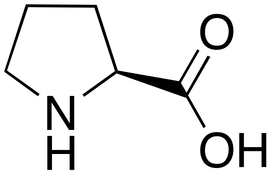
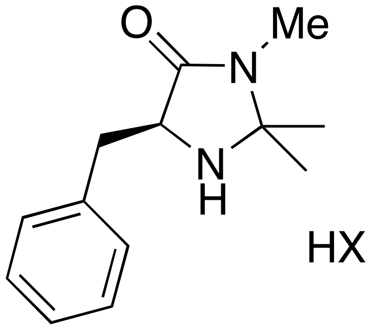
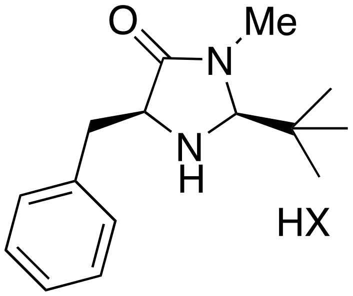
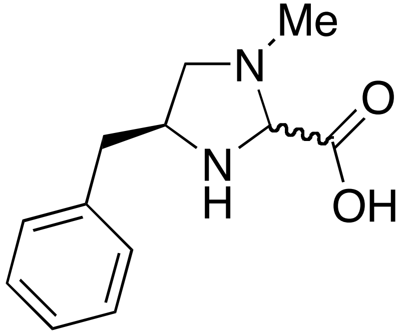
Enamine/Iminium catalysis: Highlights from the evolution of pyrolidine-type catalysts



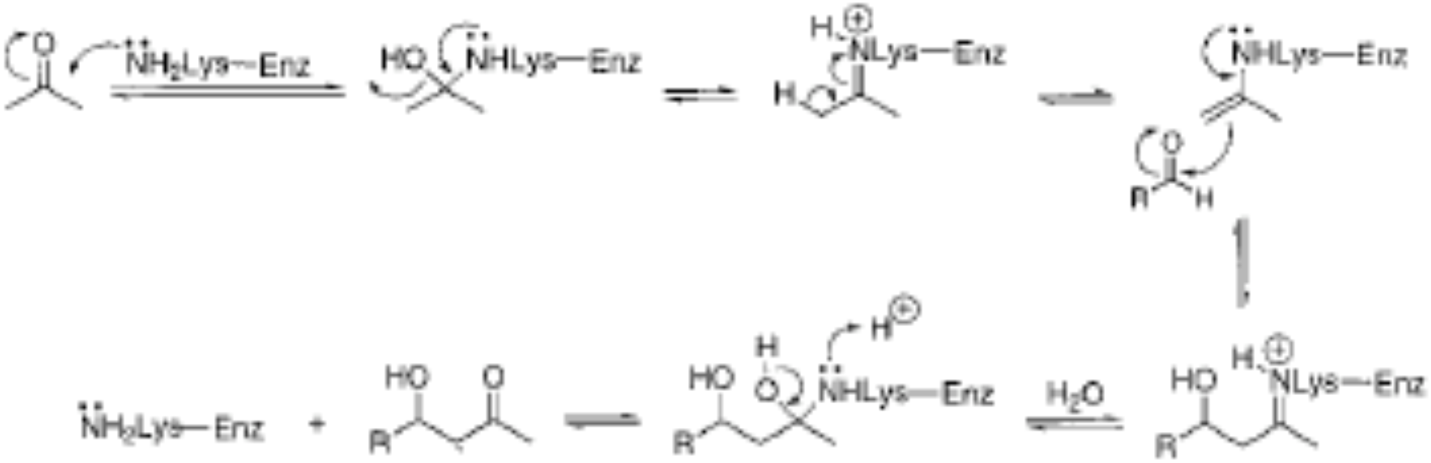




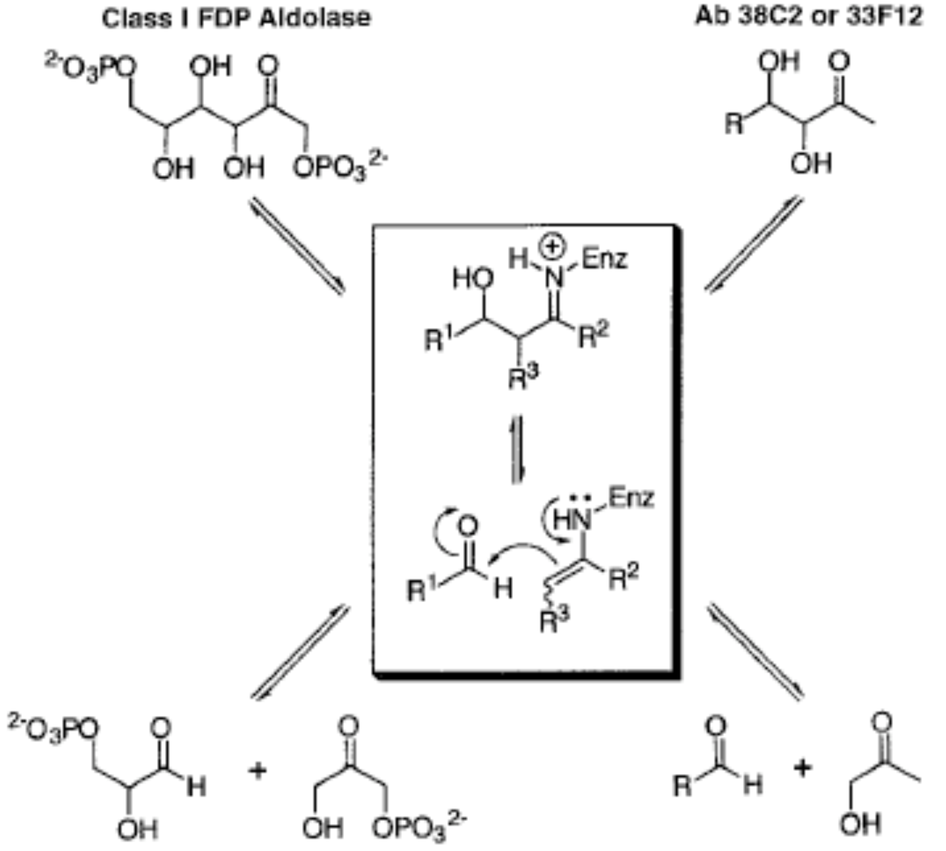


PART 1: ENAMINE CATALYSIS

Lessons from nature: Aldolases catalyzed aldol reaction

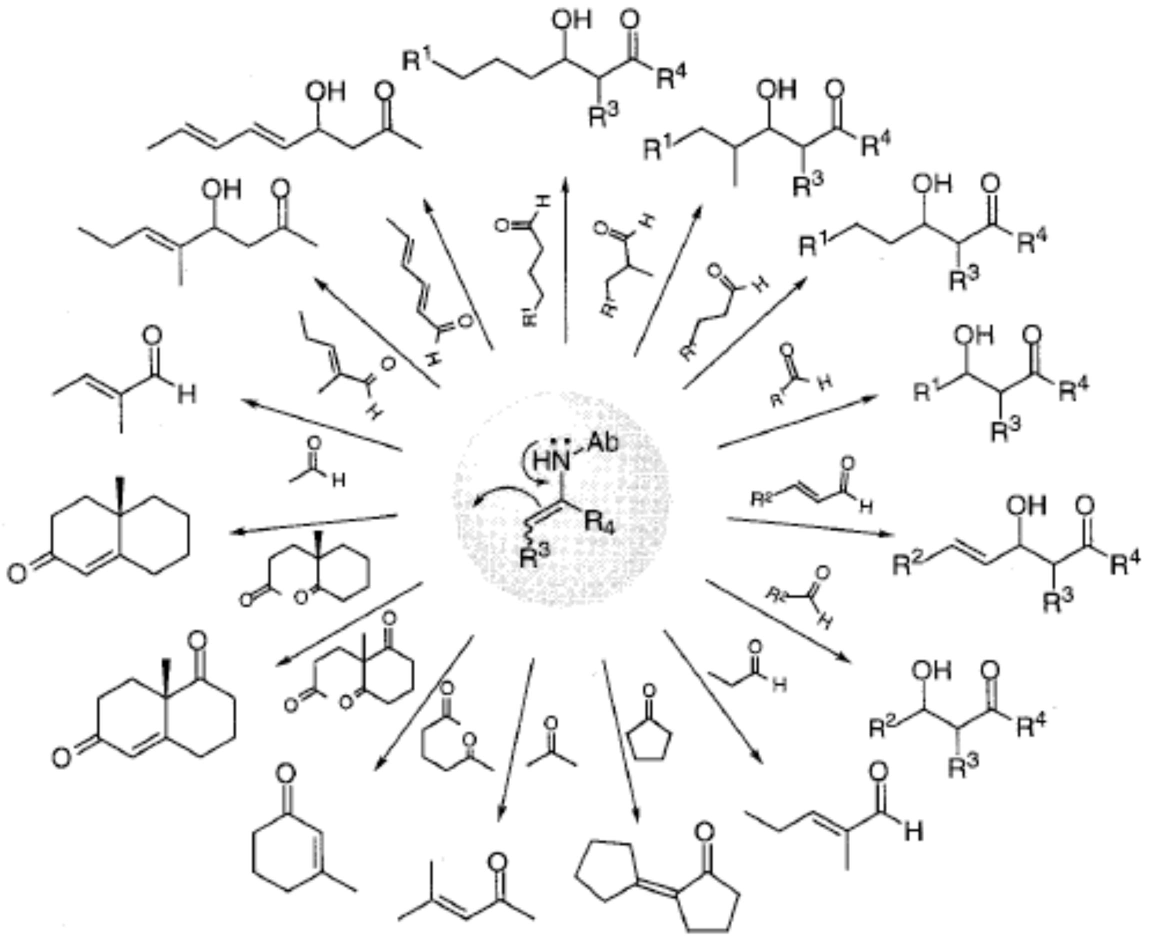


FDP Aldolase vs antibody aldolase



Barbas et al, *Science* **1997,** *278*, 2085

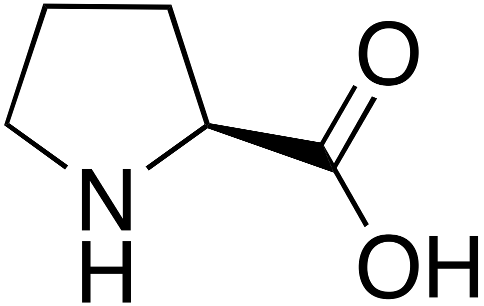
Antibody catalyzed aldol rxn with broad reaction scope



Barbas et al, *Science* **1997,** *278*, 2085

Benjamin List
(ex-Scripps, now
Max-Planck)

Carlos Barbas
(Scripps)



L-proline

Proline-catalyzed direct asymmetric aldol reactions

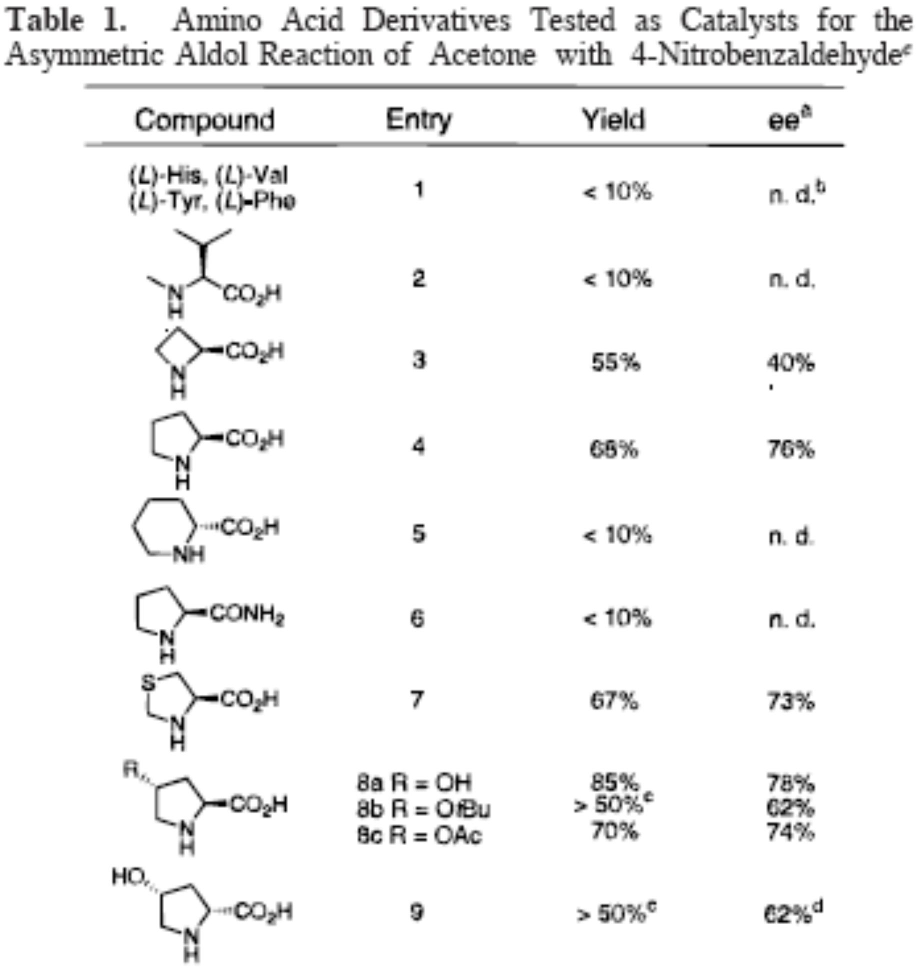


Table 1. Amino Acid Derivatives Tested as Catalysts for the Asymmetric Aldol Reaction of Acetone with 4-Nitrobenzaldehyde[e]

Compound	Entry	Yield	ee[a]
(*L*)-His, (*L*)-Val (*L*)-Tyr, (*L*)-Phe	1	< 10%	n. d.[b]
	2	< 10%	n. d.
	3	55%	40%
	4	68%	76%
	5	< 10%	n. d.
	6	< 10%	n. d.
	7	67%	73%
	8a R = OH	85%	78%
	8b R = O*t*Bu	> 50%[c]	62%
	8c R = OAc	70%	74%
	9	> 50%[c]	62%[d]

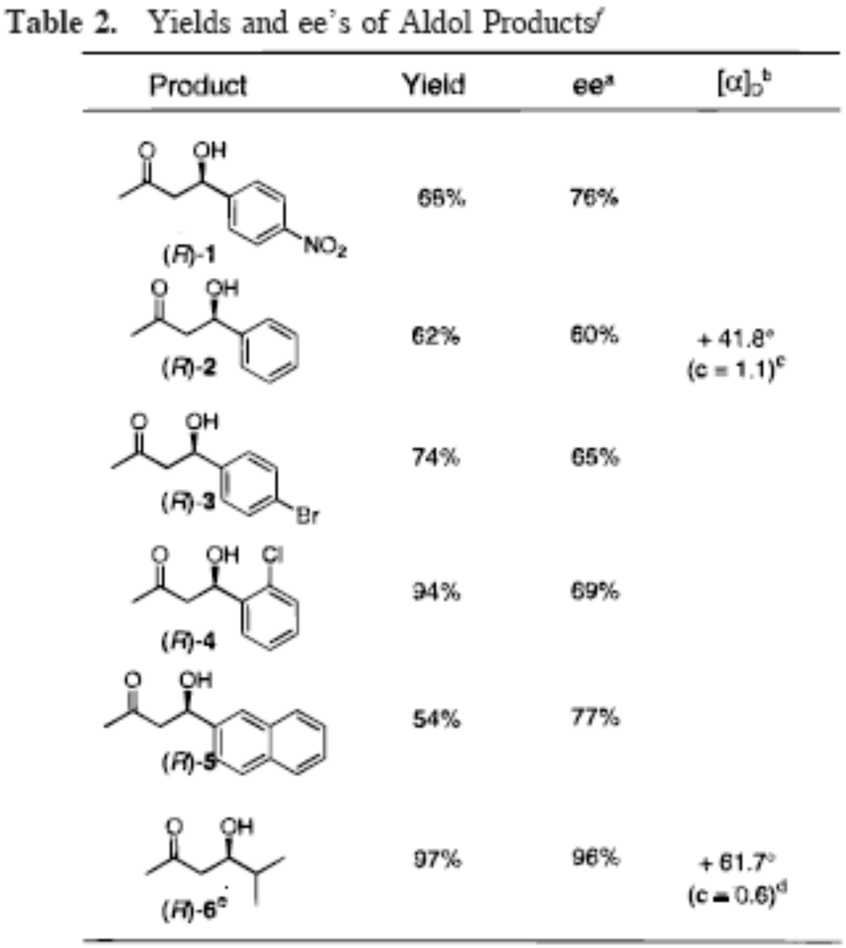
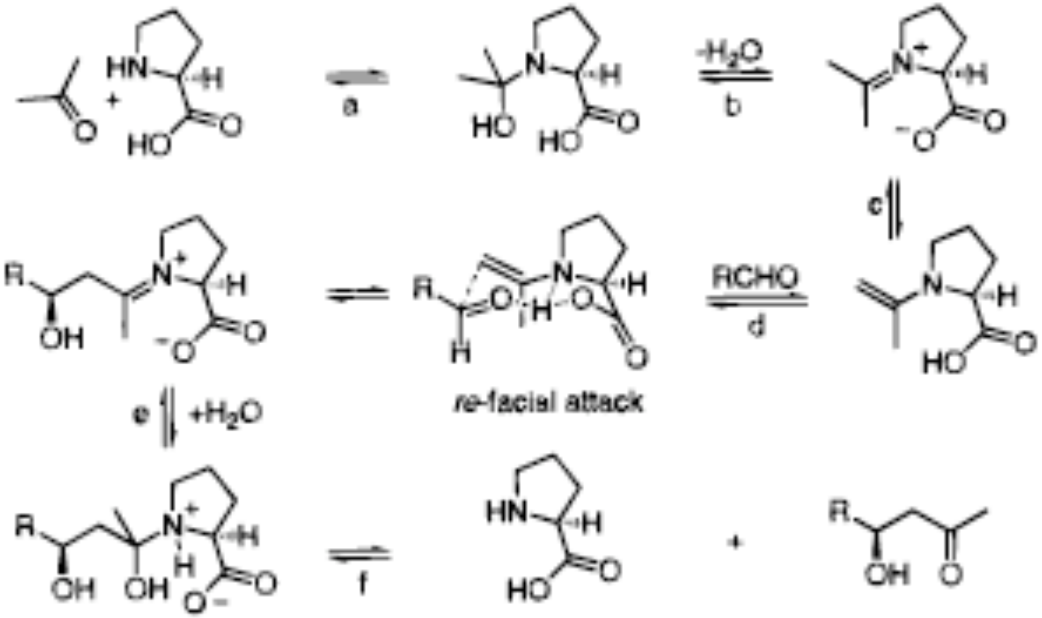


Table 2. Yields and ee's of Aldol Products[f]

Product	Yield	ee[a]	$[\alpha]_D$[b]
(*R*)-1	68%	76%	
(*R*)-2	62%	60%	+ 41.8° (c = 1.1)[c]
(*R*)-3	74%	65%	
(*R*)-4	94%	69%	
(*R*)-5	54%	77%	
(*R*)-6[e]	97%	96%	+ 61.7° (c = 0.6)[d]

Barbas / List *JACS* **2000,** *122*, 2395

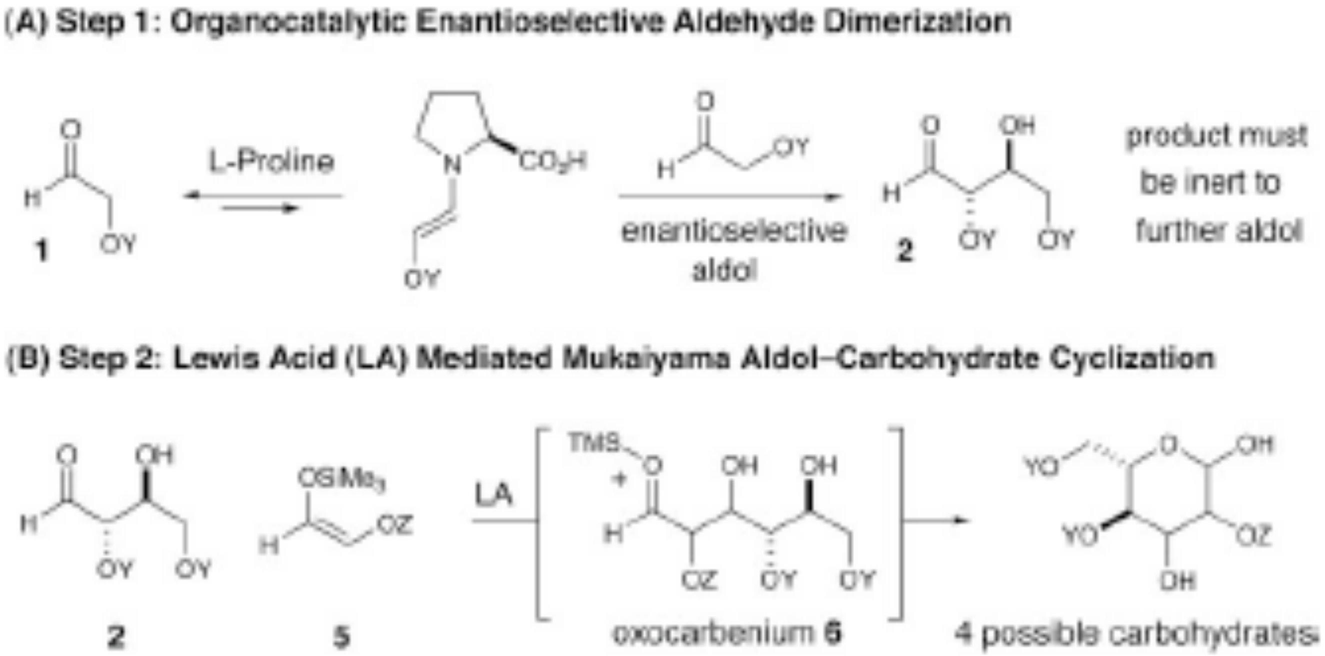
Mechanism of proline-catalyzed aldol



Barbas / List *JACS* **2000,** *122*, 2395

Two -step synthesis of carbohydrates

The concept:


(A) Step 1: Organocatalytic Enantioselective Aldehyde Dimerization

(B) Step 2: Lewis Acid (LA) Mediated Mukaiyama Aldol–Carbohydrate Cyclization

Fig. 1. (A) Step 1: Proline-catalyzed enantioselective dimerization of α-oxyaldehydes. (B) Step 2: Mukaiyama aldol-carbohydrate cyclization.

Mac Millan, *Science* **2004**, *305*, 1752

Two -step synthesis of carbohydrates

The results:

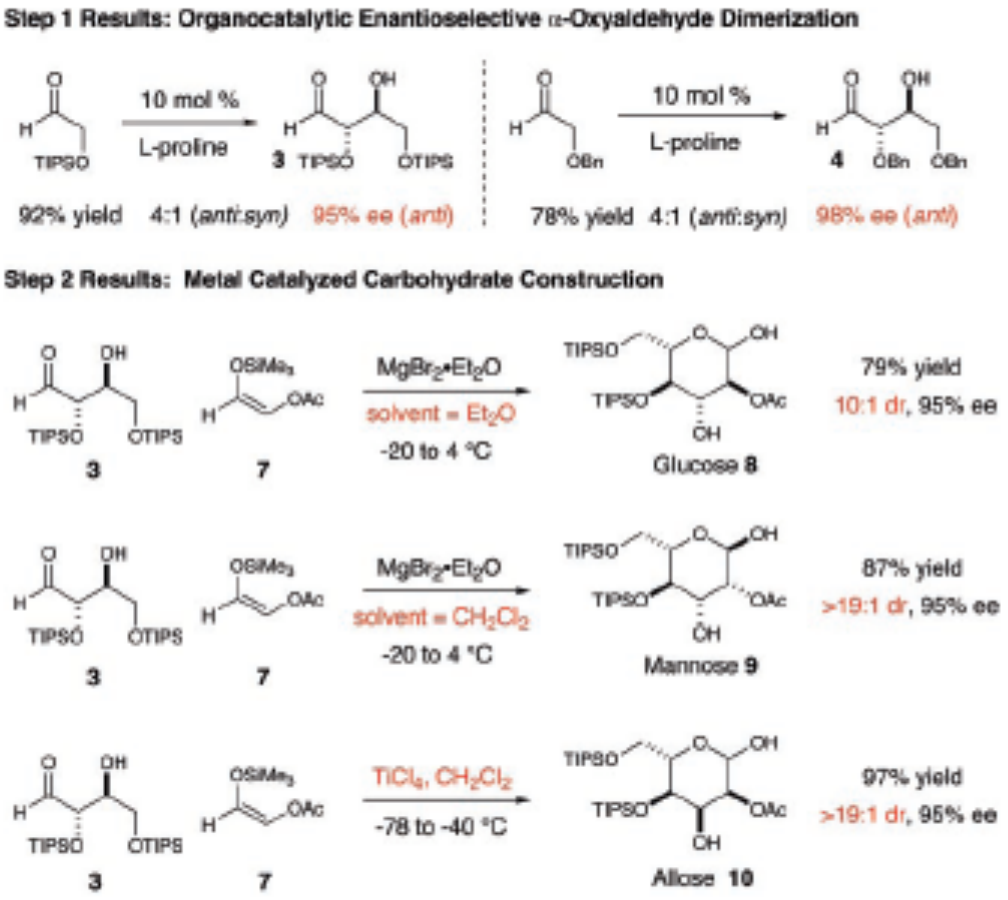


Fig. 2. Step 1 Results: The enantioselective dimerization of α-oxyaldehydes. Step 2 Results: The Lewis acid–mediated Mukaiyama aldol-carbohydrate cyclization.

Mac Millan, *Science* **2004**, *305*, 1752

Two -step synthesis of carbohydrates

Scope:

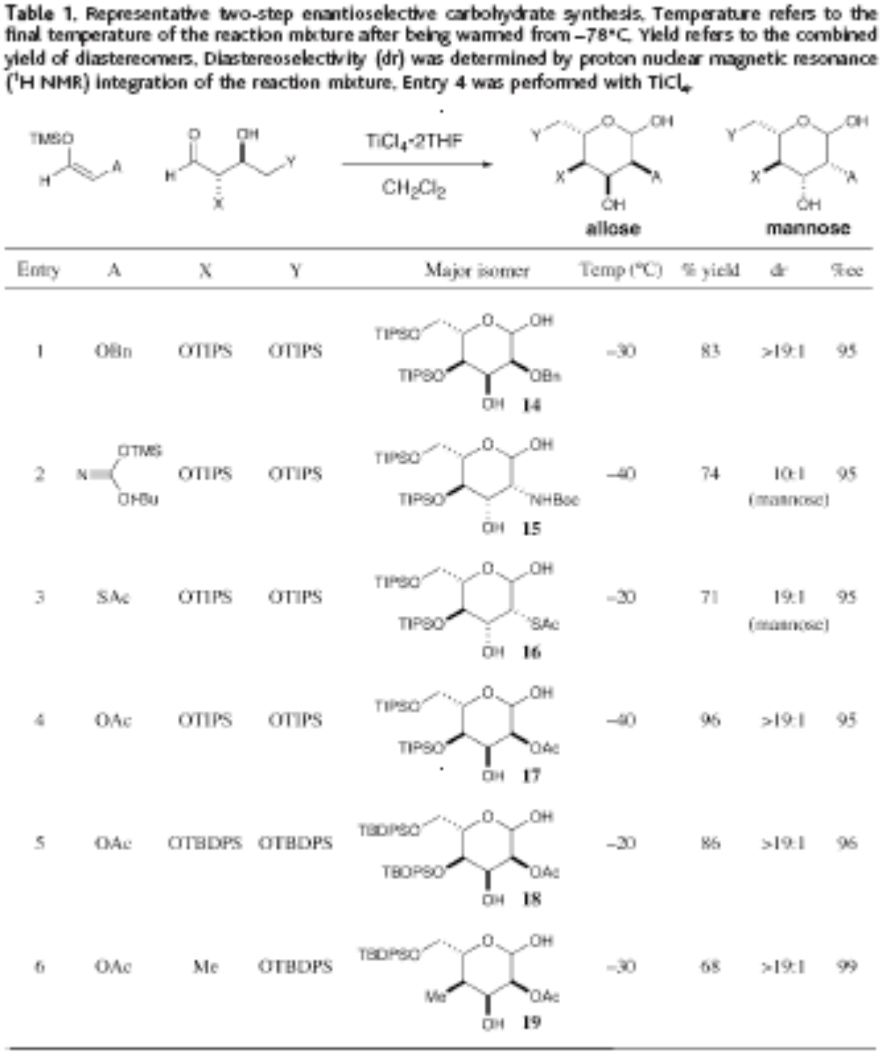


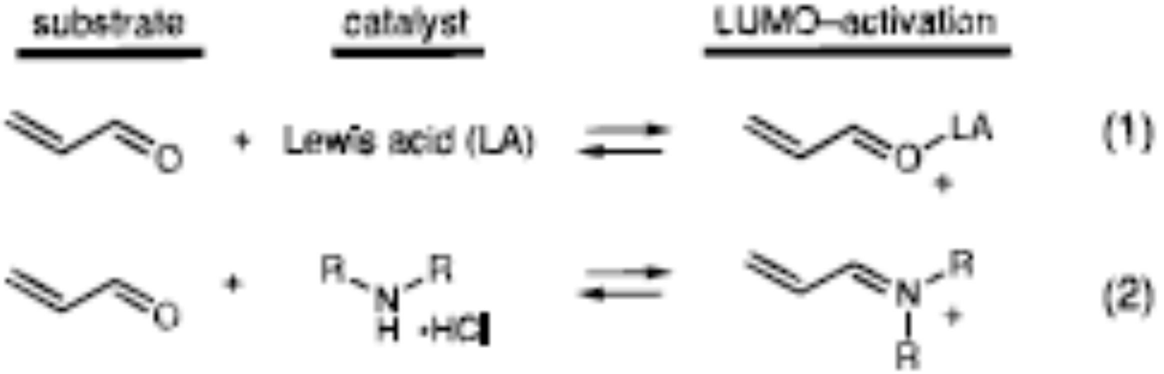
Table 1. Representative two-step enantioselective carbohydrate synthesis. Temperature refers to the final temperature of the reaction mixture after being warmed from −78°C. Yield refers to the combined yield of diastereomers. Diastereoselectivity (dr) was determined by proton nuclear magnetic resonance (^{1}H NMR) integration of the reaction mixture. Entry 4 was performed with $TiCl_4$.

Entry	A	X	Y	Major isomer	Temp (°C)	% yield	dr	%ee
1	OBn	OTIPS	OTIPS	**14**	−30	83	>19:1	95
2	OTMS N OtBu	OTIPS	OTIPS	**15**	−40	74	10:1 (mannose)	95
3	SAc	OTIPS	OTIPS	**16**	−20	71	19:1 (mannose)	95
4	OAc	OTIPS	OTIPS	**17**	−40	96	>19:1	95
5	OAc	OTBDPS	OTBDPS	**18**	−20	86	>19:1	96
6	OAc	Me	OTBDPS	**19**	−30	68	>19:1	99

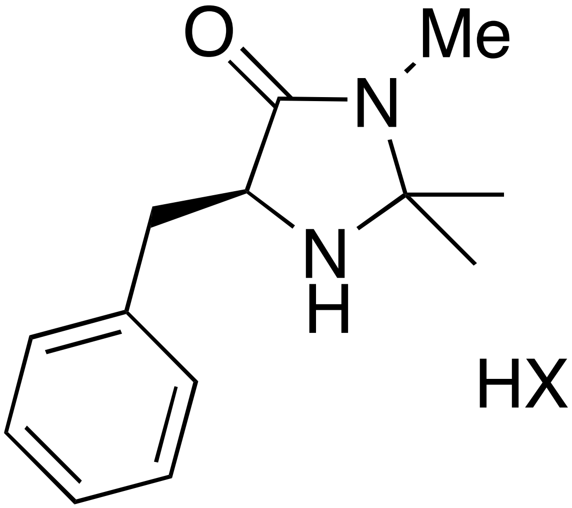
Mac Millan, *Science* **2004**, *305*, 1752

PART 2 : IMINIUM CATALYSIS

The concept:

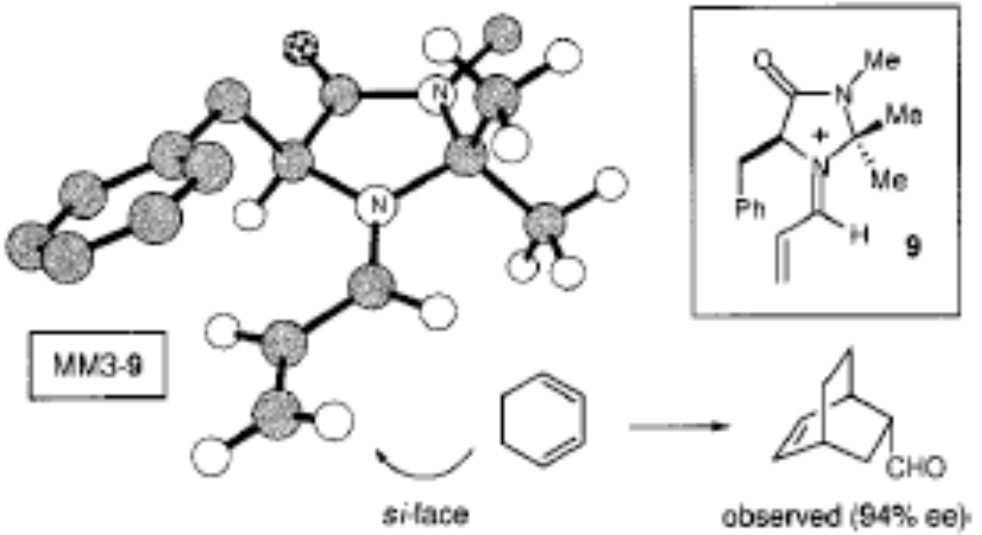


Mac Millan
(Princeton)



"1st generation catalyst"

Diels Alder: Stereochemical Control with MacMillan’s cat.



Mac Millan et al, *JACS* **2000**, *122*, 4243

The first organocatalytic Diels-Alder

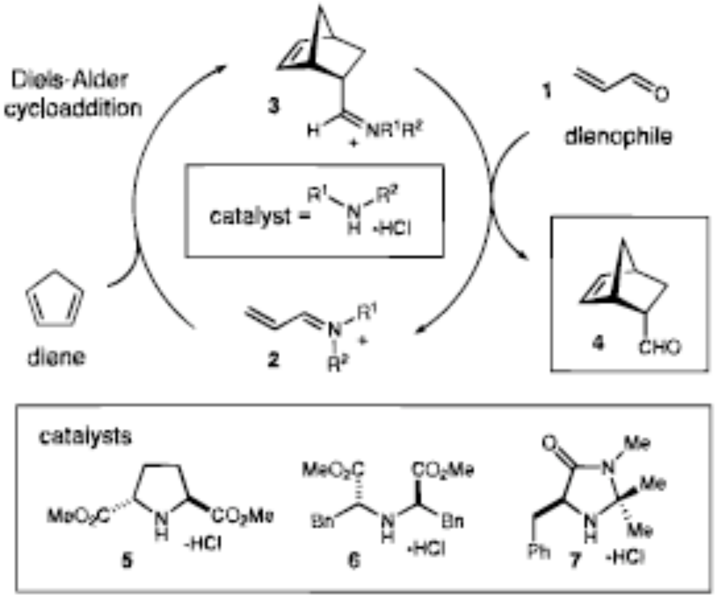
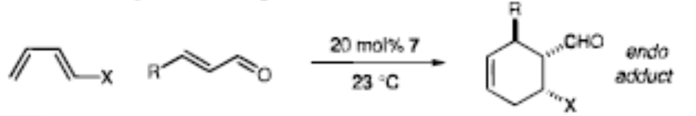
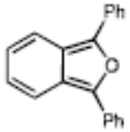
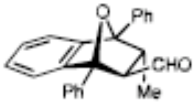
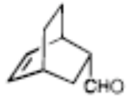
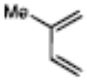
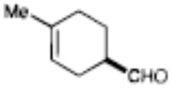
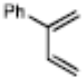
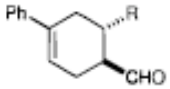
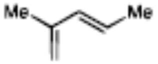
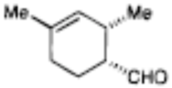
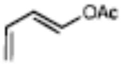
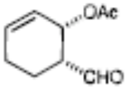


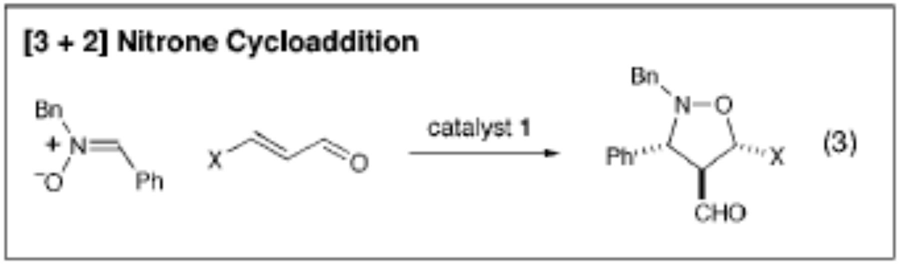
Table 3. Organocatalyzed Diels–Alder Reaction between Acrolein or Crotonaldehyde and Representative Dienes

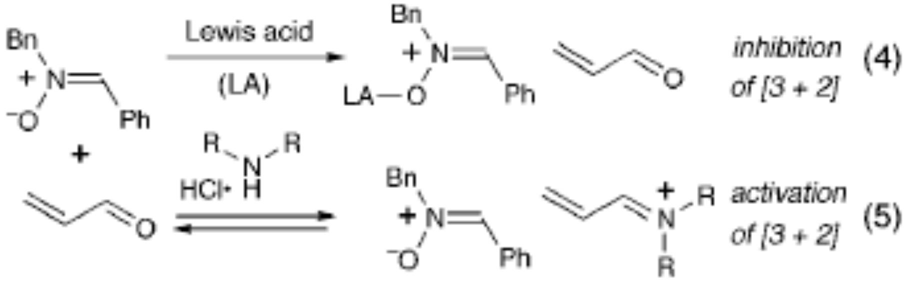


entry	diene	R	product	yield	*exo*:*endo*	% ee^{a,b}
1		Me		75	35:1	96^{c}
2		H		82	1:14	94^{d}
3		H		84	--	89
4		H		90	--	83
5		Me		75	--	90
6		H		75	1:5	90
7		H		72	1:11	85

Mac Millan et al, *JACS* **2000**, *122*, 4243

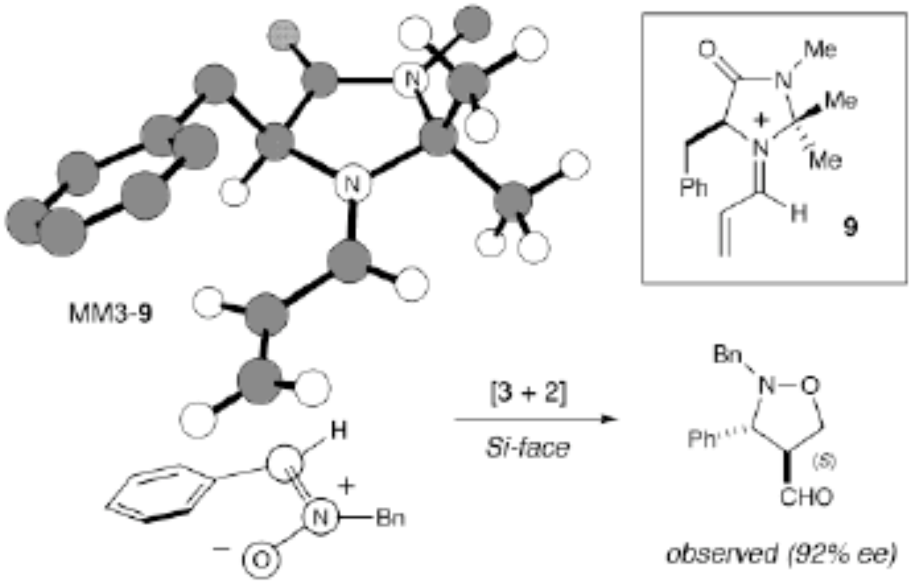
Nitrone cycloaddition: The concept





Mac Millan et al, *JACS* **2000**, *122*, 9874

The first organocatalytic nitrone cycloaddition



MM3-9

9

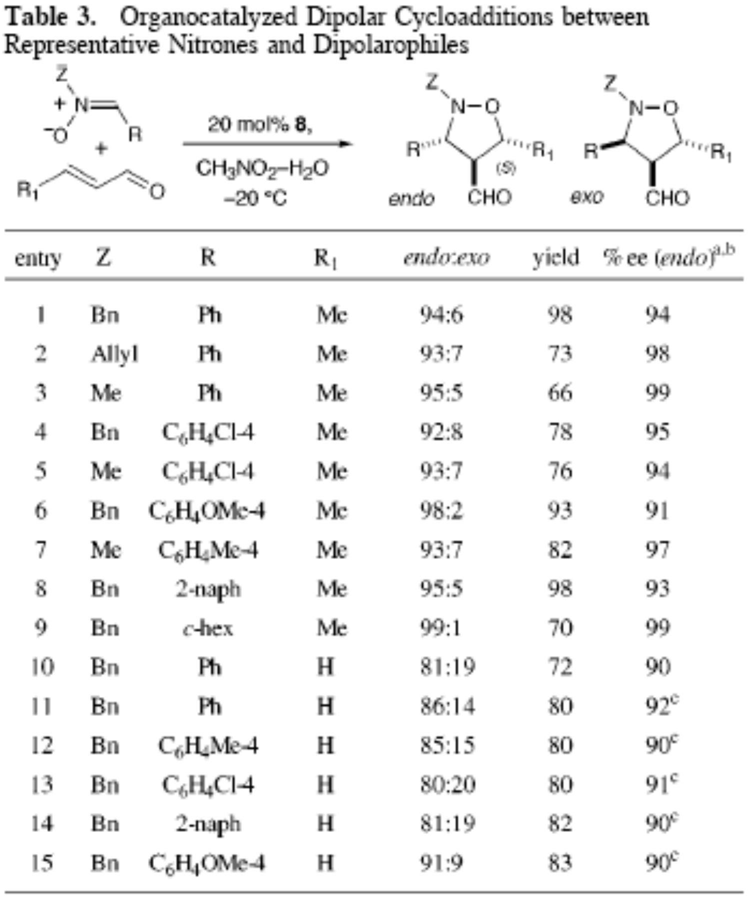
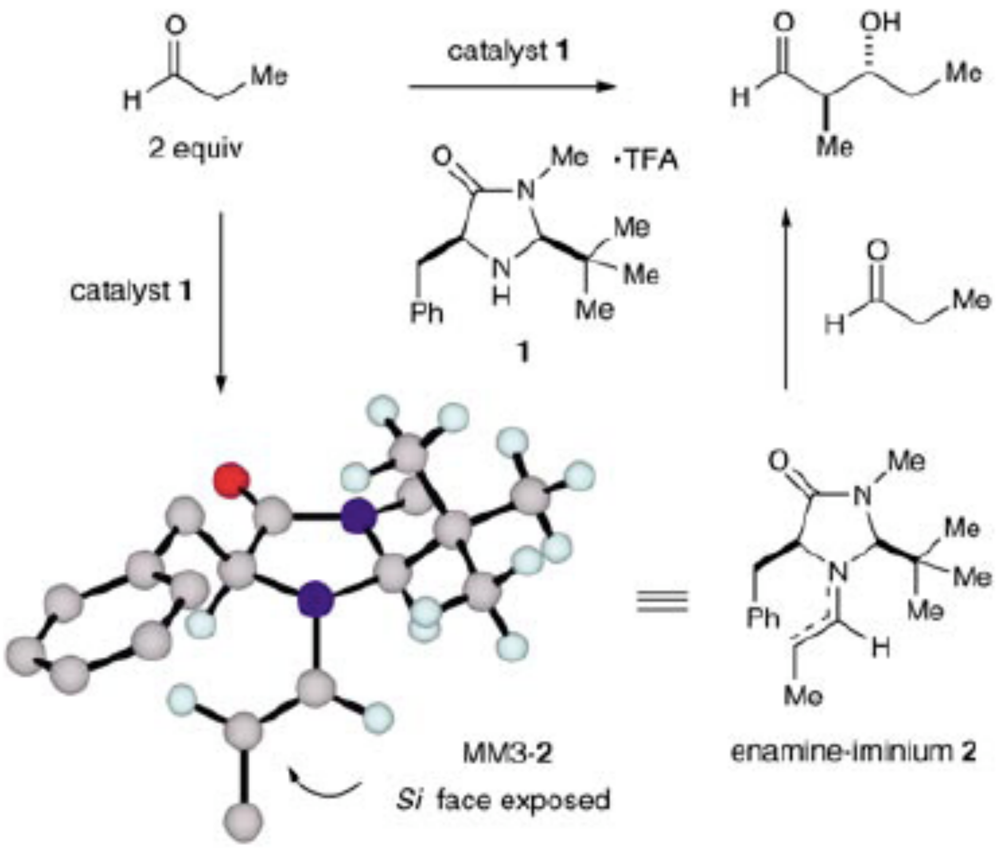


Table 3. Organocatalyzed Dipolar Cycloadditions between Representative Nitrones and Dipolarophiles

entry	Z	R	R_1	*endo:exo*	yield	% ee (*endo*)[a,b]
1	Bn	Ph	Me	94:6	98	94
2	Allyl	Ph	Me	93:7	73	98
3	Me	Ph	Me	95:5	66	99
4	Bn	C_6H_4Cl-4	Me	92:8	78	95
5	Me	C_6H_4Cl-4	Me	93:7	76	94
6	Bn	C_6H_4OMe-4	Me	98:2	93	91
7	Me	C_6H_4Me-4	Me	93:7	82	97
8	Bn	2-naph	Me	95:5	98	93
9	Bn	*c*-hex	Me	99:1	70	99
10	Bn	Ph	H	81:19	72	90
11	Bn	Ph	H	86:14	80	92[c]
12	Bn	C_6H_4Me-4	H	85:15	80	90[c]
13	Bn	C_6H_4Cl-4	H	80:20	80	91[c]
14	Bn	2-naph	H	81:19	82	90[c]
15	Bn	C_6H_4OMe-4	H	91:9	83	90[c]

Mac Millan et al, *JACS* **2000**, *122*, 9874

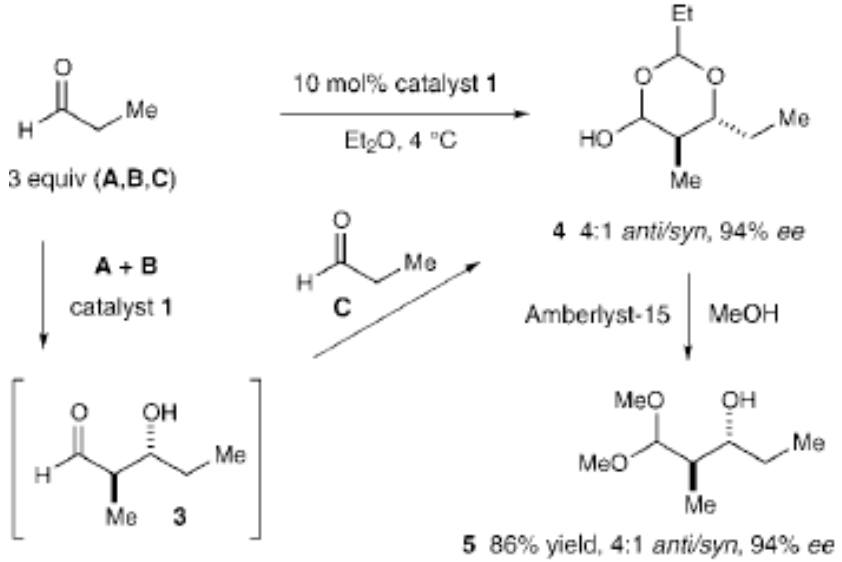
“Second generation” Mac Millan catalyst: More efficient stereocontrol of iminium geometry



Scheme 2. Imidazolidinone-catalyzed aldehyde–aldehyde aldol reaction.

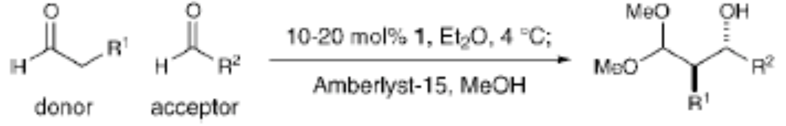
Mac Millan et al, *ACIE,* **2004**, *43*, 6722

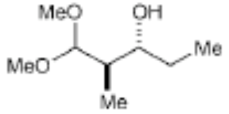
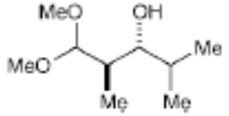
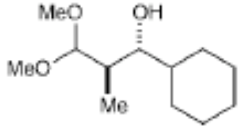
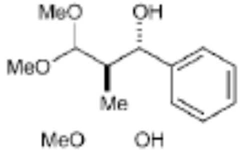
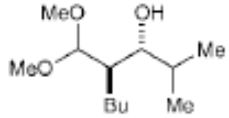
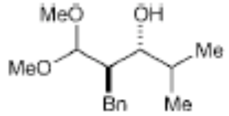
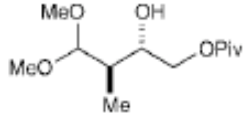
Aldehyde-aldehyde aldol reaction



Scheme 3. Imidazolidinone-catalyzed aldol reaction: initial results.

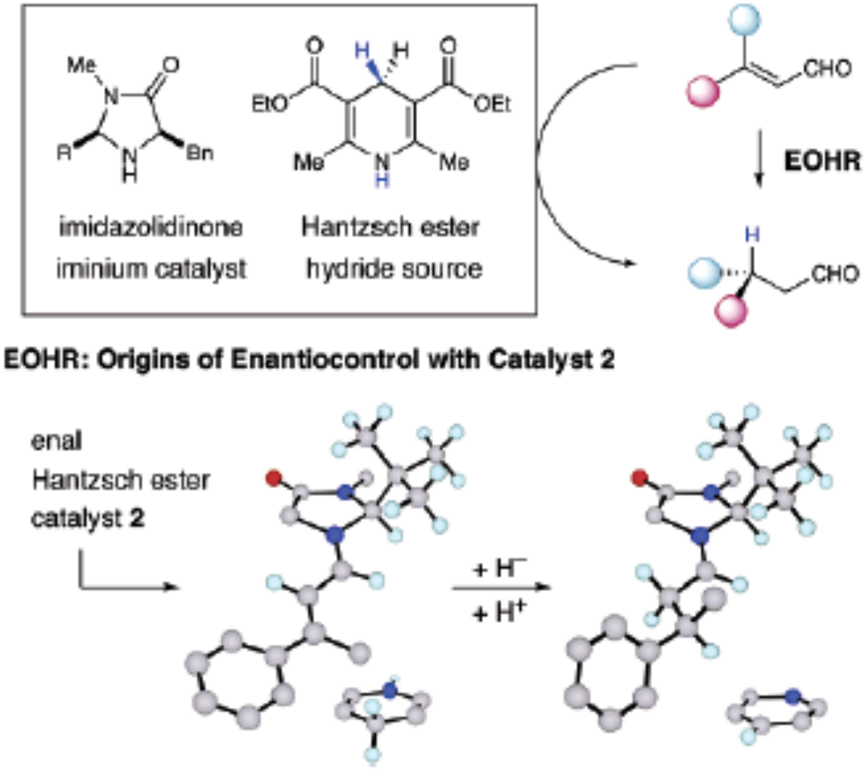
Table 1: Imidazolidinone-catalyzed direct aldol condensation: reaction scope.

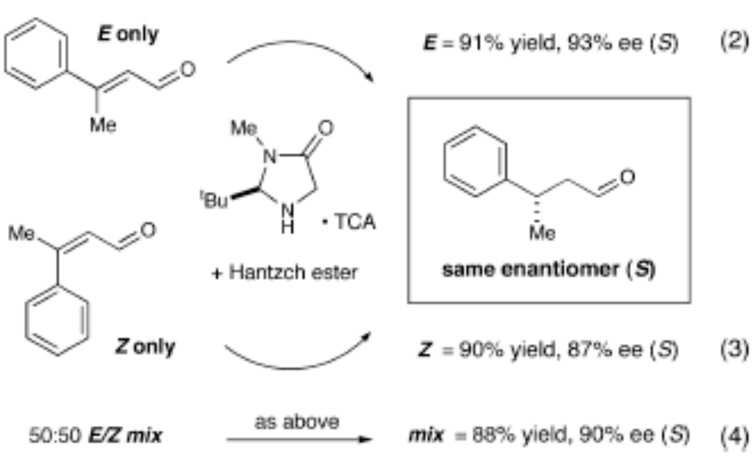


Entry	R^1	R^2	Product	Yield [%][a]	*anti*/*syn*[b]	*ee* [%][c,d]
1	Me	Me		86	4:1	94
2	Me	*i*Pr		90	5:1	95
3	Me	*c*-C$_6$H$_{11}$		81	5:1	97
4	Me	Ph		61	4:1	93
5	*n*Bu	*i*Pr		72	6:1	91
6	Bn	*i*Pr		80	5:1	91
7	Me	OPiv		58	4:1	90

Mac Millan et al, *ACIE,* **2004**, *43*, 6722

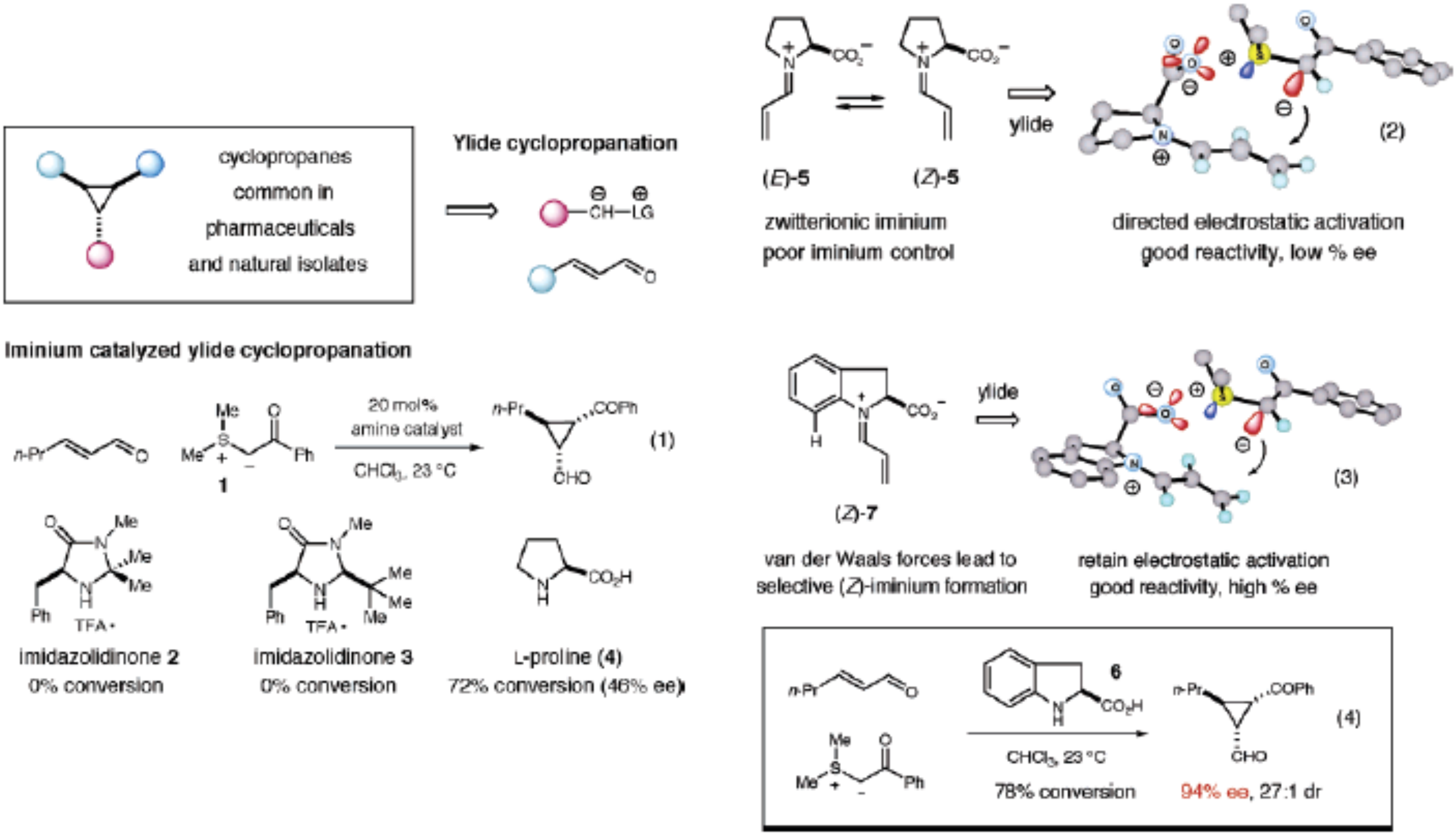
Organocatalytic hydride reduction





Mac Millan et al, *JACS* **2005**, *127*, 32

Cyclopropanation :Identification of a new “proline-type” catalyst



Mac Millan et al, *JACS* **XXX, XXX**

Scope of Organocatalytic yilide-cyclopropanation

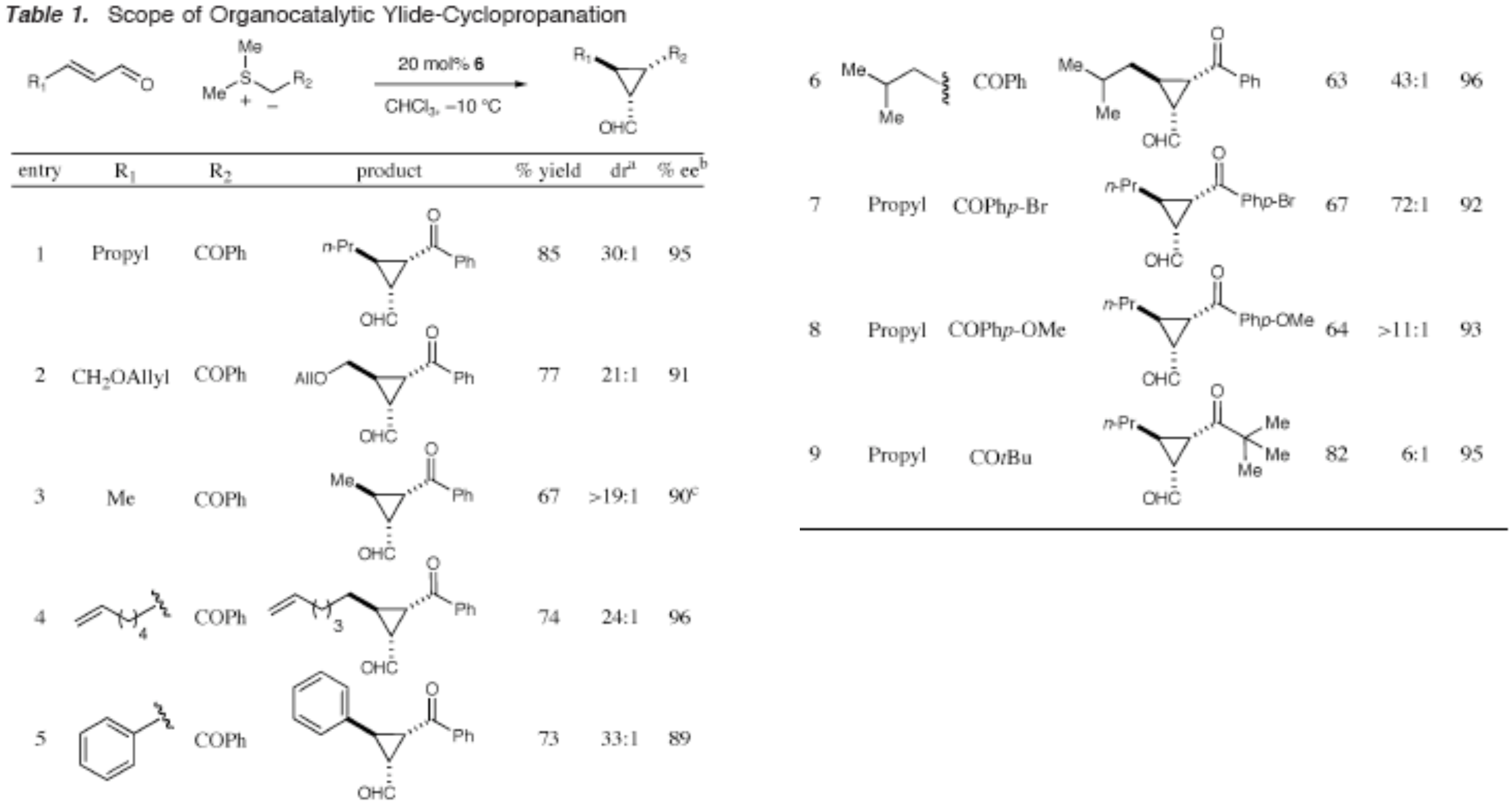


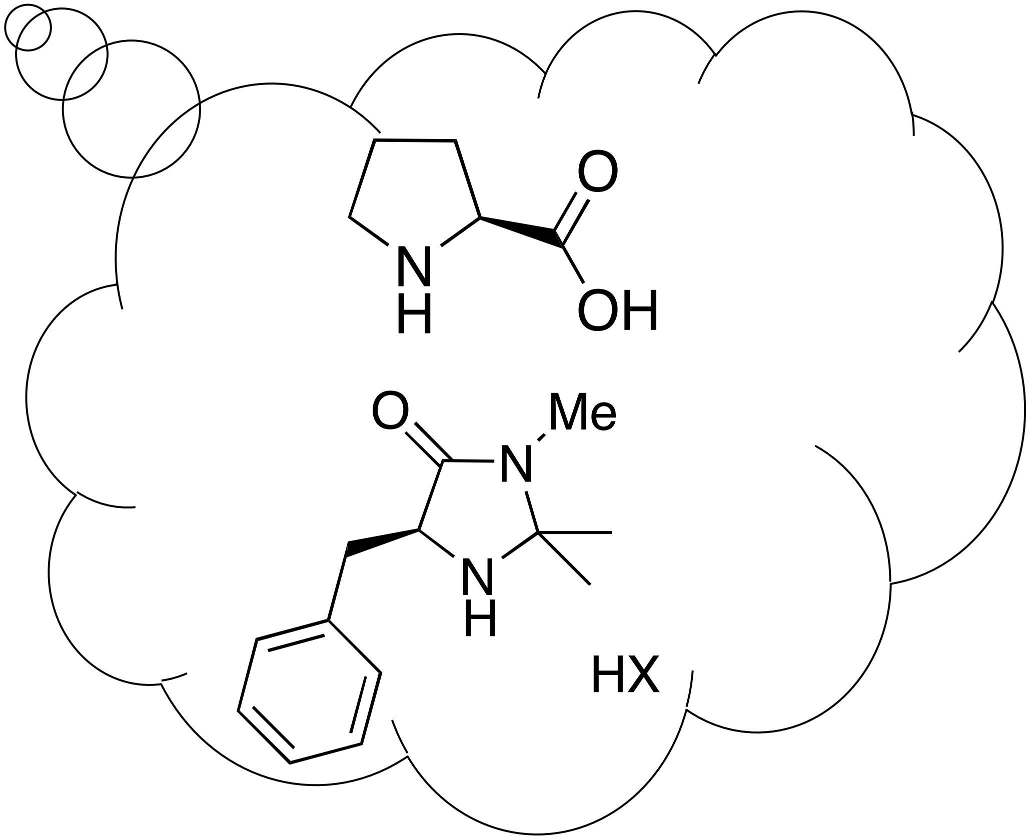
Table 1. Scope of Organocatalytic Ylide-Cyclopropanation

20 mol% **6**

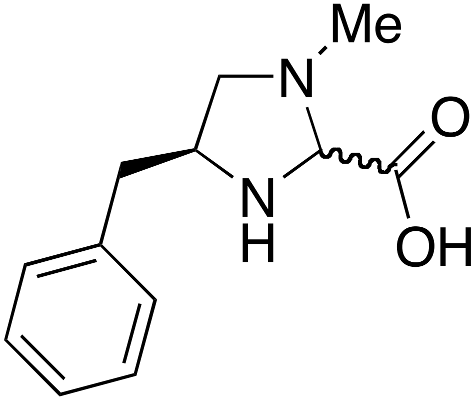
CHCl$_3$, −10 °C

entry	R_1	R_2	product	% yield	dr[a]	% ee[b]
1	Propyl	COPh		85	30:1	95
2	CH_2OAllyl	COPh		77	21:1	91
3	Me	COPh		67	>19:1	90[c]
4		COPh		74	24:1	96
5		COPh		73	33:1	89
6		COPh		63	43:1	96
7	Propyl	COPh*p*-Br		67	72:1	92
8	Propyl	COPh*p*-OMe		64	>11:1	93
9	Propyl	CO*t*Bu		82	6:1	95

Jorgensen
(Aarhus Univ.)

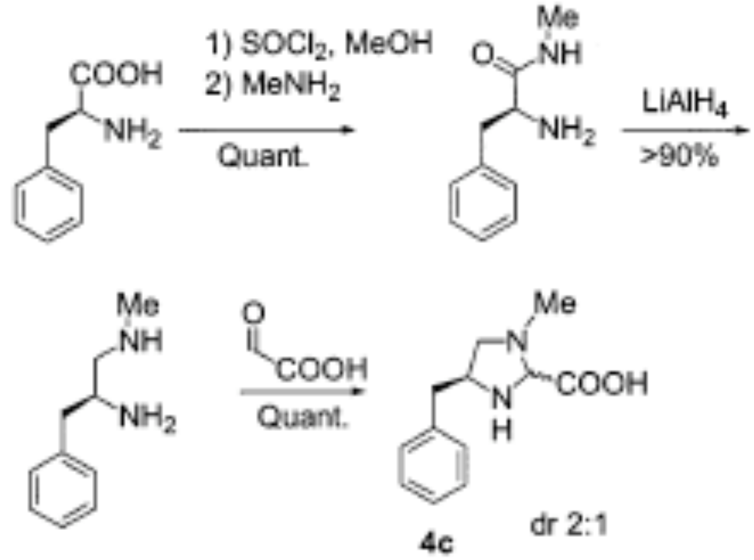


Jorgensen
(Aarhus Univ.)



Synthesis of Jorgensen’s catalyst from phenylalanine

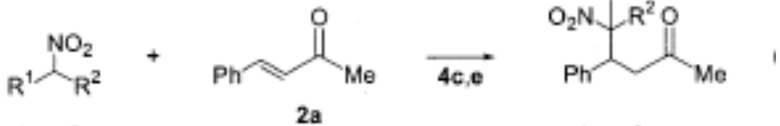
SCHEME 1. Synthesis of Catalyst 4c



(cis/trans=2/1)

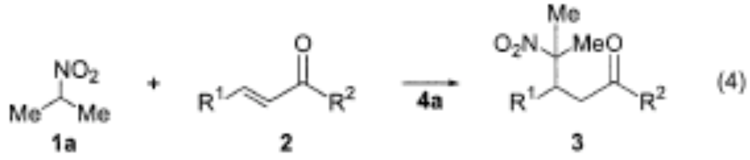
J.Org.Chem. **2002**, *67*, 8331

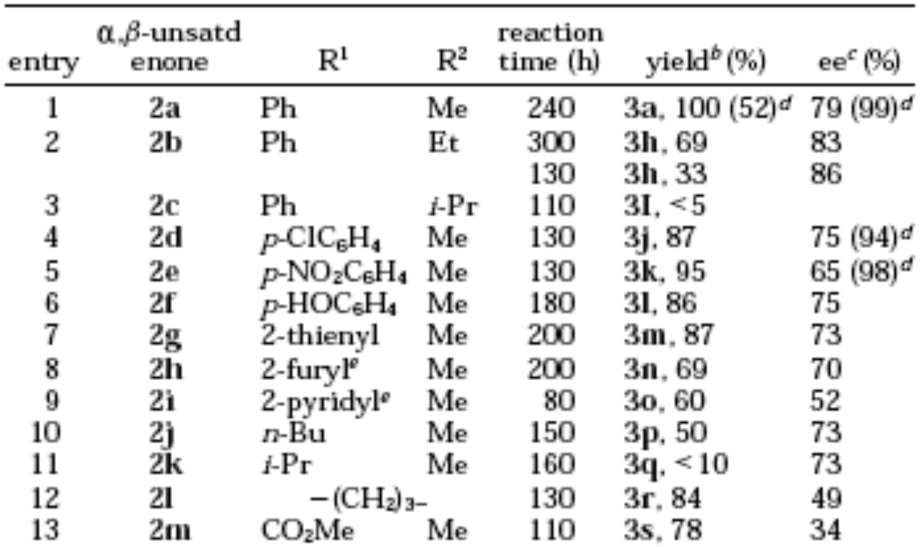
Enantioselective addition of 2-nitropropane to chalcone



1a: $R^1 = R^2 = Me$
1b: $R^1 = R^2 = H$
1c: $R^1 = H, R^2 = Me$
1d: $R^1 = R^2 = (CH_2)_4$
1e: $R^1 = R^2 = (CH_2)_5$
1f: $R^1 = H, R^2 = CO_2Et$
1g: $R^1 = H, R^2 = Ph$

3a: $R^1 = R^2 = Me$
3b: $R^1 = R^2 = H$
3c: $R^1 = H, R^2 = Me$
3d: $R^1 = R^2 = (CH_2)_4$
3e: $R^1 = R^2 = (CH_2)_5$
3f: $R^1 = H, R^2 = CO_2Et$
3g: $R^1 = H, R^2 = Ph$





entry	α,β-unsatd enone	R^1	R^2	reaction time (h)	yield[b] (%)	ee[c] (%)
1	**2a**	Ph	Me	240	**3a**, 100 (52)[d]	79 (99)[d]
2	**2b**	Ph	Et	300	**3h**, 69	83
				130	**3h**, 33	86
3	**2c**	Ph	*i*-Pr	110	**3I**, <5	
4	**2d**	*p*-ClC_6H_4	Me	130	**3j**, 87	75 (94)[d]
5	**2e**	*p*-$NO_2C_6H_4$	Me	130	**3k**, 95	65 (98)[d]
6	**2f**	*p*-HOC_6H_4	Me	180	**3l**, 86	75
7	**2g**	2-thienyl	Me	200	**3m**, 87	73
8	**2h**	2-furyl[e]	Me	200	**3n**, 69	70
9	**2i**	2-pyridyl[e]	Me	80	**3o**, 60	52
10	**2j**	*n*-Bu	Me	150	**3p**, 50	73
11	**2k**	*i*-Pr	Me	160	**3q**, <10	73
12	**2l**	$-(CH_2)_3-$		130	**3r**, 84	49
13	**2m**	CO_2Me	Me	110	**3s**, 78	34

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Imnium Structure

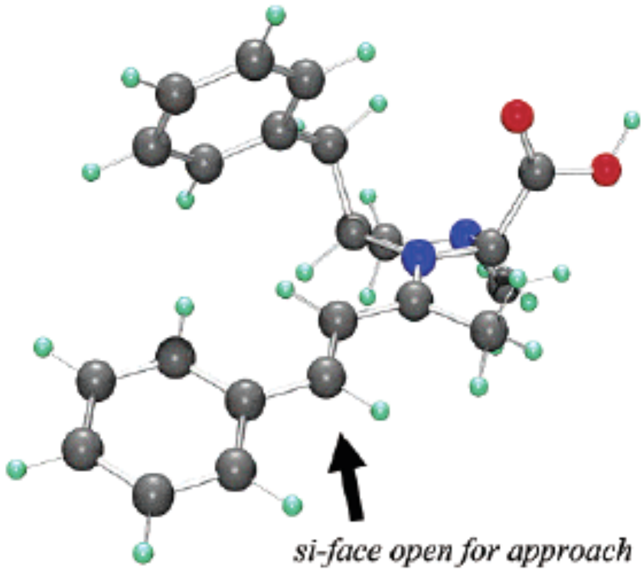
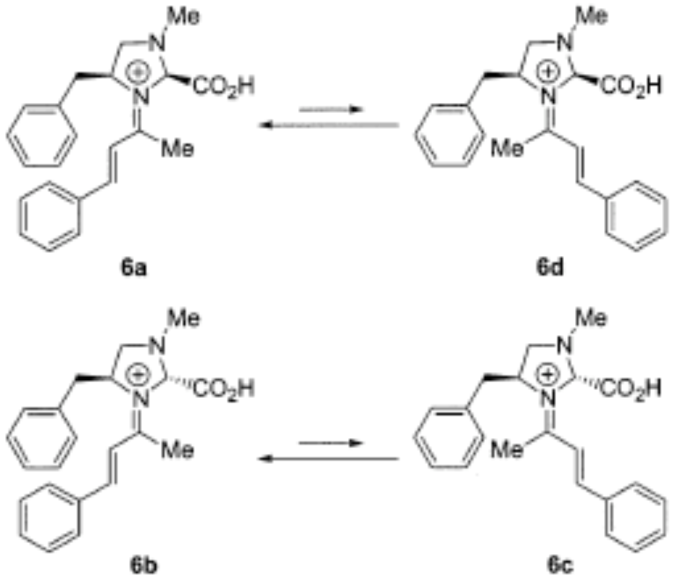


FIGURE 1. PM3-minimized structure of iminium ion **6a**.

SCHEME 2. Possible Catalyst–Substrate Iminium Intermediates, 6a–d



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