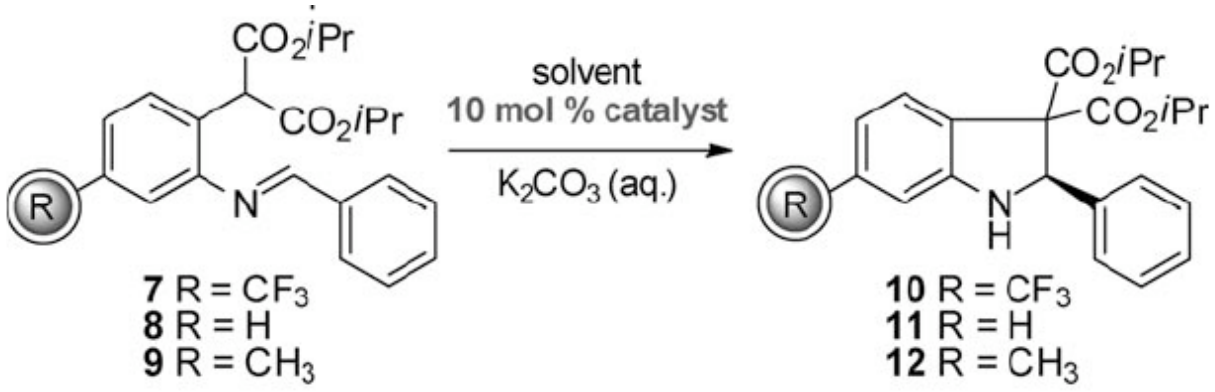
1 R^1 = Ph, R^2 = H, R^3 = H
2 R^1 = anthracenyl, R^2 = H, R^3 = H
3 R^1 = Ph, R^2 = allyl, R^3 = H
4 R^1 = Ph, R^2 = H, R^3 = OMe



5 R^1 = Ph, R^2 = H
6 R^1 = Ph, R^2 = allyl

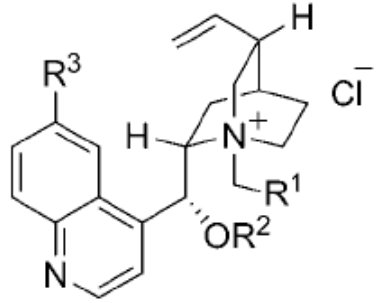
Maciver, E. E.; Thompson, S.; Smith, M. D. *Angew. Chem.* **2009** ASAP.

Substrate Scope



7 R = CF_3
8 R = H
9 R = CH_3

10 R = CF_3
11 R = H
12 R = CH_3

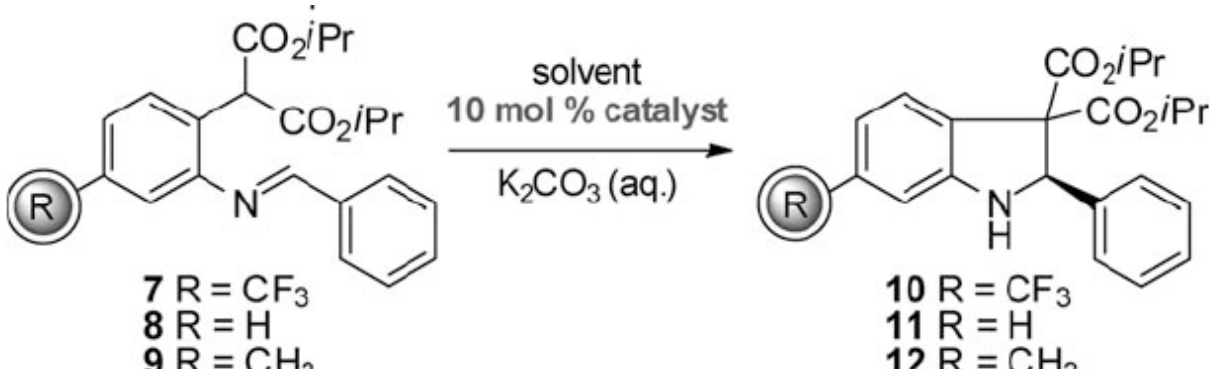


1 R^1 = Ph, R^2 = H, R^3 = H

R	Solvent	Cat.	*T*	Yield[b]	*ee* [%][c]
3-CF_3	$CHCl_3$/xylene	1	RT	85	(+) 86
3-CF_3	$CHCl_3$/xylene	1	RT	89	(+) 74
3-CF_3	hexane	1	RT	85	(+) 84
3-CF_3	toluene	1	RT	81	(+) 86
3-CF_3	THF	1	RT	81	(+) 80
3-CF_3	DCM	1	RT	88	(+) 76
3-CF_3	toluene	1	0 °C	81	(+) 89

Maciver, E. E.; Thompson, S.; Smith, M. D. *Angew. Chem.* **2009** ASAP.

Substrate Scope



7 R = CF_3
8 R = H
9 R = CH_3

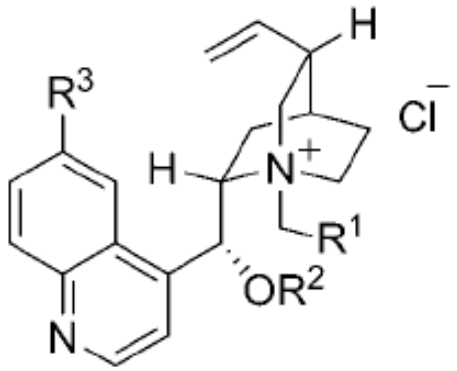
10 R = CF_3
11 R = H
12 R = CH_3

R	Solvent	Cat.	*T*	Yield[b]	*ee* [%][c]
3-CF_3	toluene	1	−15 °C	83	(+) 93
3-CF_3	toluene	1[d]	−15 °C	85	(+) 88
3-CF_3	toluene	1	−15 °C	99	(+) 97[e]
3-CF_3	toluene	2	−15 °C	96	(+) 85[e]
3-CF_3	toluene	3	−15 °C	95	(−) 36[e]
3-CF_3	toluene	4	−15 °C	97	(+) 98[e]
3-CF_3	toluene	5	−15 °C	96	(−) 63[e]
3-CF_3	toluene	6	−15 °C	95	(−) 5[e]
H	$CHCl_3$/xylene	1	−15 °C	70	(+) 93[e]
3-Me	$CHCl_3$/xylene	1	−15 °C	99	(+) 87[e]

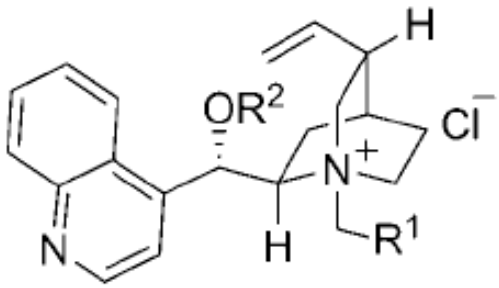
d) 1 mol% catalyst, e) purified imine

Maciver, E. E.; Thompson, S.; Smith, M. D. *Angew. Chem.* **2009** ASAP.

Catalyst



1 R^1 = Ph, R^2 = H, R^3 = H
2 R^1 = anthracenyl, R^2 = H, R^3 = H
3 R^1 = Ph, R^2 = allyl, R^3 = H
4 R^1 = Ph, R^2 = H, R^3 = OMe

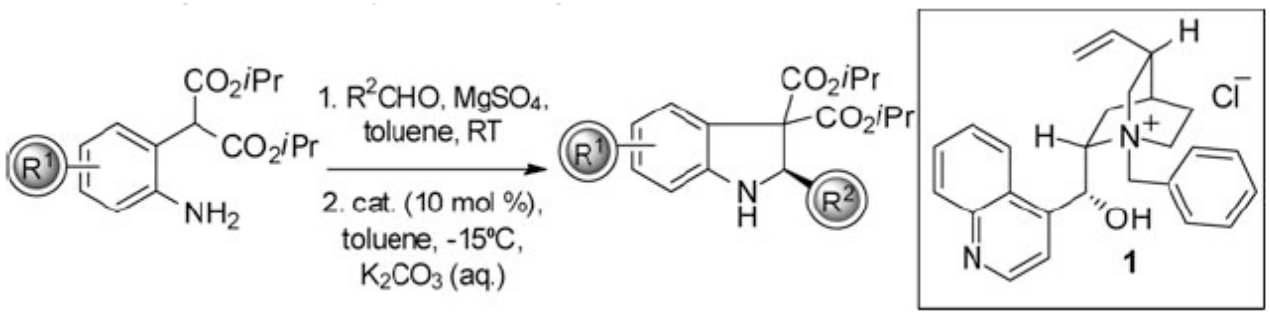


5 R^1 = Ph, R^2 = H
6 R^1 = Ph, R^2 = allyl

Red = -*ee*

Maciver, E. E.; Thompson, S.; Smith, M. D. *Angew. Chem.* **2009** ASAP.

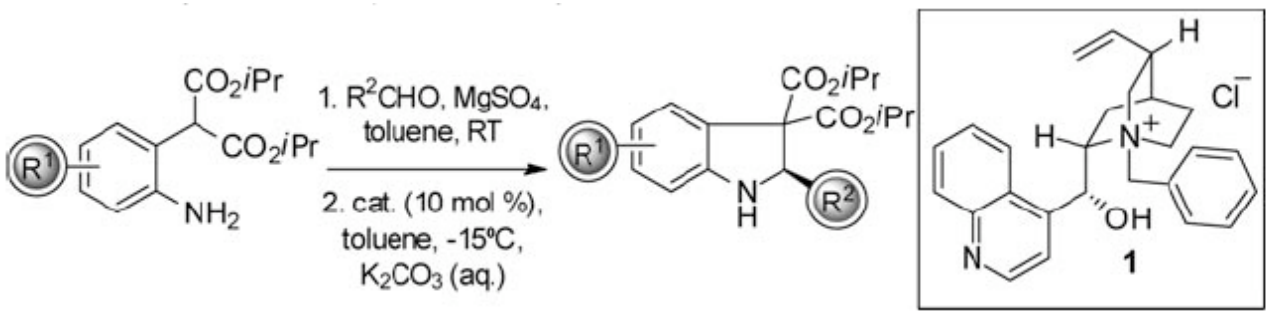
Substrate Scope



Cmpd.	R^1	R^2	Yield[b]	*ee* [%][c]
10	3-CF_3	Ph	87	94
13	3-CF_3	*m*-ClC_6H_4	84	86
14	3-CF_3	*p*-ClC_6H_4	69	93
15	3-CF_3	*p*-$(NO_2)C_6H_4$	75	98
16	3-CF_3	*m*-$(OMe)C_6H_4$	76	92
17	3-CF_3	*p*-BrC_6H_4	80	93
18	3-CF_3	2-naphthyl	92	92
19	3-CF_3	piperonyl	90	85
20	3-CF_3	*o*-ClC_6H_4	78	91
21	3-CF_3	*o*-$(NO_2)C_6H_4$	89	76

Maciver, E. E.; Thompson, S.; Smith, M. D. *Angew. Chem.* **2009** ASAP.

Substrate Scope

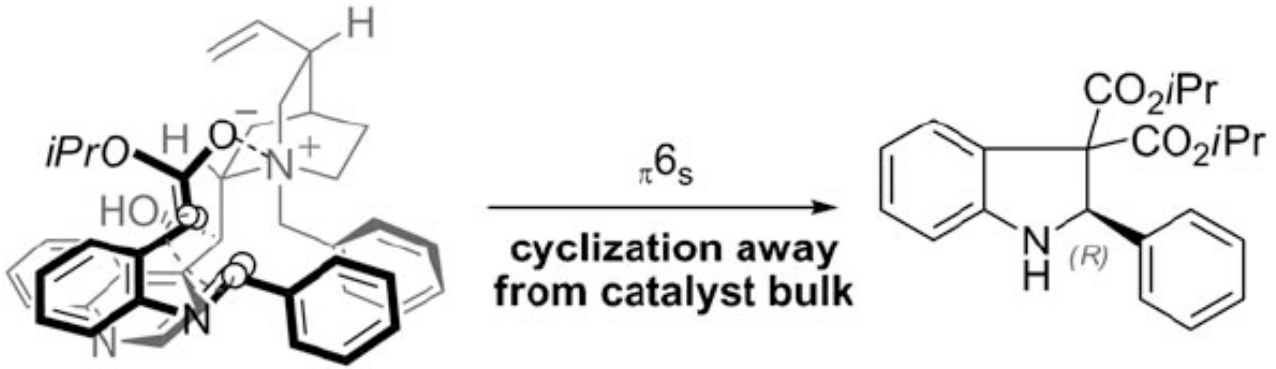


Cmpd.	R^1	R^2	Yield[b]	*ee* [%][c]
22[d]	H	*p*-BrC_6H_4	70	90
23[d]	H	2-furyl	68	86
24[d]	H	*p*-$(NO_2)C_6H_4$	89	89
25[e]	H	isopropyl	52	73
26[e]	H	cyclohexyl	94	90
27	2-F	*p*-BrC_6H_4	65	91
28	3-F	*p*-BrC_6H_4	67	91
29	3-F	Ph	60	91
30	4-F	*p*-BrC_6H_4	72	89

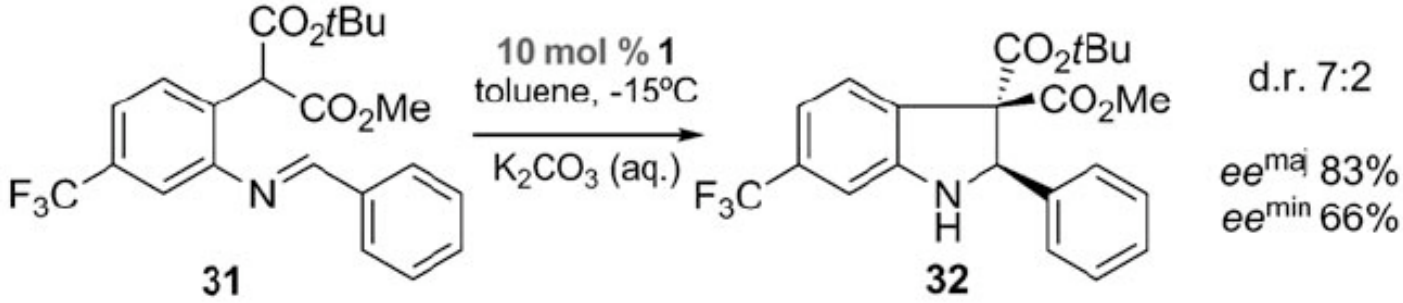
d) Solvent = toluene/Chloroform 5:1 (v/v) e) CsOH H20, Toluene, -55 C

Maciver, E. E.; Thompson, S.; Smith, M. D. *Angew. Chem.* **2009** ASAP.

Catalyst Model and Enantio- and Diastereoselectivity



Scheme 5. Stereochemical model for asymmetric electrocyclization (only one ester group is depicted for clarity).



Scheme 3. Diastereo- and enantioselective cyclization. Conditions: 1 mmol imine, 0.5 mL solvent, 0.2 mL 33 % aq. K_2CO_3.

Maciver, E. E.; Thompson, S.; Smith, M. D. *Angew. Chem.* **2009** ASAP.

Thank You

Merry Christmas