

Literature Report

***N*-Heterocyclic Carbene Catalyzed [4+3] Annulation of Enals and *o*-Quinone Methides: Highly Enantioselective Synthesis of Benzo- ϵ -Lactones**

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Date: 2013-09-03

Ye, S. *et al.*
***Angew. Chem. Int. Ed.* 2013, 52, 8607-8610.**



Institute
of Chemistry

Contents

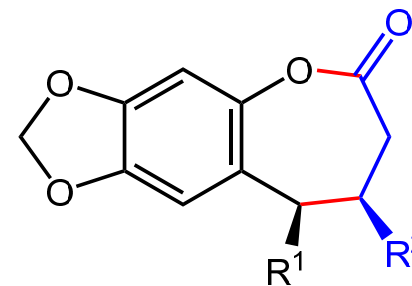
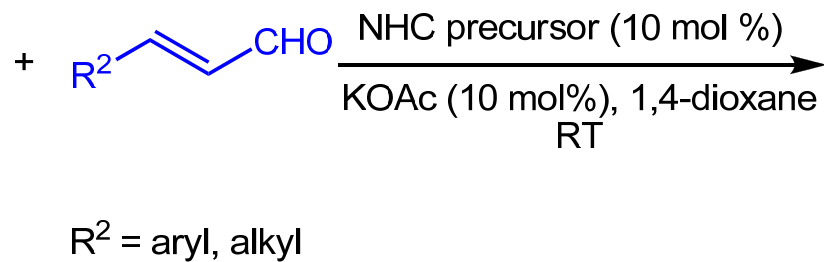
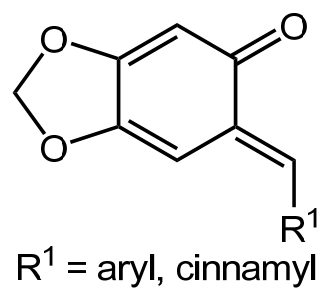
1 NHC-Catalyzed [3+4] Annulation of Enals

2 NHC-Catalyzed [3+3] Annulation of Enals

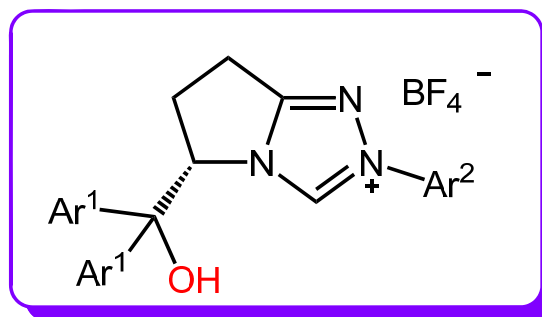
3 NHC-Catalyzed [3+2] Annulation of Enals

4 Summary

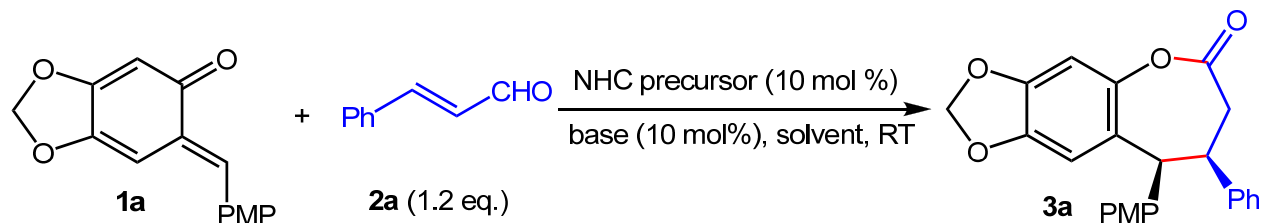
NHC-Catalyzed [3+4] Annulation of Enals



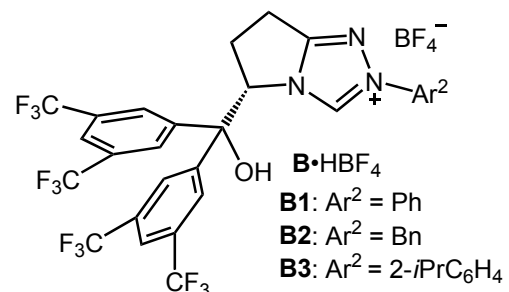
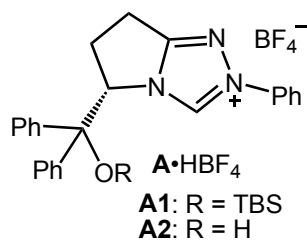
79-97% yield
3:1-20:1 d.r.,
81-98% ee



Optimization Studies



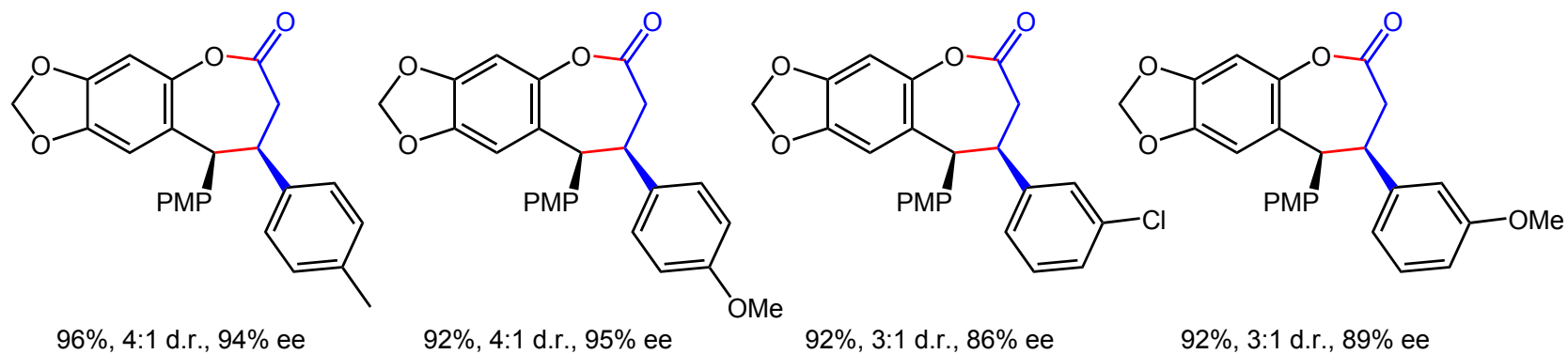
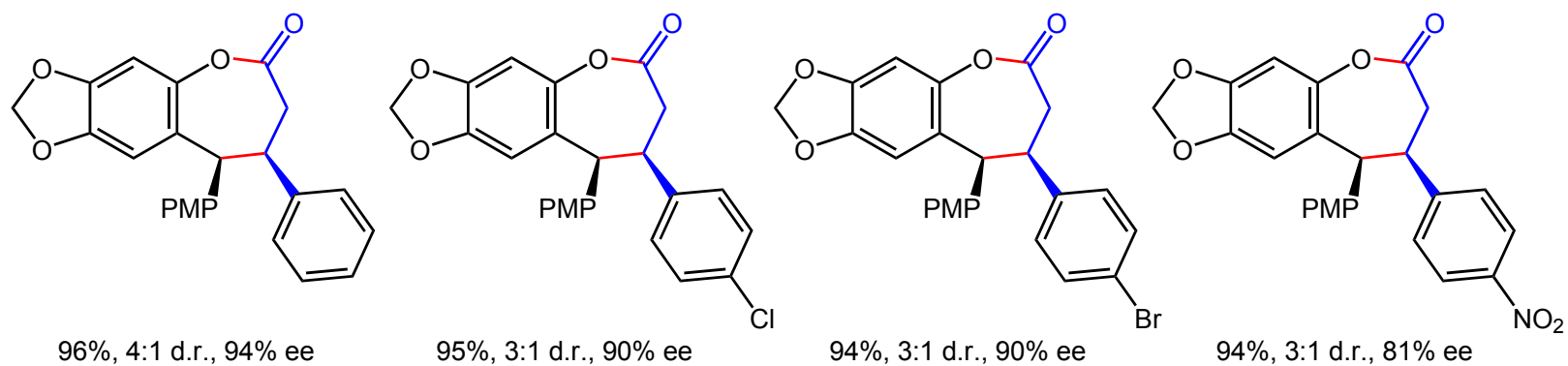
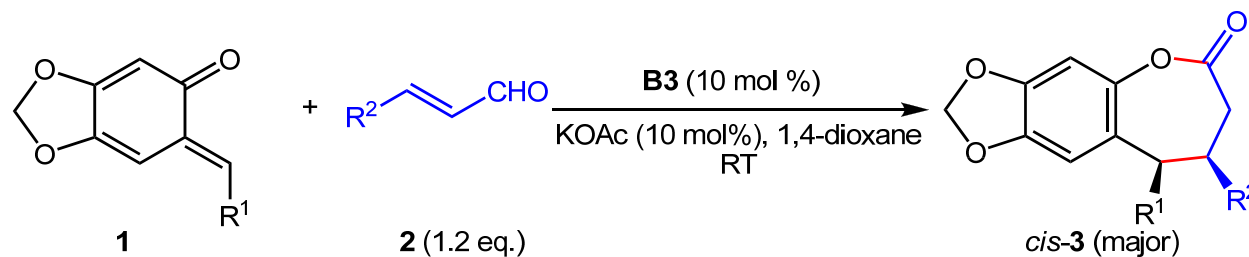
Entry	Cat.	Base	Solvent	Yield [%] ^a	d.r. ^b	Ee (%) ^c
1	A1	DBU	THF	trace	n.d.	n.d. (n.d.)
2	A2	DBU	THF	49	5:1	96 (n.d.)
3	B1	DBU	THF	30	5:1	90 (15)
4	B2	DBU	THF	63	2:1	88 (23)
5	B3	DBU	THF	90	3:1	94 (42)
6	B3	DBU	Toluene	94	2:1	87 (48)



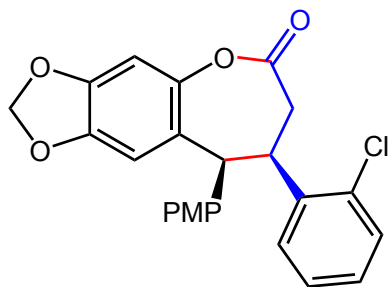
Entry	Cat.	Base	Solvent	Yield [%] ^a	d.r. ^b	Ee (%) ^c
7	B3	DBU	DCM	88	3:1	92 (43)
8	B3	DBU	Et ₂ O	61	5:1	94 (20)
9	B3	DBU	DME	96	3:1	92 (17)
10	B3	DBU	1,4-dioxane	97 (96) ^d	4:1	94 (29)
11	B3	DBU	CH ₃ CN	55	3:1	92 (19)
12 ^e	B3	DBU	1,4-dioxane	98	3:1	93 (40)
13 ^e	B3	DBU	1,4-dioxane	99	3:1	93 (33)
14 ^e	B3	DBU	1,4-dioxane	88	3:1	95 (33)
15	B3	Cs ₂ CO ₃	1,4-dioxane	38	3:1	94 (25)
16	B3	Et ₃ N	1,4-dioxane	99	3:1	93 (33)
17	B3	KOAc	1,4-dioxane	98 (96) ^d	4:1	94 (40)
18 ^f	B3	KOAc	1,4-dioxane	(84) ^d	4:1	92 (n.d.)

^a Combined yield of the two diastereomers as determined by ¹H NMR spectroscopy. ^b Diastereoselectivity ¹H NMR analysis of unpurified reaction mixture. ^c Enantiomeric excess of *cis-3a* and *trans-3a* determined by HPLC on a chiral column. ^d Combined yield of isolated diastereomers. ^e 10 mol% of Mg(OTf)₂, LiClO₄ or Cu(OTf)₂ was used as the additive for the reaction in entries 12-14. ^f The reaction was carried out at 0 °C

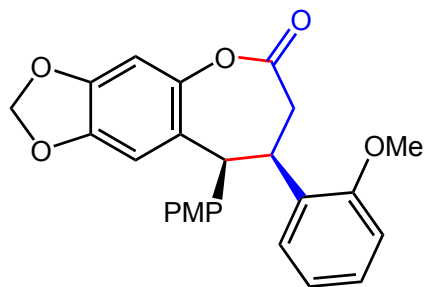
Substrate Scope of Enals and *o*-Quinone Methides



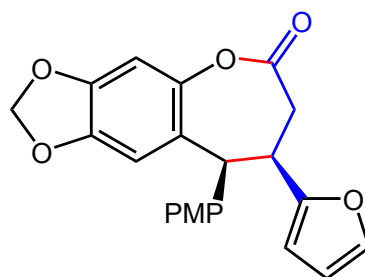
Substrate Scope of Enals and *o*-Quinone Methides



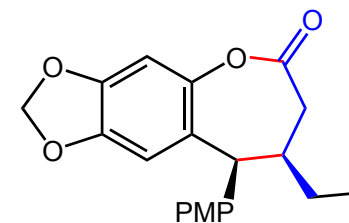
92%, 3:1 d.r., 82% ee



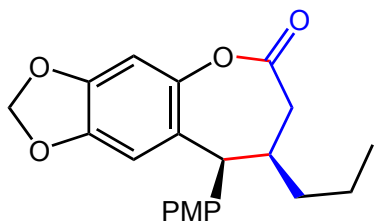
79%, 3:1 d.r., 90% ee



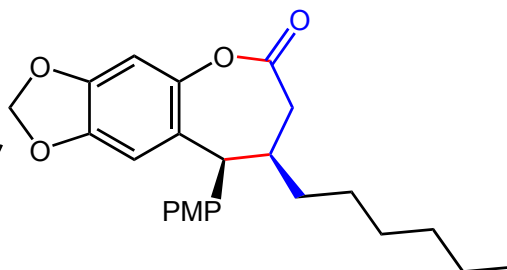
95%, 5:1 d.r., 94% ee



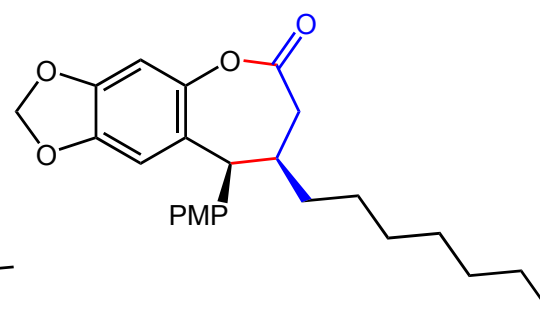
91%, >20:1 d.r., 98% ee



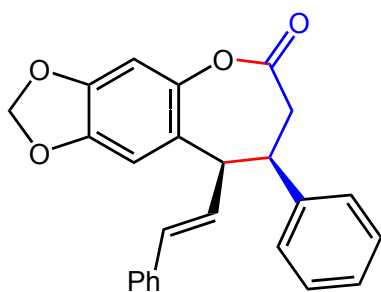
83%, >20:1 d.r., 97% ee



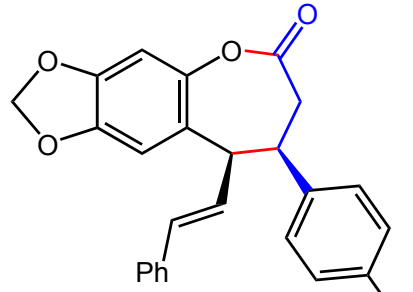
88%, >20:1 d.r., 97% ee



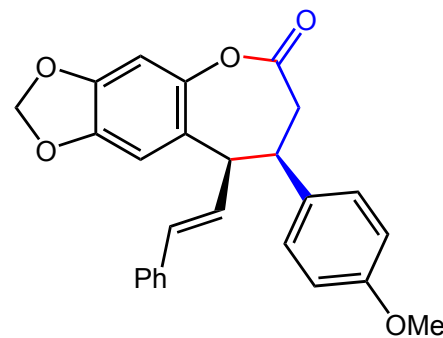
97%, >20:1 d.r., 93% ee



91%, 3:1 d.r., 93% ee

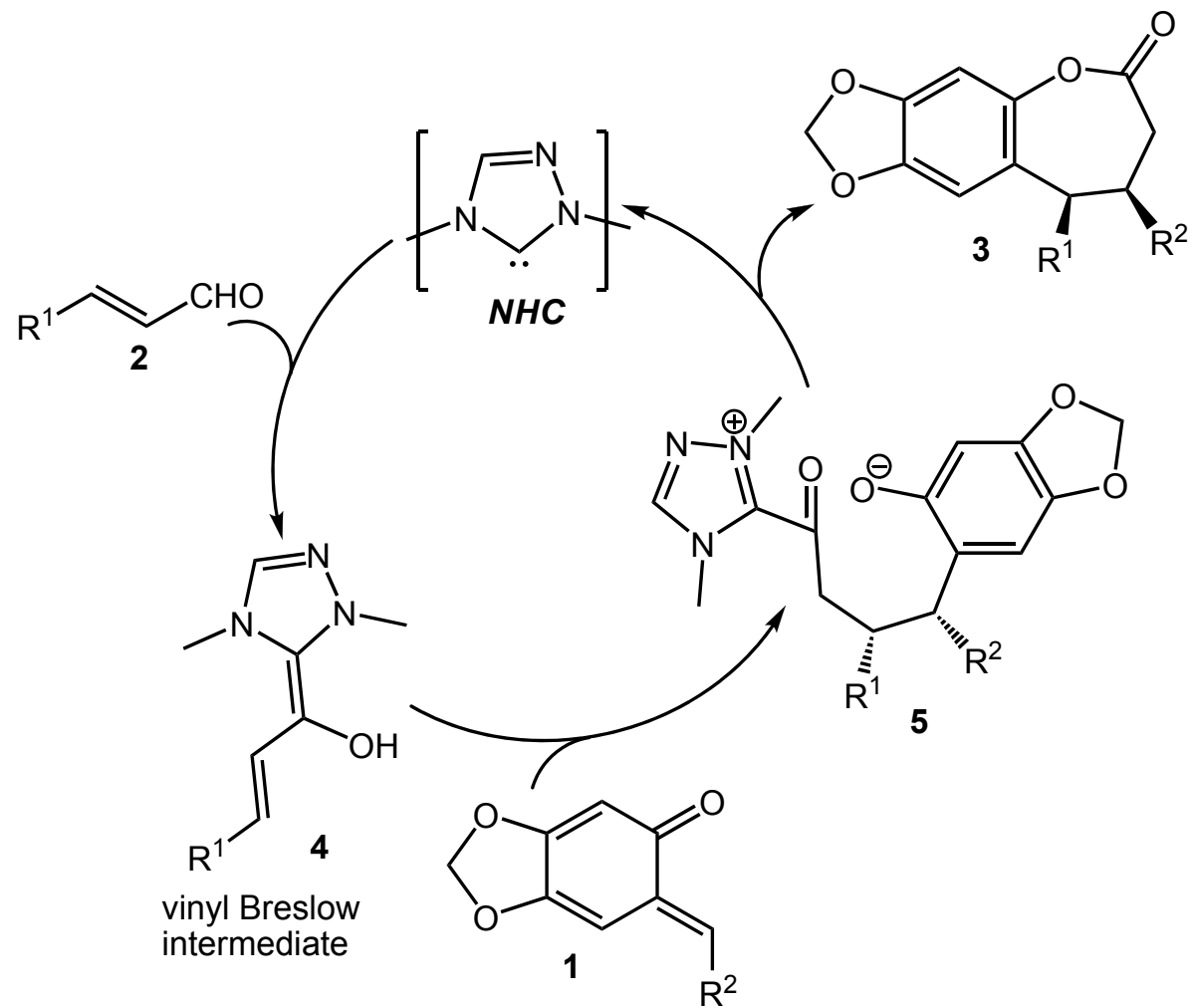


86%, 3:1 d.r., 89% ee

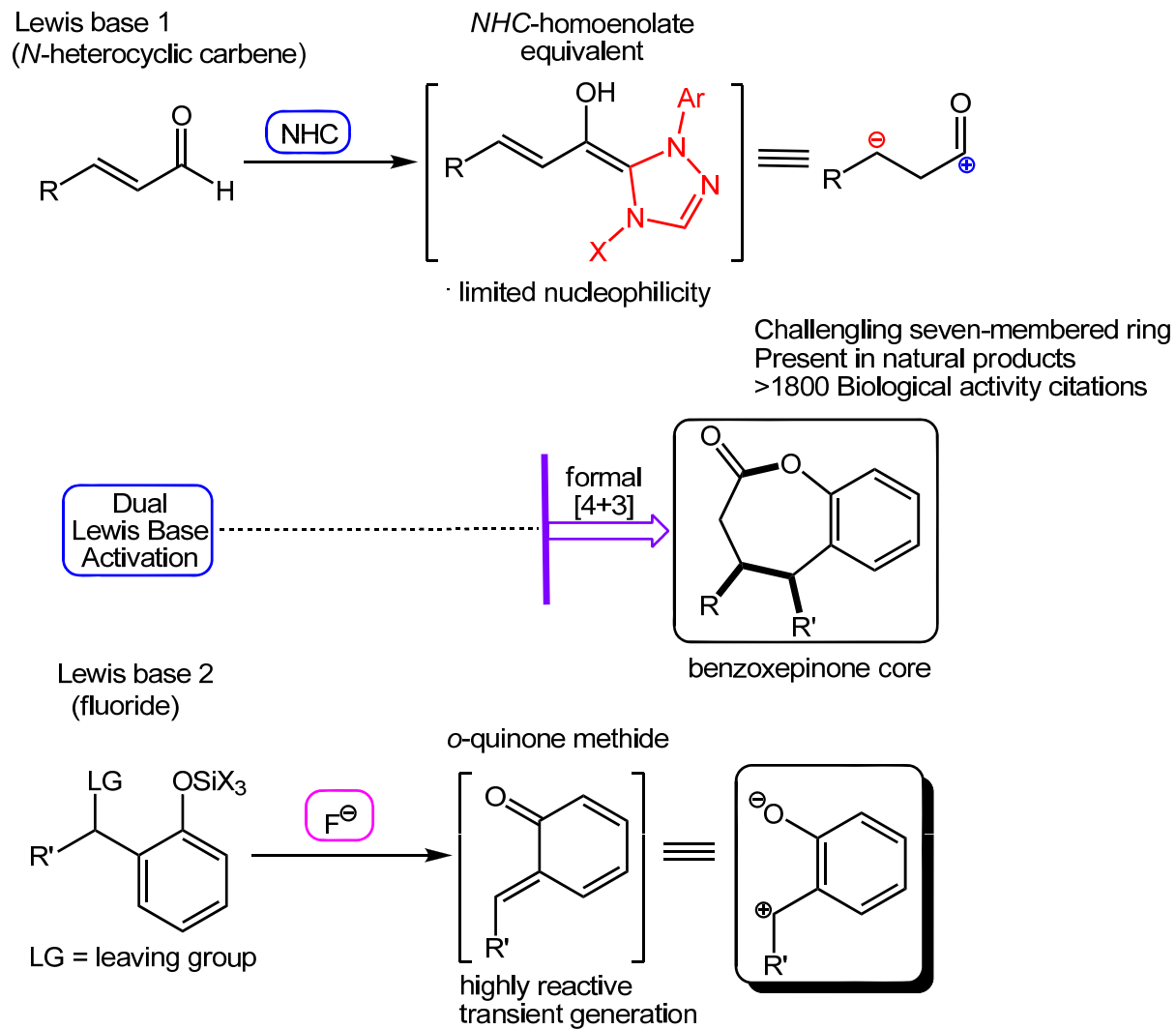


93%, 3:1 d.r., 94% ee

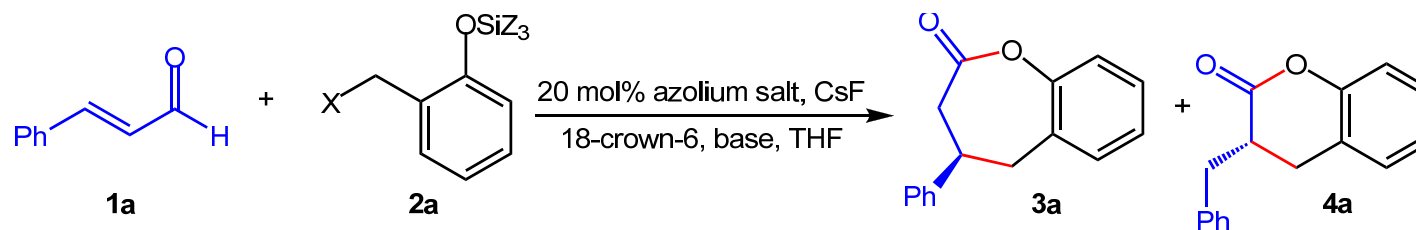
Proposed Catalytic Cycle



A Dual Lewis Base Activation Strategy for Enantioselective Carbene-Catalyzed Annulations



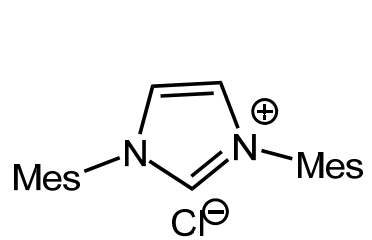
NHC/Fluoride-Promoted Reaction of **1a** and **2a**



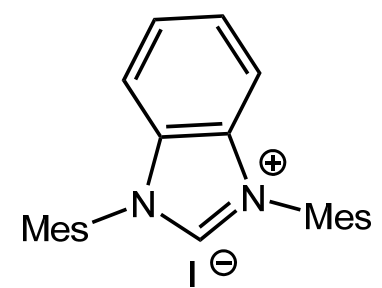
Entry	Azolium	Base	X/SiZ ₃	Ratio (3a : 4a)	Yield [%]	Ee (%) ^b
1	A	Cs ₂ CO ₃	Br/TBS	4:1	32	/
2	A	CsOAc	Br/TBS	4.5:1	37	/
3	B	CsOAc	Br/TBS	4:1	57	/
4	C	CsOAc	Br/TBS	4.5:1	47	82
5	C	CsOAc	Cl/TBS	4.5:1	45	74
6	C	CsOAc	Br/TIPS	4.5:1	42	78
7	C	CsOAc	Br/TES	/	/	/
8	C	<i>n</i> -Bu ₄ N•OAc	Br/TBS	4.5:1	62	84
9^c	C	<i>n</i> -Bu ₄ N•OAc	Br/TBS	5.5:1	64	92

^a Conditions: **1a** (1 equiv), **2a** (2 equiv), CsF (2 equiv), 18-crown-6 (2 equiv), base (30 mol %), THF (0.15 M in **1a**), 23 °C, 3 h, unless otherwise noted. Mes = 2,4,6-Me₃C₆H₂.

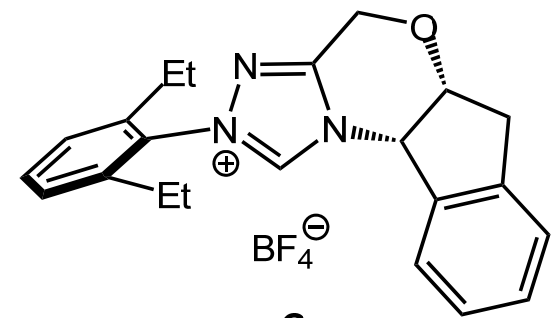
^b Determined by chiral stationary-phase HPLC. ^c The reaction was run at -18 °C for 12 h.



A

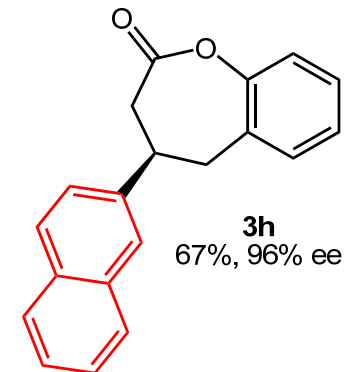
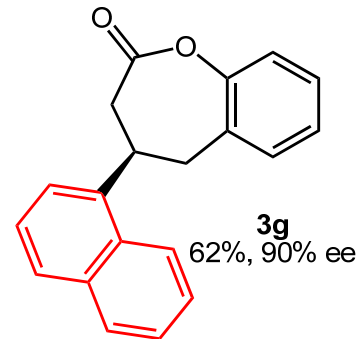
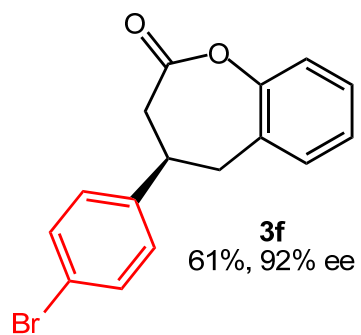
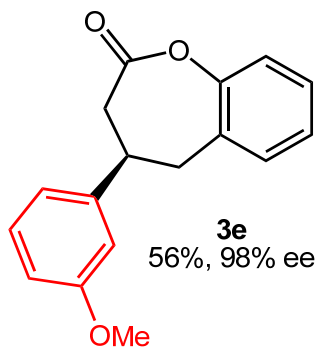
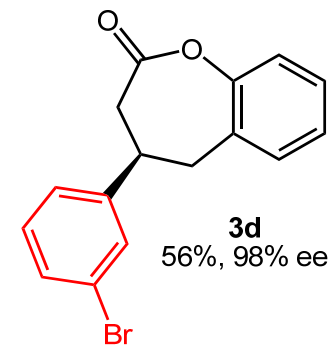
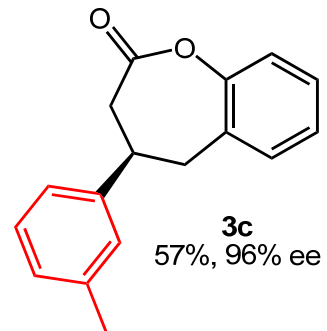
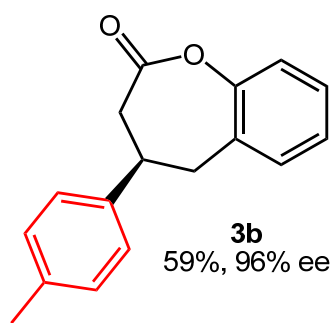
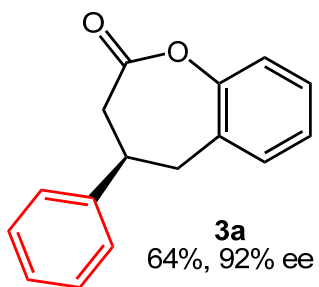
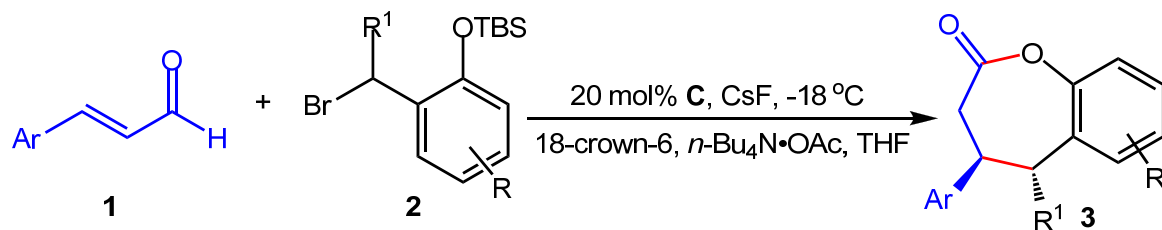


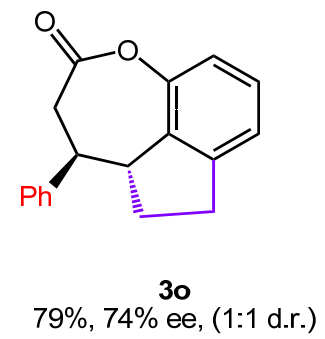
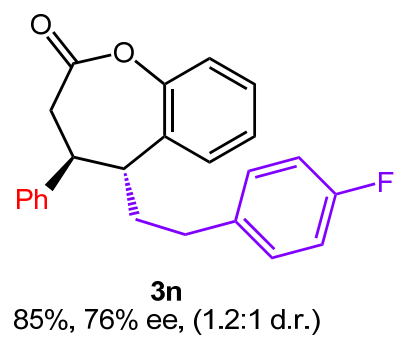
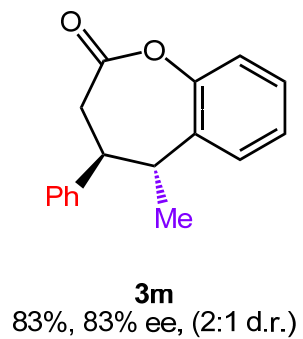
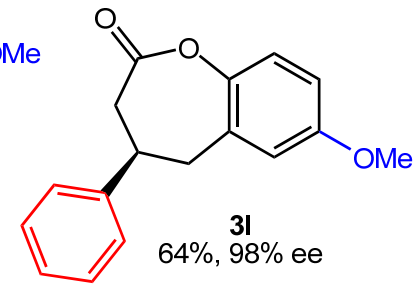
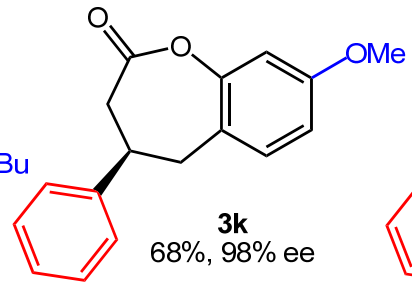
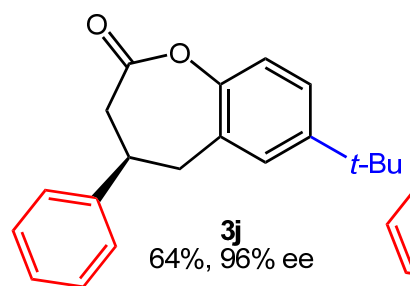
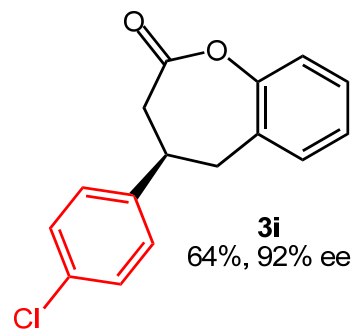
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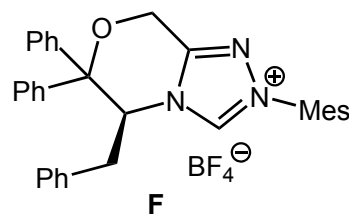
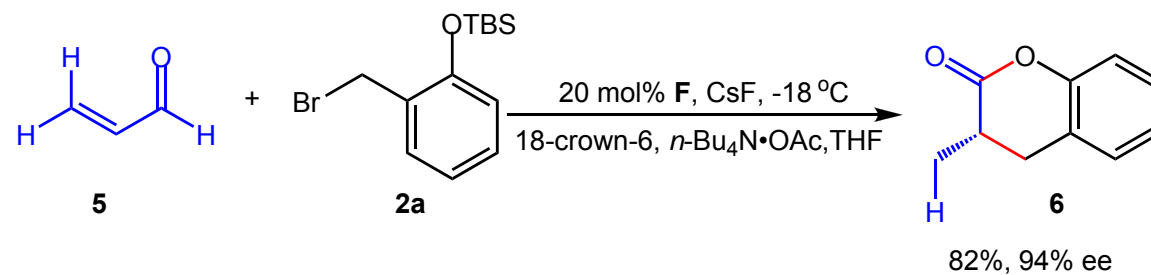
C

Scope of Dual-Activation Formal [4 + 3] Annulation

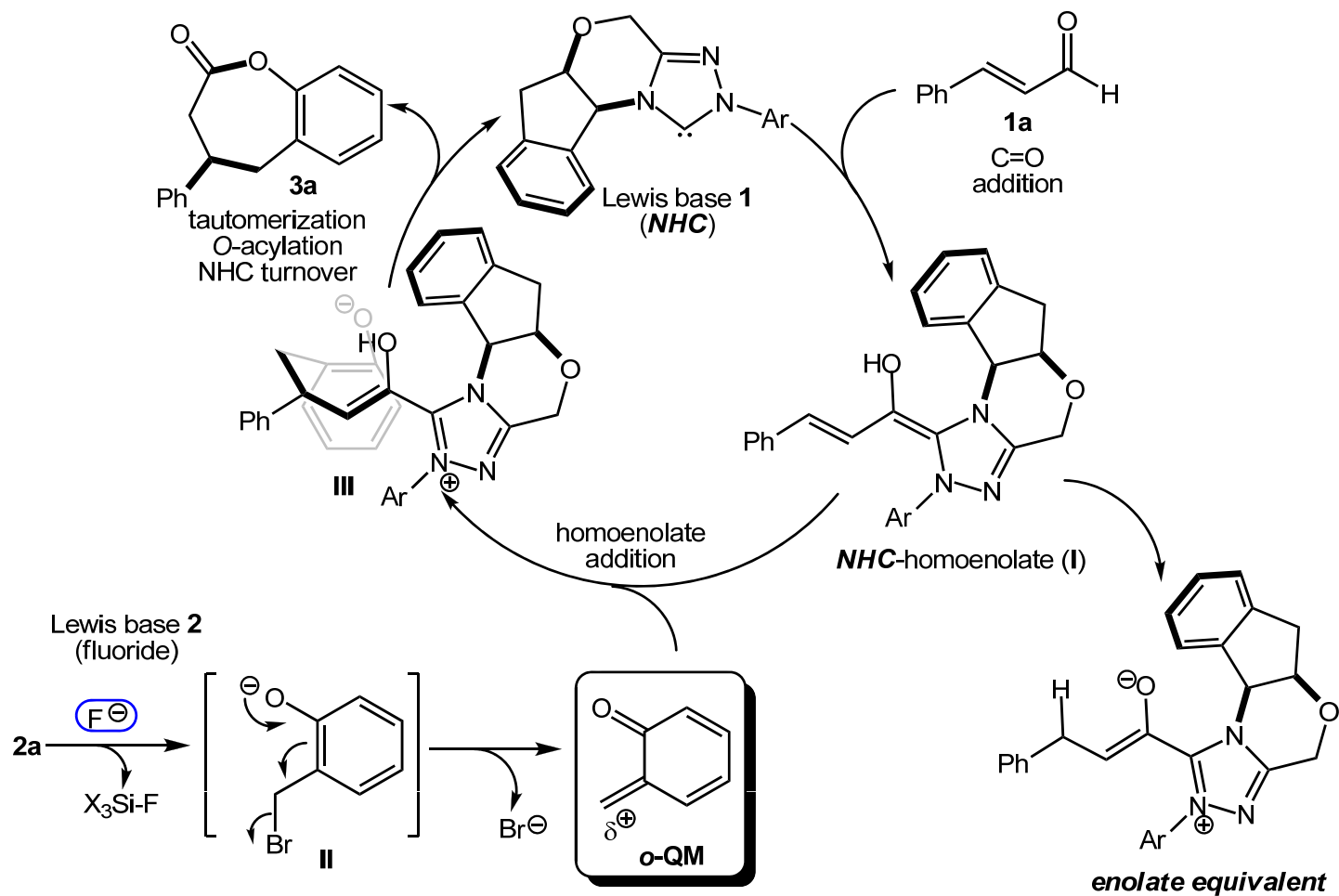




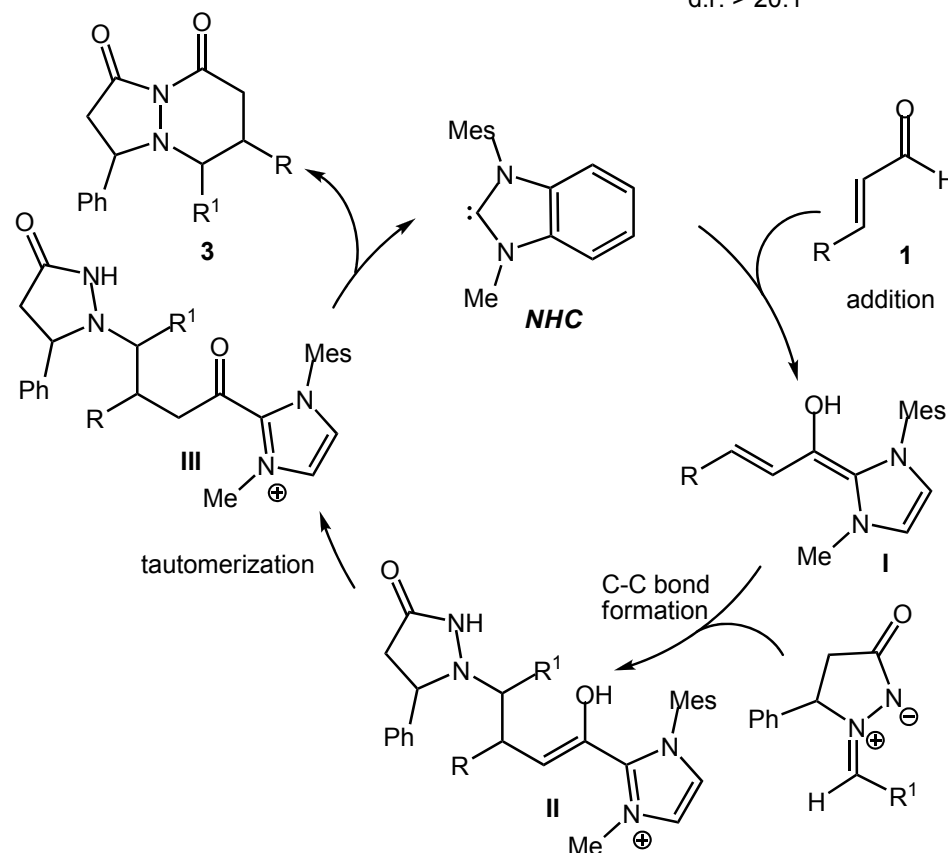
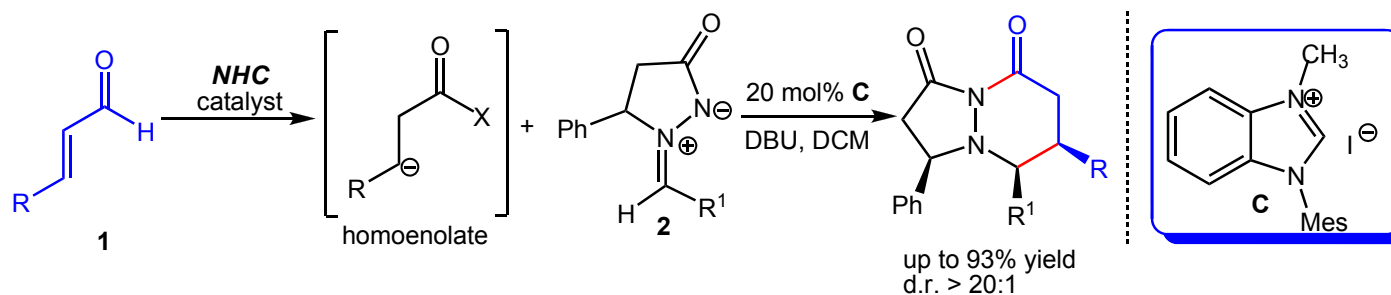
Formal [4 + 2] Reaction with Acrolein



Reaction Pathway

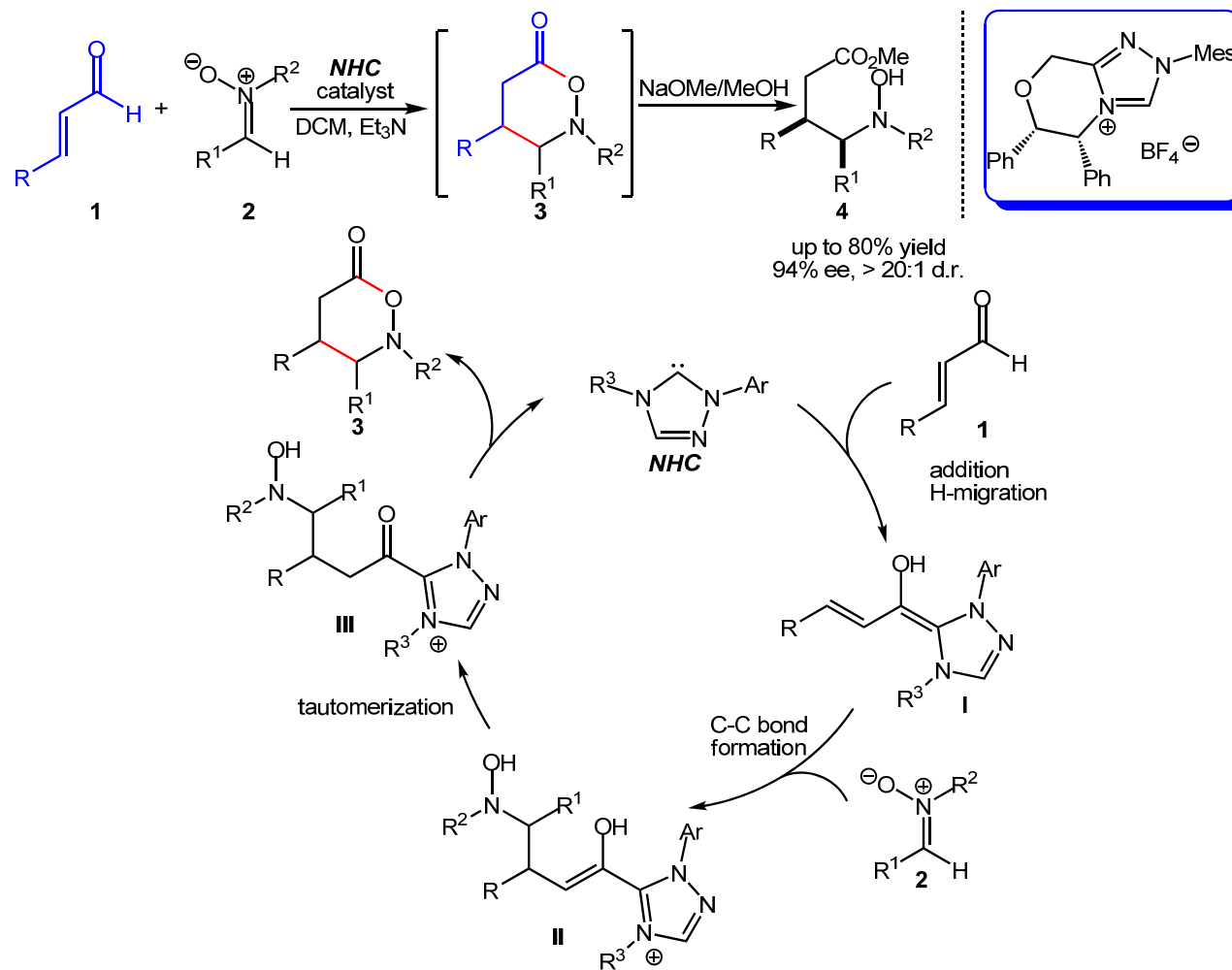


Highly Stereoselective Formal [3+3] Cycloaddition of Enals and Azomethine Imines Catalyzed by *N*-Heterocyclic Carbenes

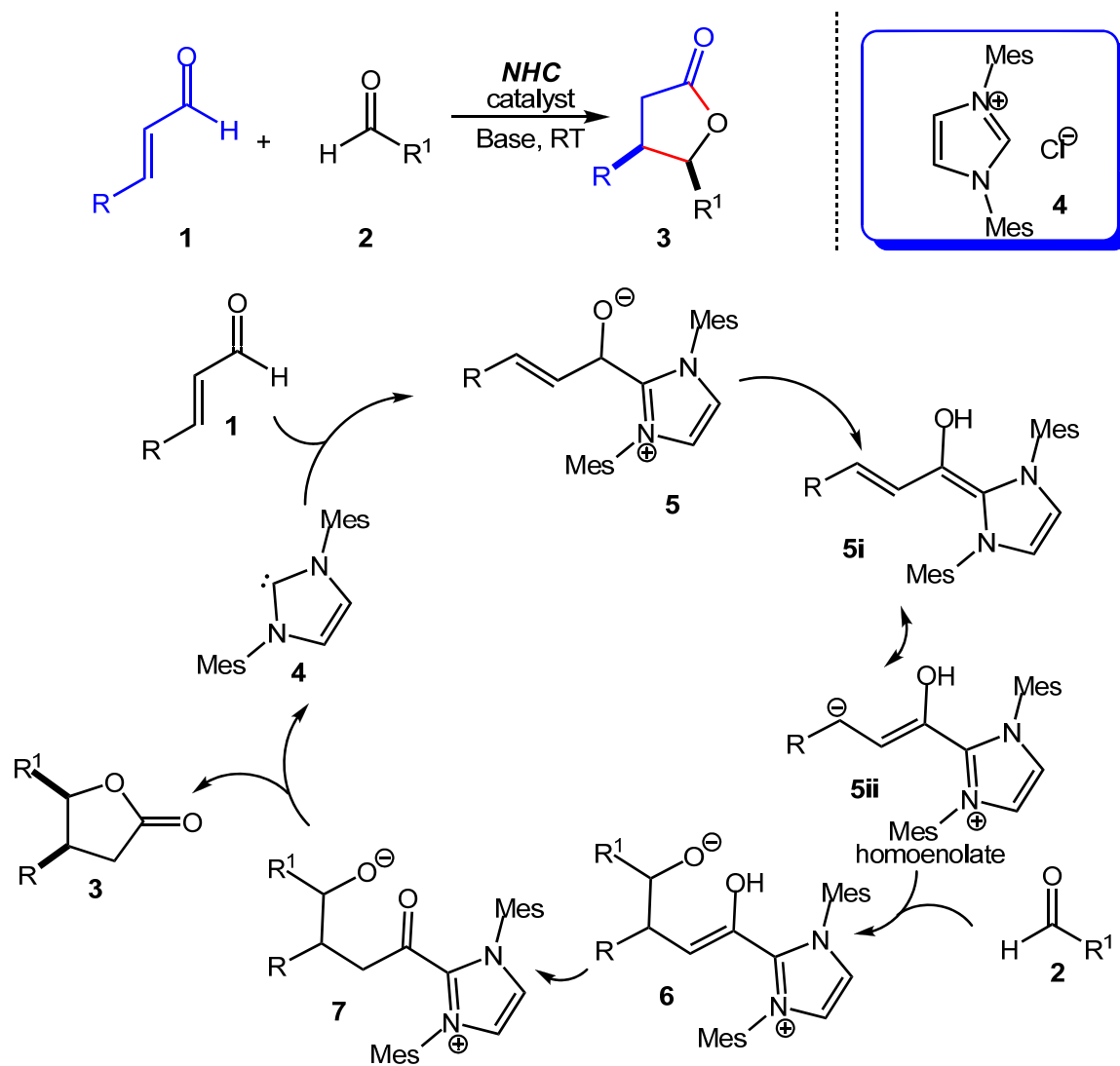


Scheidt, K. A. *et al.* *J. Am. Chem. Soc.* **2007**, *129*, 5334-5335.

Highly Diastereo- and Enantioselective Additions of Homoenolates to Nitrones Catalyzed by *N*-Heterocyclic Carbenes

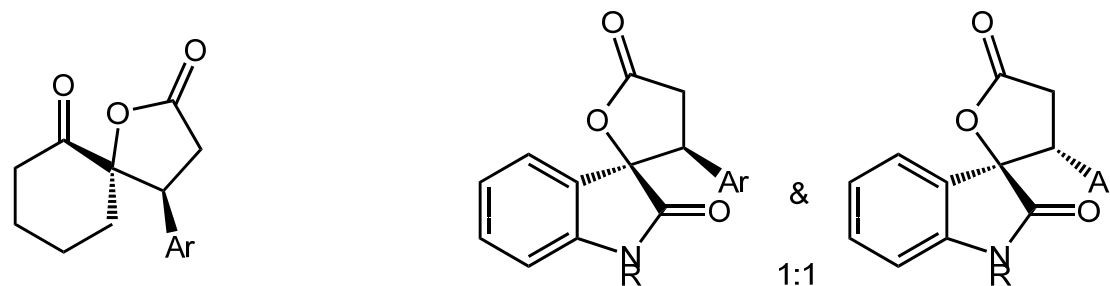
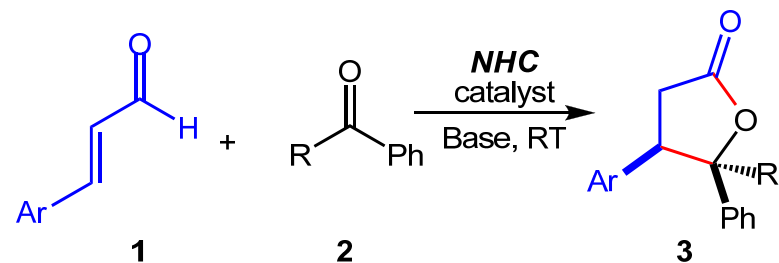


N-Heterocyclic Carbene Catalyzed [3+2] Annulation of Enals and Aldehydes

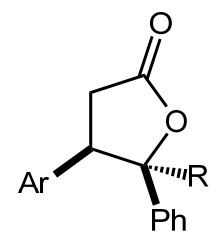


Bode, J. W. *et al.* *J. Am. Chem. Soc.* **2004**, 126, 14370-14371;
Glorius, F. *et al.* *Angew. Chem. Int. Ed.* **2004**, 43, 6205-6208.

N-Heterocyclic Carbene Catalyzed [3+2] Annulation of Enals and Ketones

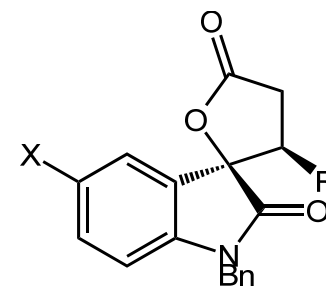


Nair, V. *et al. Org. Lett.* **2006**, 8, 507-509.



R = CF₃, CO₂Et

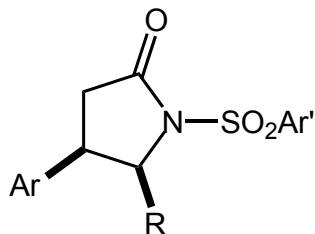
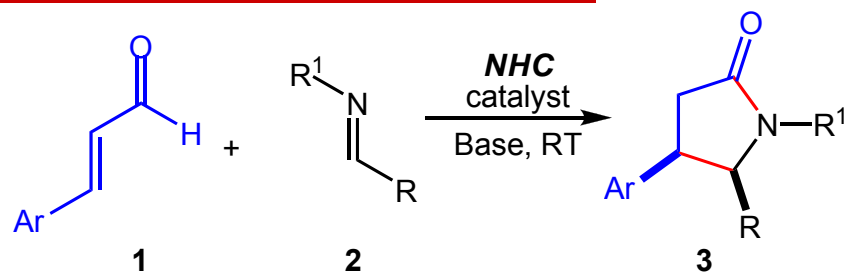
You, S.-L. *et al. Adv. Synth. Catal.* **2008**, 350, 1885-1890.



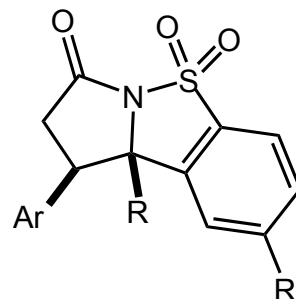
dr > 20:1, up to 99% ee

Ye, S. *et al. Chem. Commun.* **2011**, 47, 10136-10138.

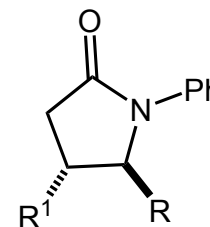
N-Heterocyclic Carbene Catalyzed [3+2] Annulation of Enals and Imines



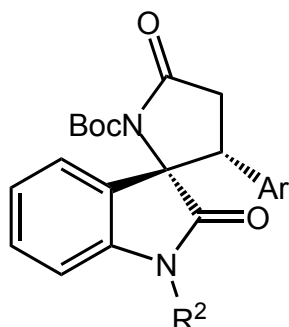
Bode, J. W. *et al. Org. Lett.*,
2005, 7, 3131-3134.



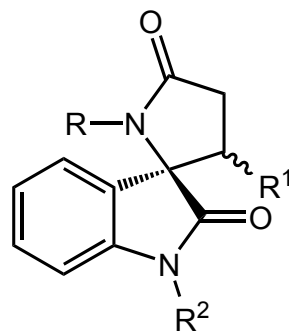
Bode, J. W. *et al. J. Am. Chem. Soc.*
2008, 130, 17266-17267.



Rovis, T. *et al. J. Am. Chem. Soc.*
2011, 133, 12466-12469.

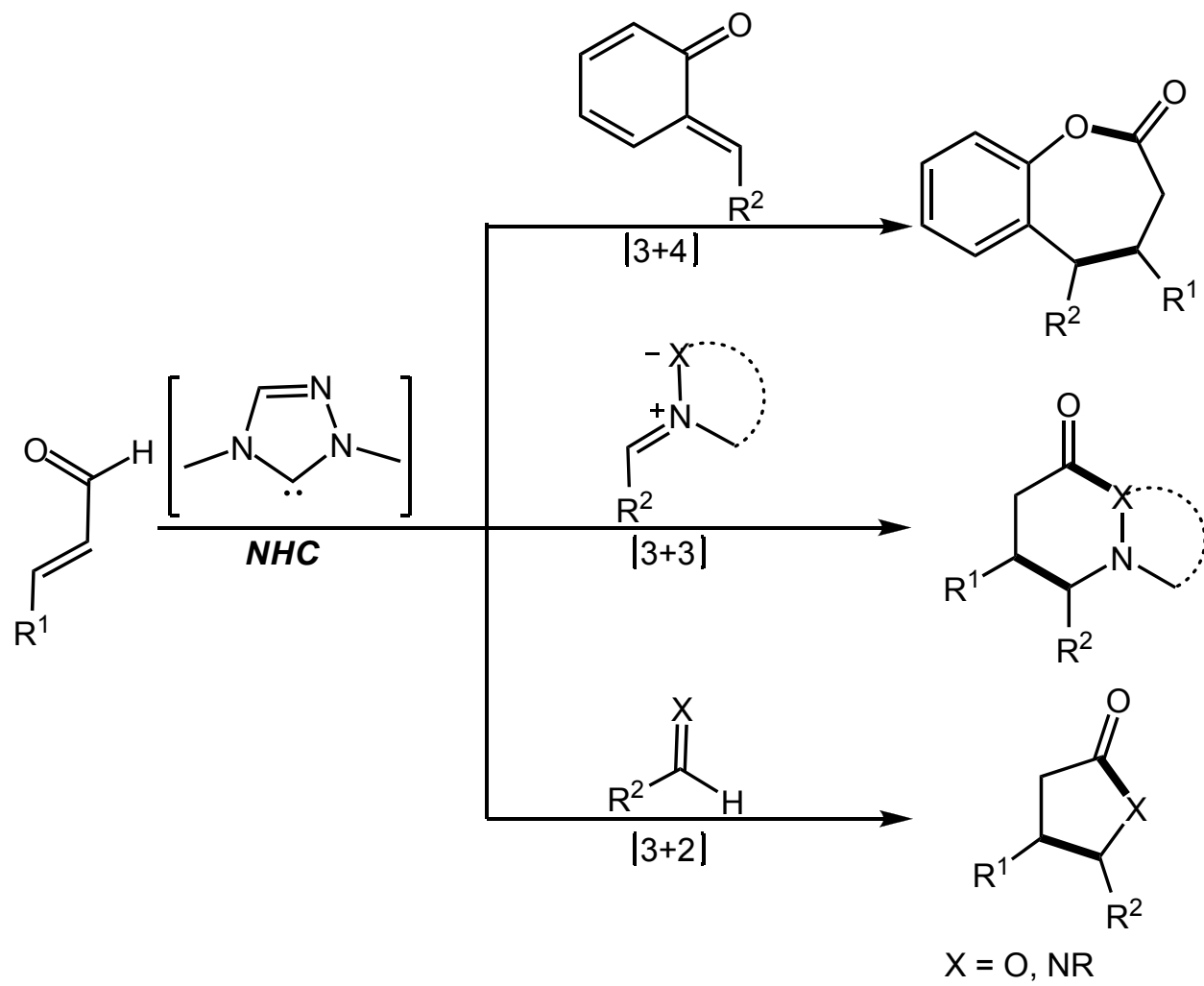


Chi, Y. R. *et al. Org. Lett.*,
2012, 14, 5412-5415.



Ye, S. *et al. Chem. Eur. J.*
2012, 18, 9198-9203.

Summary



ϵ -Lactones are privileged motifs occurring in a wide variety of biologically active natural and unnatural products. Therefore, the synthesis of ϵ -lactones has received considerable attention. The most applied approach to ϵ -lactones is the Bayer–Villiger oxidation of cyclohexanone. In addition, several other interesting methodologies, including metal-catalyzed ring expansion of 3-(2-hydroxyphenyl) cyclobutanones, metal-catalyzed carbonylation of 2-allylphenols, and *N*-heterocyclic carbene catalyzed ring expansion of aldehydes have been reported. However, most of these approaches are intramolecular reactions. The intermolecular reaction for the synthesis of ϵ -lactones has rarely been reported. More importantly, the catalytic enantioselective synthesis of ϵ -lactones has far less established.

In summary, an unprecedented NHC-catalyzed [4+3] annulation of enals with *o*-quinone methides has been established. The reaction worked well for both β -aryl and β -alkyl enals, thus giving the corresponding benzo- ϵ -lactones in high yields with moderate (for β -aryl enals) to excellent (for β -alkyl enals) diastereoselectivities. High to excellent enantioselectivities (81–98% ee) were achieved by using a chiral triazolium NHC with a free hydroxy group. Further investigation on the reaction scope and related other NHC-catalyzed annulation reactions are underway in our laboratory.