Catalytic enantioselective synthesis of indanes by a cation-directed 5-*endo-trig* cyclization

Reporter: Ji Zhou

Checker: Bo Wu

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Robert S. Paton. *et al.*
Nature Chem. **2015**, *7*, 171-178.

Robert S. Paton
University of Oxford

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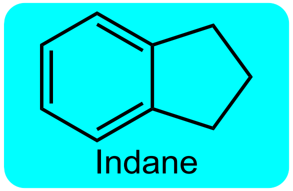
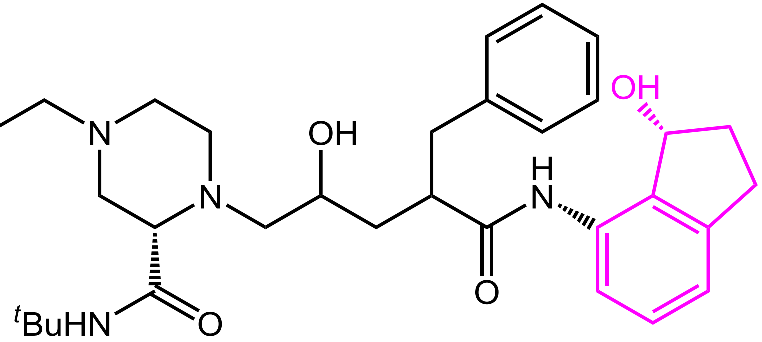
Introduction





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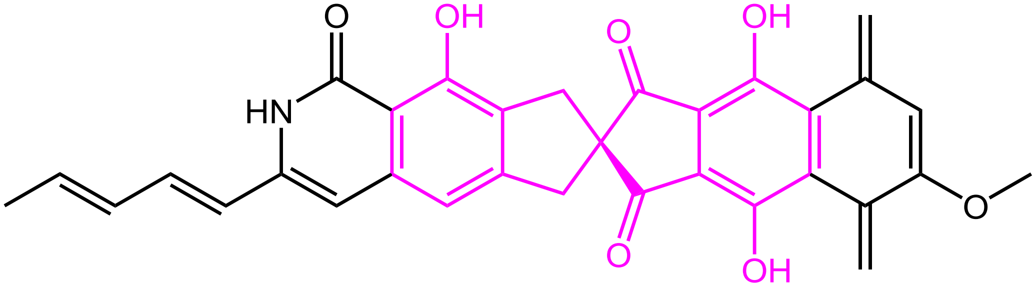


B

Introduction

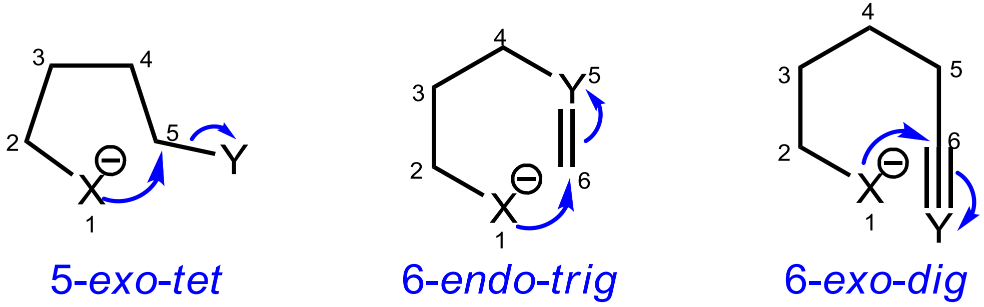
Baldwin's rules

The abbreviations to describe the ring forming processes were established by Baldwin in 1976.

●The prefixed number specifies the size of the generated ring.

●The words *exo* or *endo* are used to picture if the breaking bond is *exo*- or *endo*-cyclic to the smallest ring formed.

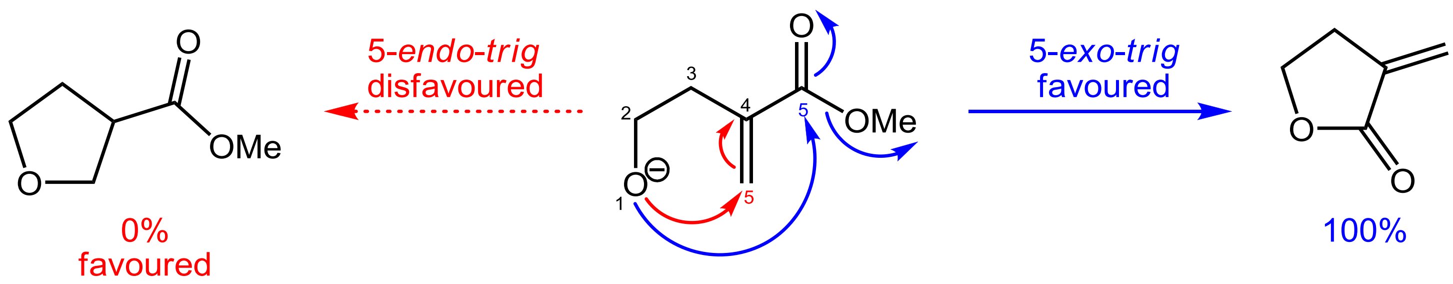
●The suffixes *tet*, *trig* or *dig* indicate the geometry of the carbon atom undergoing the ring closure reaction [*tet* = tetragonal (sp^3), *trig* = trigonal (sp^2), *dig* = digonal (sp)]



Baldwin, J. E. *et al*. *J. Chem. Soc. Chem. Commun.* **1976**, 734.

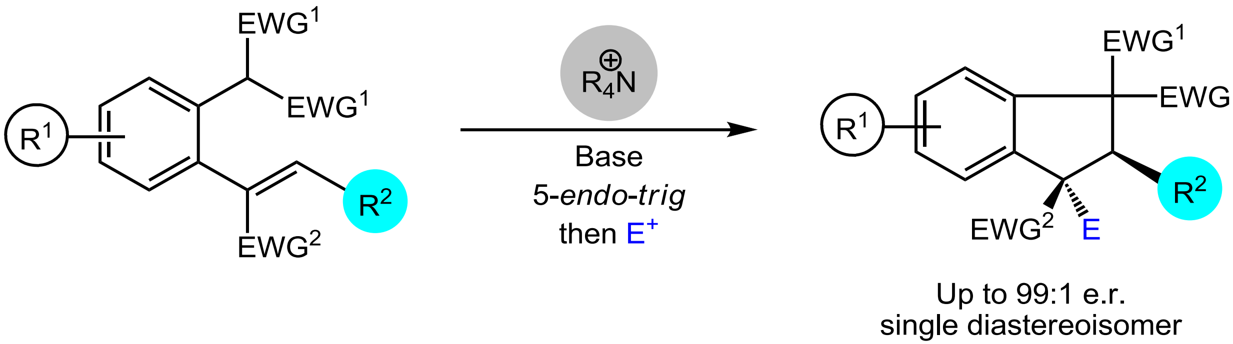
Introduction

5-*Endo*/*Exo*-*Trig* Reactions



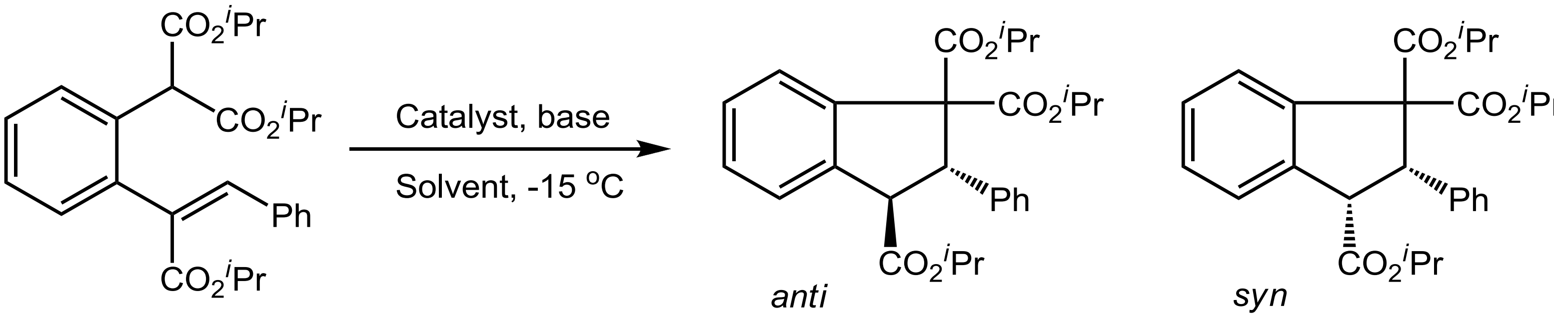
Baldwin, J. E. *et al*. *J. Chem. Soc. Chem. Commun.* **1976**, 736.

Intramolecular 5-*endo*-*trig* cyclization



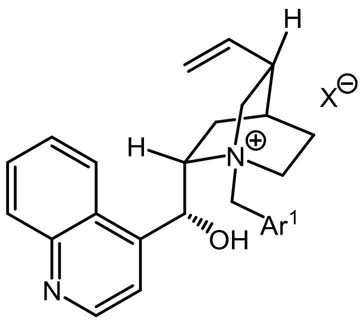
Paton, R. S. *et al. Nature Chem*. **2015**, *7*, 171.

Intramolecular 5-*endo-trig* cyclization

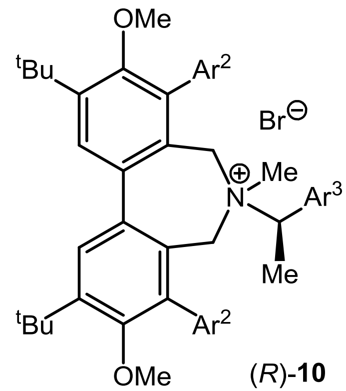


Entry	Catalyst (%)	Base	Solvent	d.r.	e.r.
1	**7**	K_2CO_3 (aq.)	Toluene	--	--
2	**7**	Cs_2CO_3 (s)	Toluene	--	--
3	**7**	$CsOH{\cdot}H_2O$ (s)	Toluene	3:1	64:36
4	**8**	$CsOH{\cdot}H_2O$ (s)	Toluene	2:1	55:45
5	**9**	$CsOH{\cdot}H_2O$ (s)	Toluene	2:1	50:50
6	**10**	KOH (aq.)	--	1:3	89:11
7	**10**	KOH (aq.)	${}^iPr_2O$	1:1	90:10
8	**10**	$CsOH{\cdot}H_2O$ (s)	Toluene	3:1	80:20
9	**12**	KOH (aq.)	Toluene	1:2	96:4
10	**12**	KOH (aq.)	Toluene/Hexane	1:3	92:8

Intramolecular 5-*endo*-*trig* cyclization

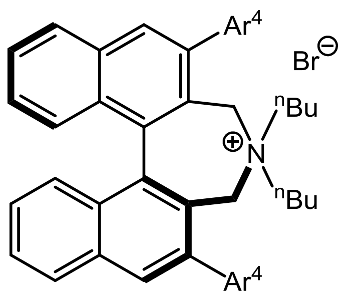


7. Ar^1 = Ph, X = Cl
8. Ar^1 = 4-CF_3-C_6H_4, X = Br
9. Ar^1 = 9-anthracenyl, X = Cl

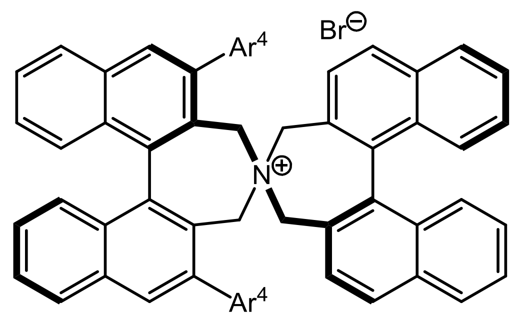


(*R*)-**10**

Ar^2 = 3,5-$(CF_3)_2$-C_6H_3
Ar^2 = 2-naphthyl



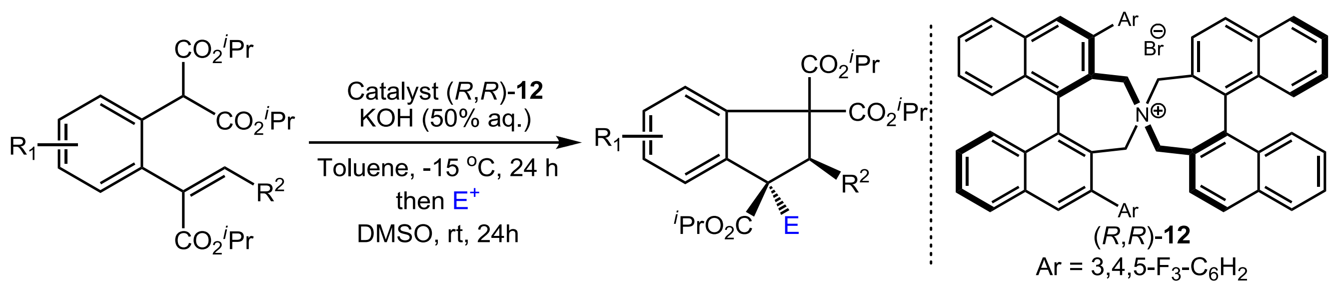
(*S*)-**11**

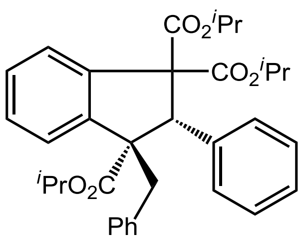


(*R*,*R*)-**12**

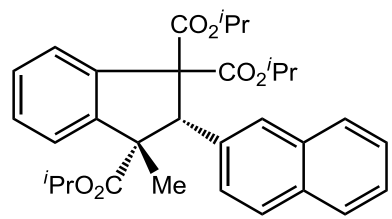
Ar^4 = 3,4,5-F_3-C_6H_2

Intramolecular 5-*endo*-*trig* cyclization

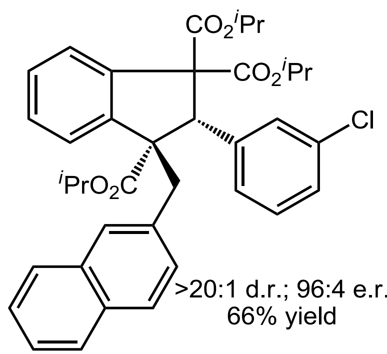




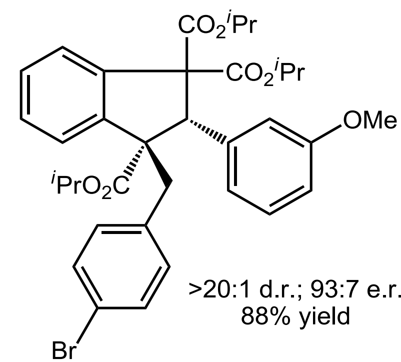
>20:1 d.r.; 95:5 e.r.
77% yield



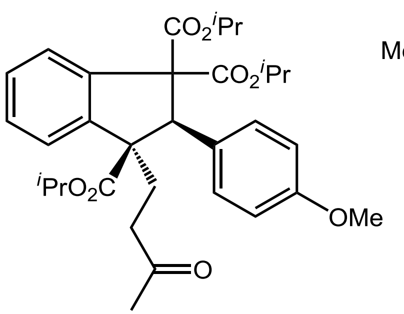
>20:1 d.r.; 96:4 e.r.
59% yield



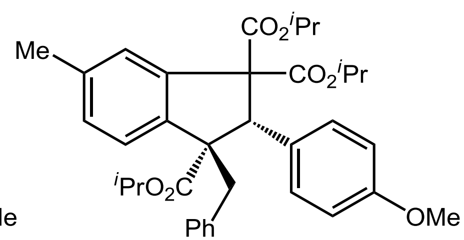
>20:1 d.r.; 96:4 e.r.
66% yield



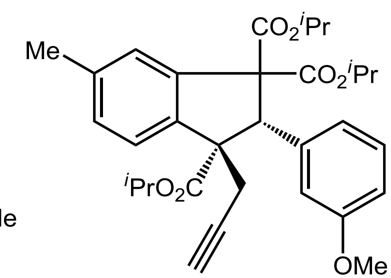
>20:1 d.r.; 93:7 e.r.
88% yield



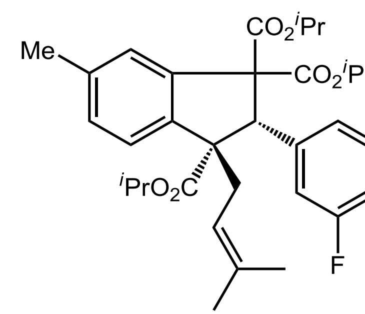
>20:1 d.r.; 97:3 e.r.
66% yield



>20:1 d.r.; 98:2 e.r.
93% yield

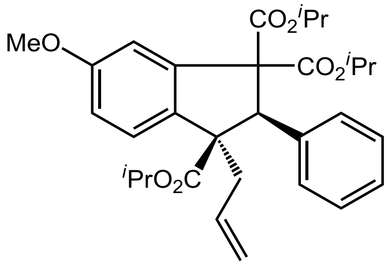


>20:1 d.r.; 94:6 e.r.
77% yield

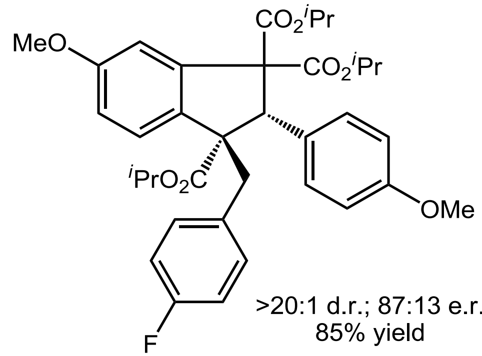


>20:1 d.r.; 99:1 e.r.
82% yield

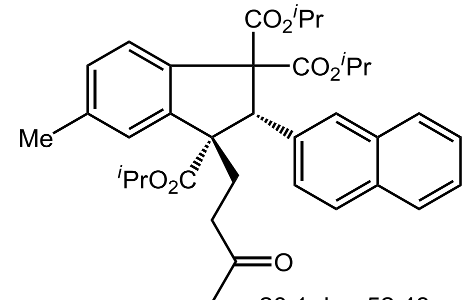
Intramolecular 5-*endo*-*trig* cyclization



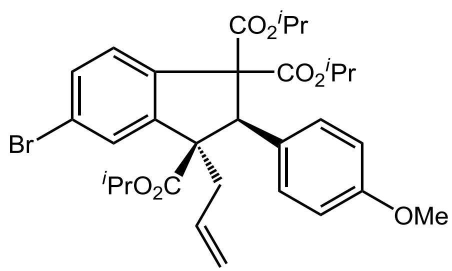
>20:1 d.r.; 88:12 e.r.
88% yield



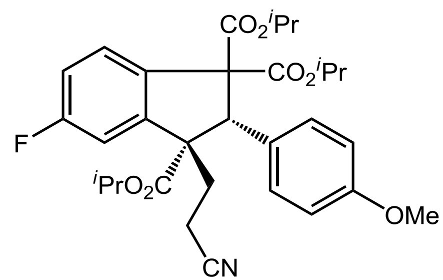
>20:1 d.r.; 87:13 e.r.
85% yield



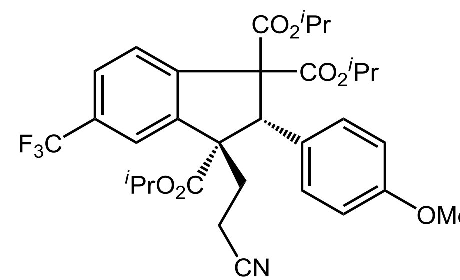
>20:1 d.r.; 52:48 e.r.
31% yield



>20:1 d.r.; 61:39 e.r.
69% yield

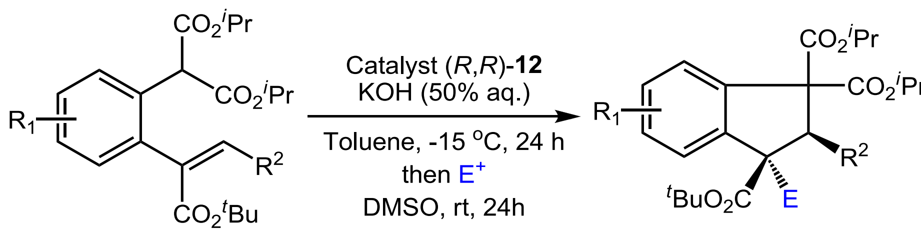


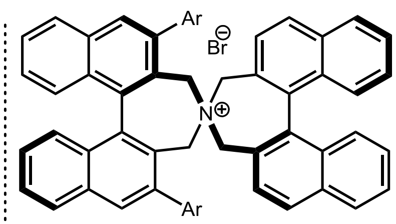
>20:1 d.r.; 71:29 e.r.
72% yield



>20:1 d.r.; 57:43 e.r.
73% yield

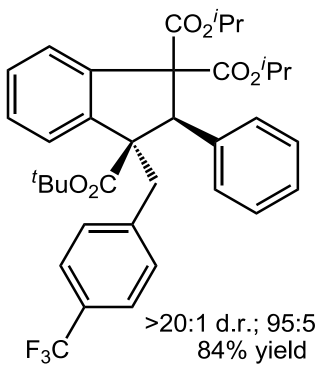
Intramolecular 5-*endo*-*trig* cyclization



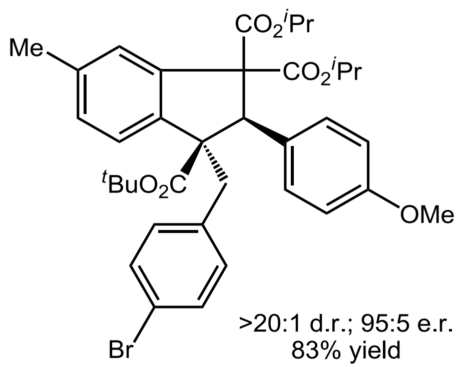


(*R*,*R*)-**12**

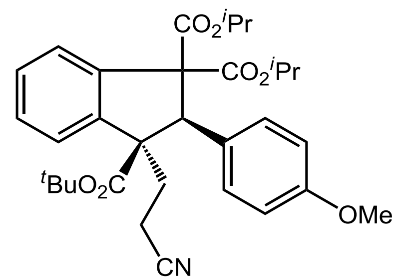
Ar = 3,4,5-F_3-C_6H_2



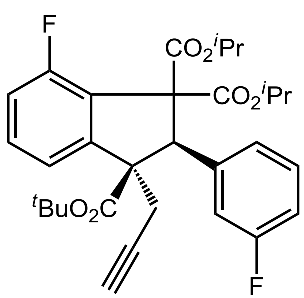
>20:1 d.r.; 95:5 e.r.
84% yield



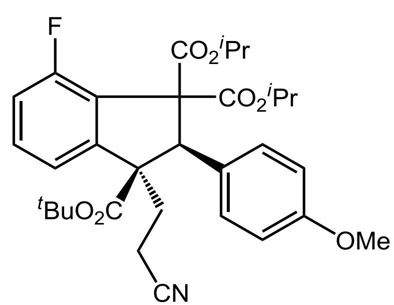
>20:1 d.r.; 95:5 e.r.
83% yield



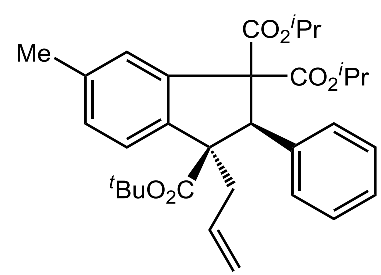
>20:1 d.r.; 96:4 e.r.
77% yield



>20:1 d.r.; 88:12 e.r.
63% yield



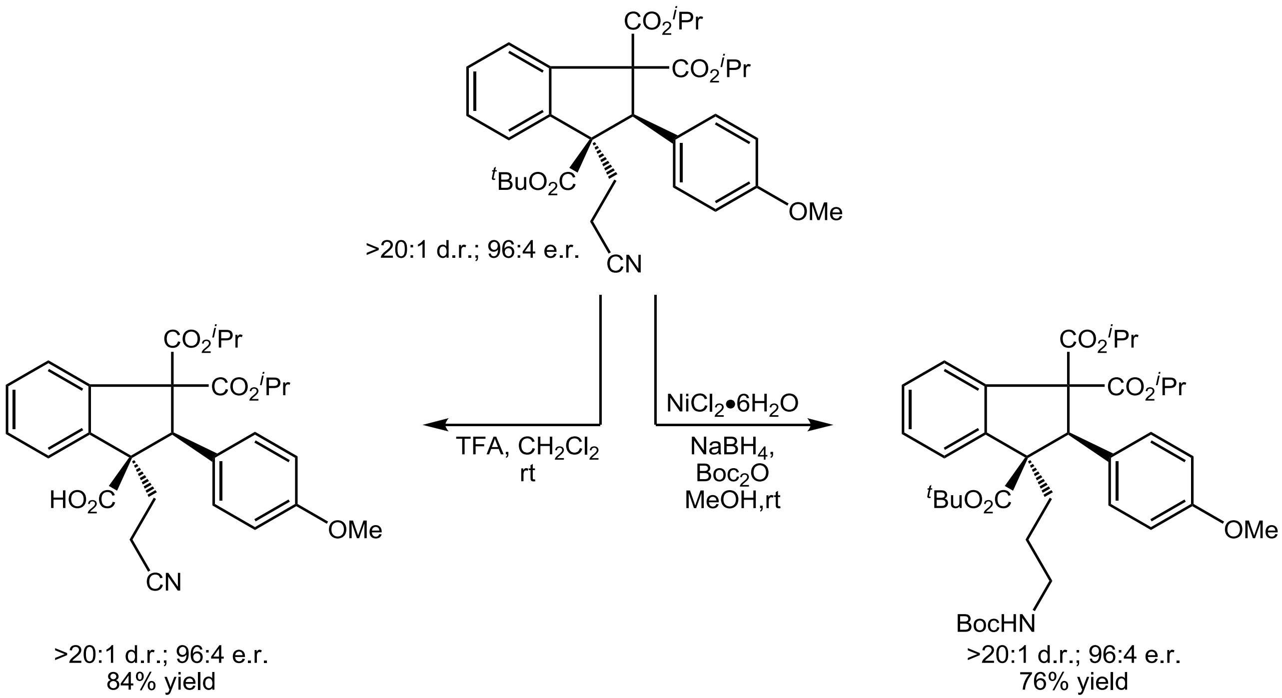
>20:1 d.r.;94:6 e.r.
62% yield



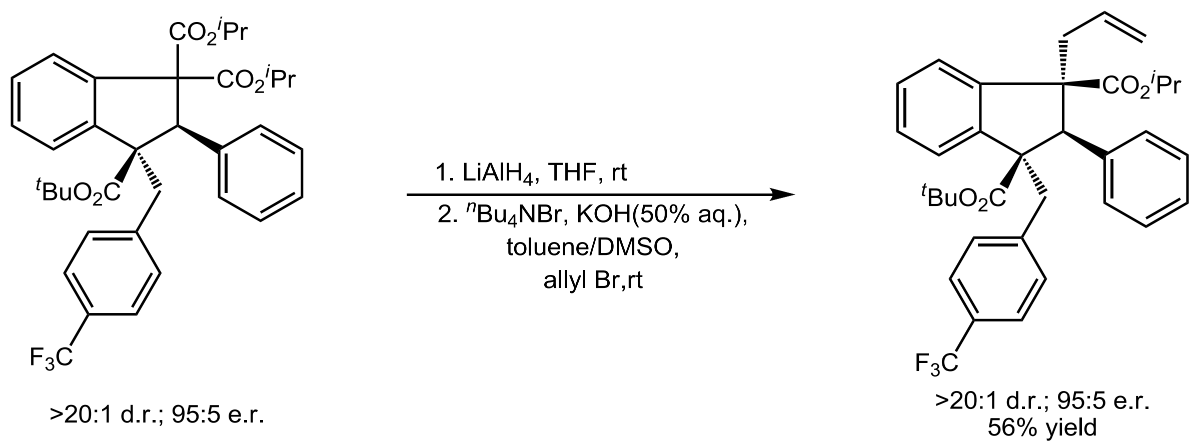
>20:1 d.r.; 95:5 e.r.
75% yield

Intramolecular 5-*endo-trig* cyclization

a.

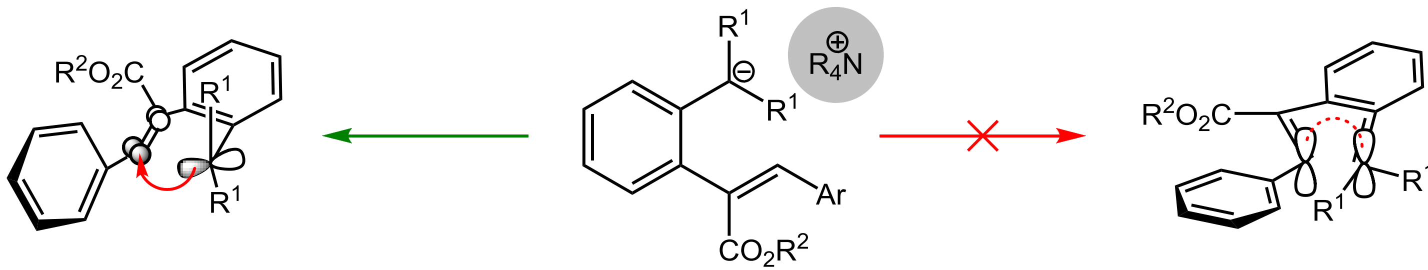


b.

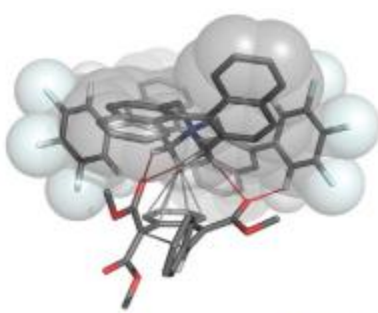


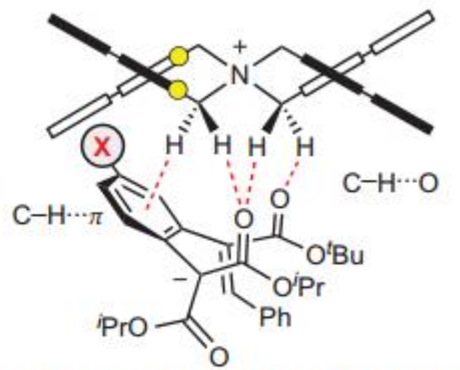
Intramolecular 5-*endo*-*trig* cyclization

Mechanistic extremes

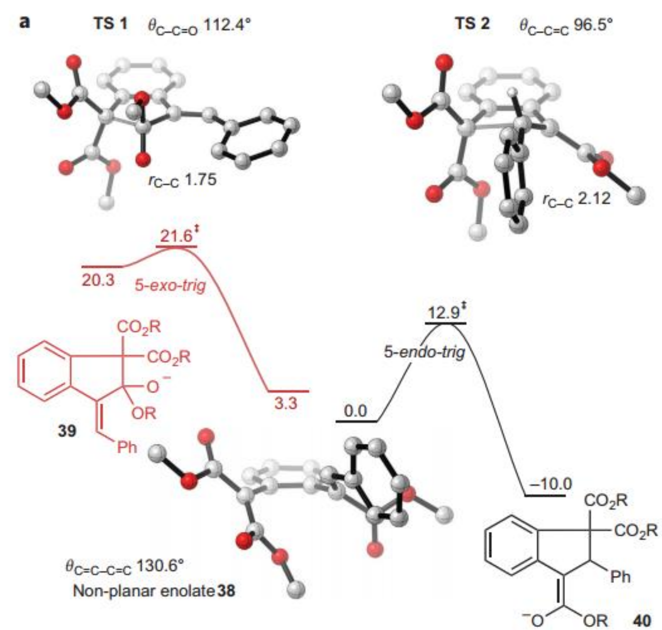


Anionic 5-*endo*-*trig*　　　$R^1 = CO_2{}^iPr$　　　$_{\pi}6_s$ electrocyclization

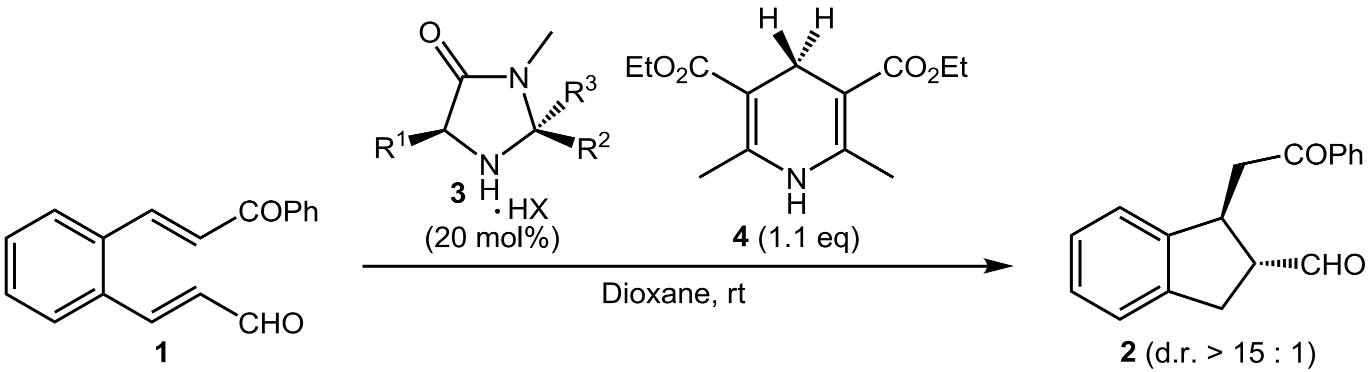




● = Site of aryl substitution (omitted for clarity)



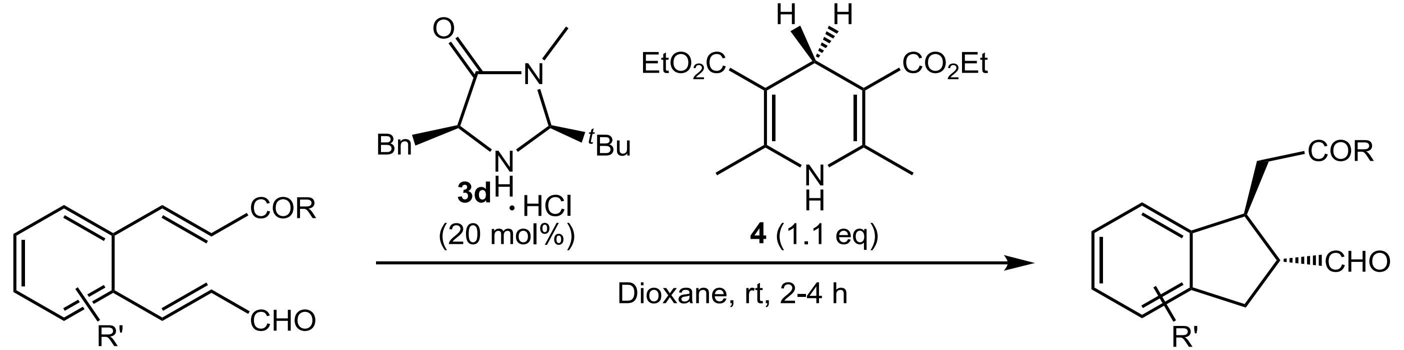
Intramolecular 5-*exo*-*trig* Michael addition

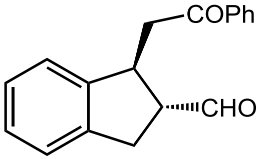


Catalyst	R^1	R^2	R^3	X	time [h]	yield [%]	ee [%]
3a	H	^{t}Bu	H	CF_3CO_2	2	82	93
3b	H	^{t}Bu	H	Cl	12	90	95
3c	H	2,6-Ph_2Ph	H	Cl	12	75	16
3d	Bn	^{t}Bu	H	Cl	3	98	96
3e	*p*-BnOBn	^{t}Bu	H	Cl	6	91	95
3f	*p*-^{t}BuOBn	^{t}Bu	H	Cl	6	90	95
3g	Bn	Me	Me	Cl	24	<10	--

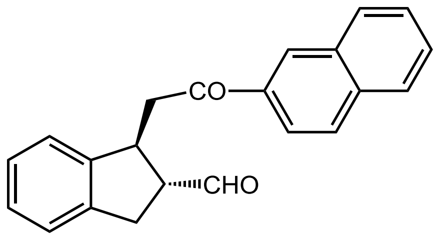
List, B. *et al*. *J. Am. Chem. Soc.* **2005**, *127*, 15036.

Intramolecular 5-*exo-trig* Michael addition

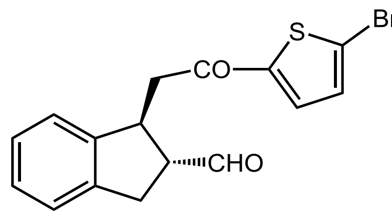




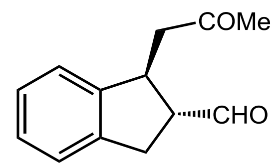
98% yield
15:1 d.r., 96% ee



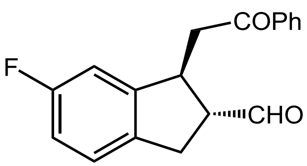
94% yield
50:1 d.r., 94% ee



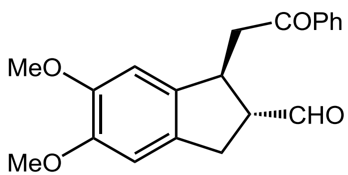
91% yield
40:1 d.r., 92% ee



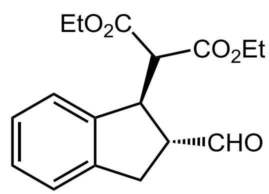
91% yield
>50:1 d.r., 91% ee



95% yield
21:1 d.r,. 97% ee

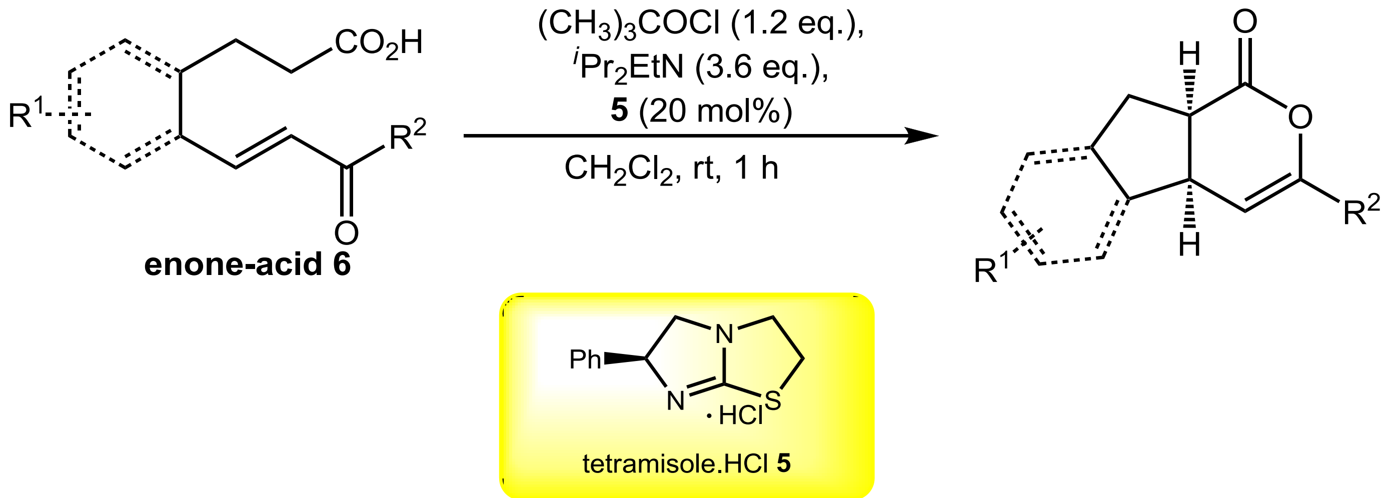


88% yield
23:1 d.r., 96% ee



86% yield
>50:1 d.r., 86% ee

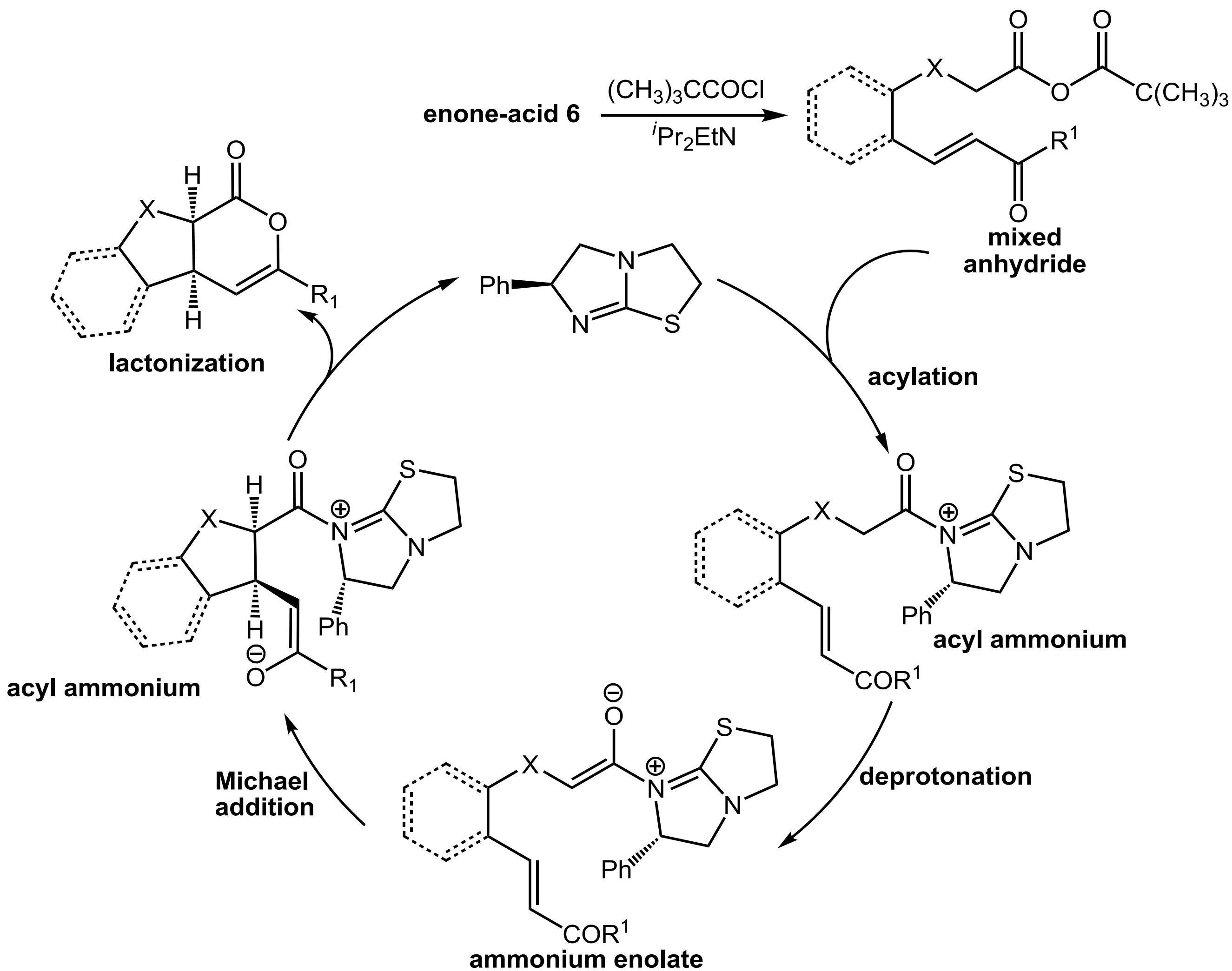
Intramolecular 5-*exo-trig* Michael addition



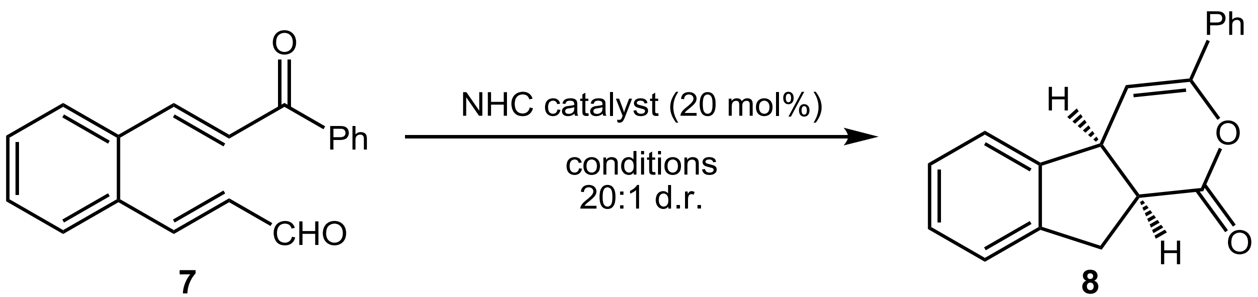
Smith, A. D. *et al*. *J. Am. Chem. Soc.* **2011**, *133*, 2714.

Intramolecular 5-*exo-trig* Michael addition

Proposed catalytic pathways



Intramolecular 5-*exo*-*trig* Michael addition



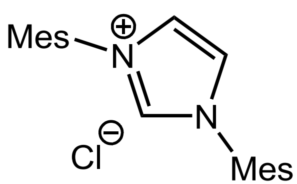
Entry	Catalyst	Conditions[a]	yield [b]	ee[%][c]
1	**A**	DBU, THF	6	-
2	**A**	$KN(SiMe_3)_2$,THF[d]	11	-
3	**A**	$^{i}Pr_2EtN$, THF, 45 ^{o}C	50	-
4	**B**	$^{i}Pr_2EtN$, toluene/THF[e]	61	-
5	**C**	$^{i}Pr_2EtN$, toluene/THF[e,f]	61	93
6	**C**	Et_3N (0.1 M), toluene/THF[e]	62	93
7	**C**	$^{i}Pr_2EtN$ (0.1 M), CH_2Cl_2, -20 ^{o}C	49	93
8	**D**	$^{i}Pr_2EtN$ (0.1 M), toluene/THF[e]	53	99

Scheidt, K. A. *et al*. *Angew. Chem. Int. Ed.* **2007**, *46*, 3107.

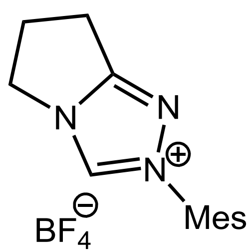
Intramolecular 5-*exo-trig* Michael addition

Entry	Catalyst	Conditions[a]	yield [b]	ee[%][c]
9	**D**	$^{i}Pr_2EtN$ (0.05 M), toluene/THF[e]	66	99
10	**D**	$^{i}Pr_2EtN$ (0.05 M), CH_2Cl_2	68	99
11	**D**[g]	$^{i}Pr_2EtN$ (0.05 M), CH_2Cl_2	68	99

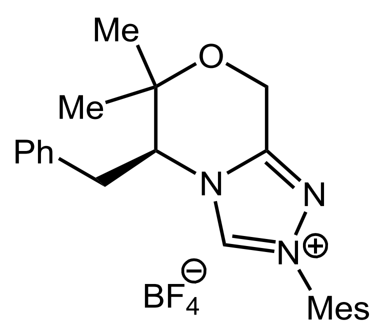
[a] Base (20 mol%), **7** (0.2 M) at 23 ºC unless otherwise noted. DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene. [b] Yield of isolated product. [c] Determined by HPLC (Chiracel AD-H). Absolute and relative configuration of **8** assigned by X-ray crystallography. [d] Carbene generated prior to addition of substrate. [e] 10:1 toluene/THF. [f] Base (1.2 equiv). [g] D (10 mol%).



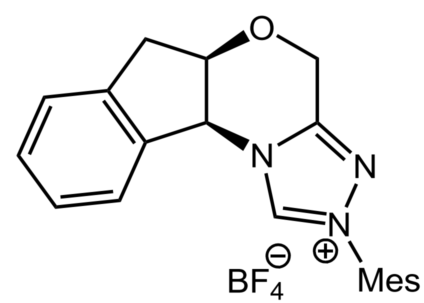
A



B

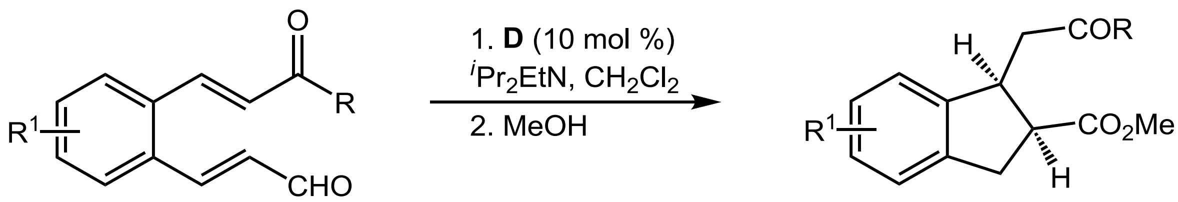


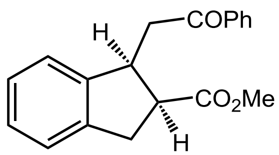
C



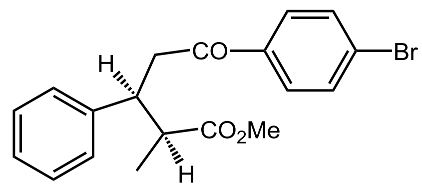
D

Intramolecular 5-*exo*-*trig* Michael addition

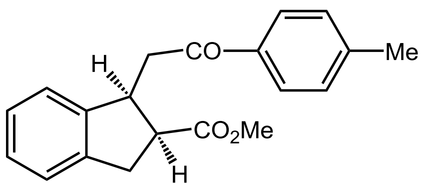




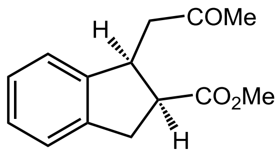
69% yield,
99% ee



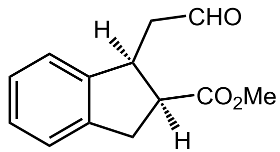
62% yield,
99% ee



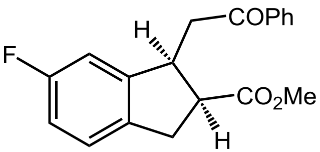
80% yield,
99% ee



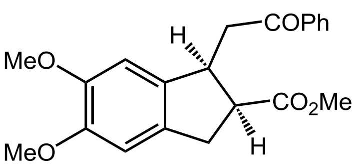
59% yield,
99% ee



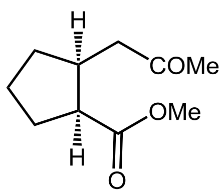
68% yield,
99% ee



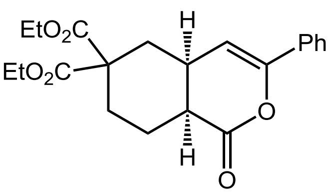
68% yield,
99% ee



73% yield,
99% ee



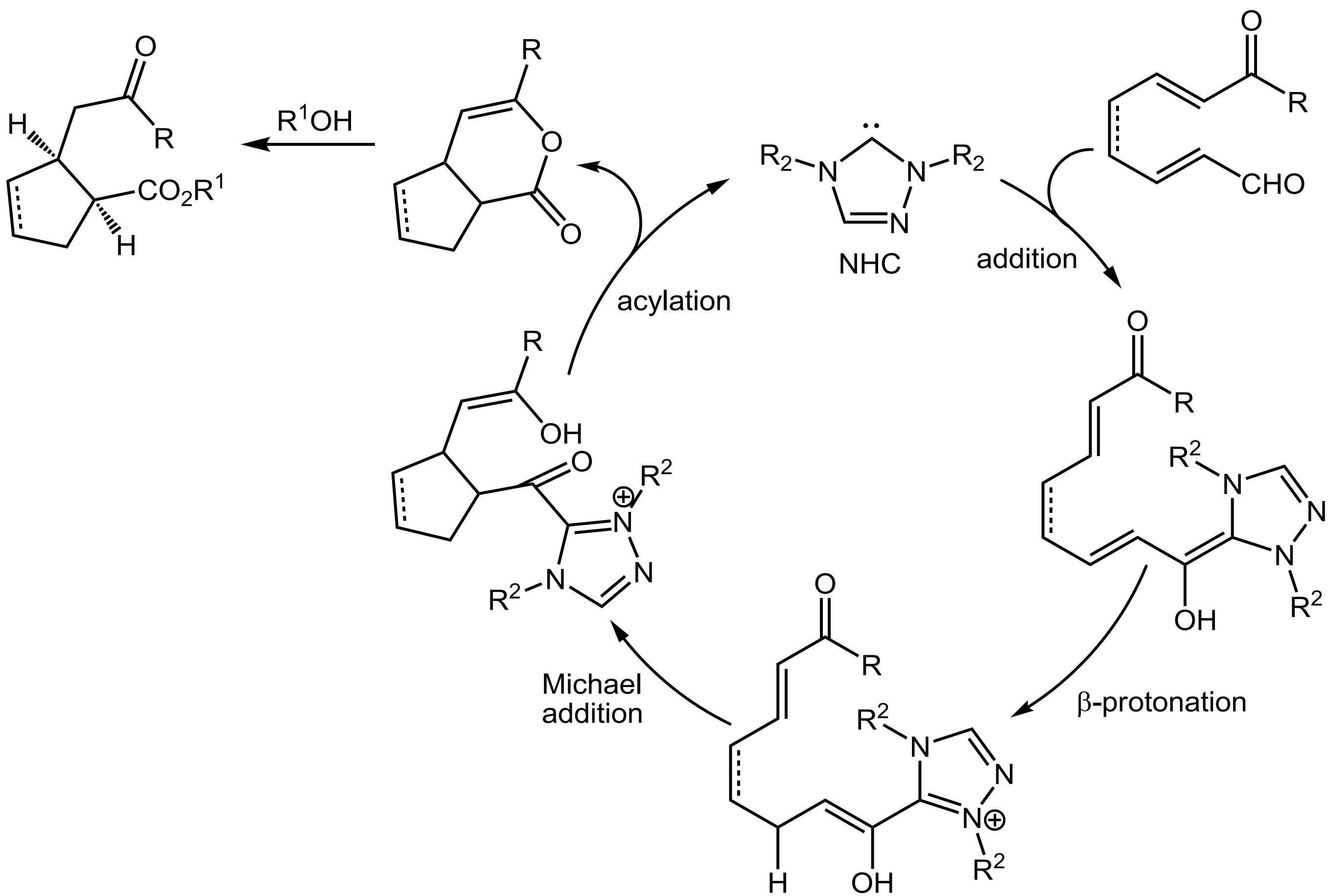
66% yield,
99% ee



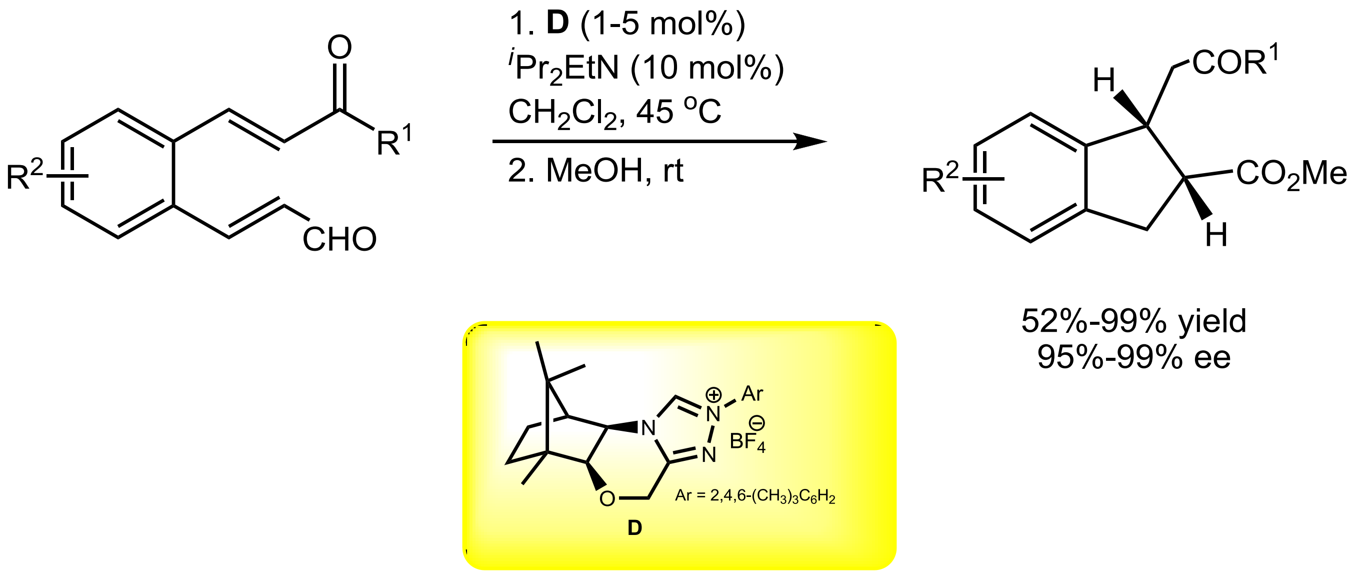
52% yield,
62% ee

Intramolecular 5-*exo-trig* Michael addition

Proposed catalytic pathway



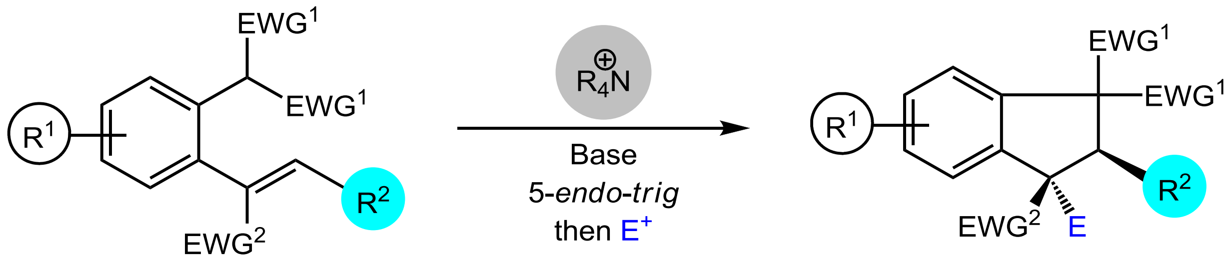
Intramolecular 5-*exo-trig* Michael addition



You, S-L. *et al*. *Chem. Commun.* **2009**, 5823.

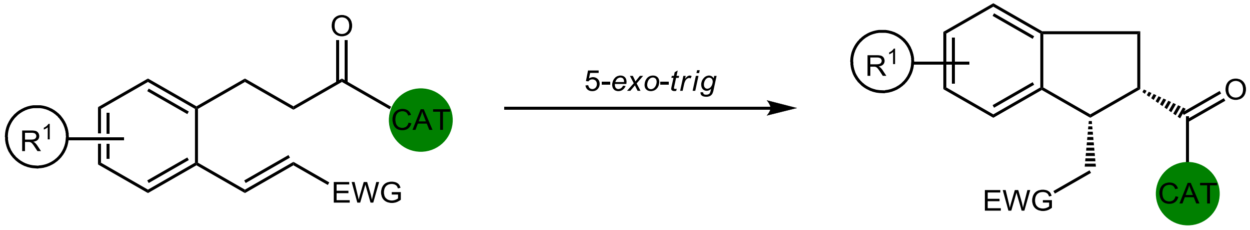
Summary

Intramolecular 5-*endo-trig* cyclization



Robert S. P. *et al*.(2015)

Intramolecular 5-*exo-trig* Michael additions



Imidazolidiones
List, B. *et al*. (2005)

Cyclic isothioureas
Smith, A. D. *et al*. (2011)

N-heterocyclic carbenes
Scheidt, K. A. *et al*. (2007)
You, S-L. *et al*. (2009)

The indane architecture is a constituent of many natural product families and a key component of clinically relevant entities and biologically active molecules, yet relatively few catalytic enantioselective procedures for its synthesis have been disclosed. Previous synthetic strategies have typically relied on intramolecular 5-*exo-trig* Michael additions to generate these carbocycles utilizing chiral imidazolidinones, cyclic isothioureas, N-heterocyclic carbenes or proline derivatives. So far, the related 5-*endo-trig* disconnection has not been explored, probably due to the fact it is considered to be a stereoelectronically disfavoured cyclization as described in Baldwin's rules. From a mechanistic perspective, this transformation can also be considered as an anionic 6π electrocyclization related to the classical pentadienyl anion cyclization.

The rules proposed by Baldwin allow the prediction of the relative facility of ring-closing reactions under kinetic control based upon the ability of the tethered nucleophile and electrophile to achieve the correct trajectory for bond formation. This is a consequence of the geometric constraints of the tethering atoms and the requirement for attack on the $\pi^*_{C=Y}$ at the Bürgi–Dunitz angle. We reasoned that a catalytic enantioselective route to densely functionalized indanes could be achieved using a chiral counterion to control the π-face selectivity in a 5-*endo-trig* cyclization reaction. We rationalized that key to achieving this would be the installation of an electron-withdrawing group on the trigonal carbon to stabilize developing charge in the transition state resulting from the ring-forming step. Quenching of this anion with an appropriate electrophile would also give access to all-carbon quaternary stereocentres. Our previous investigations into the counterion directed cyclization of delocalized anions to form indolines and indolenines have demonstrated that analogous transformations can proceed with high enantioselectivity.

A chiral cation is able to facilitate a highly enantio- and diastereoselective 5-*endo-trig* Michael reaction to generate complex indanes bearing all-carbon quaternary stereocentres. The ease with which this kinetically controlled but formally disfavoured reaction occurs led us to apply quantum calculations to probe the mechanism. This demonstrated that geometric/stereoelectronic constraints may not be decisive in the observed outcome of irreversible ringclosing reactions and we anticipate that further study of other kinetically controlled 5-*endo-trig* processes will provide new insight into the factors that control ring-closing reactions.