Enantioselective α–Allylation of Aldehydes and Ketones

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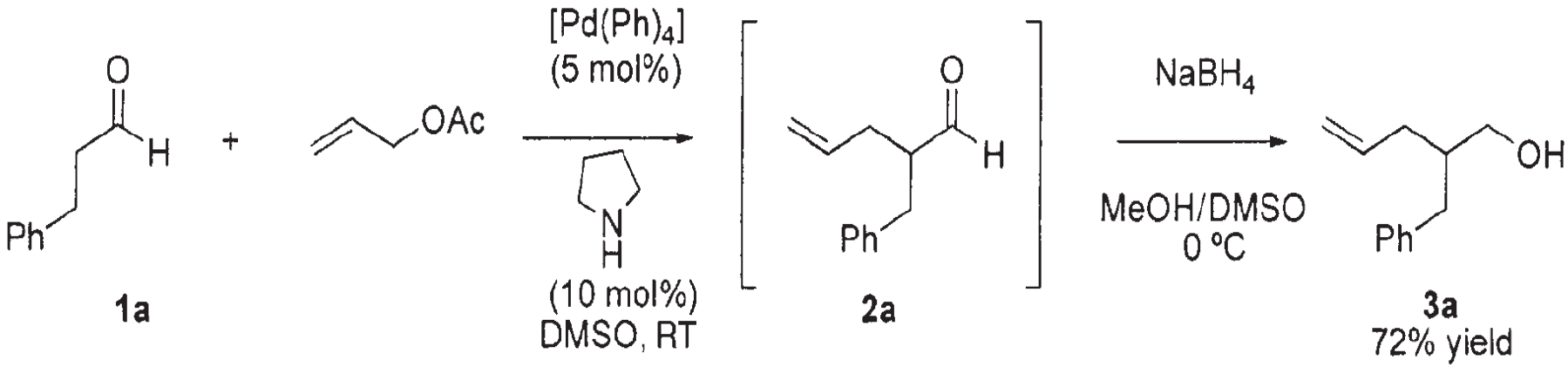
Outline

- Direct α-Allylation of Aldehydes
  - Using ACDC
  - Using SOMO Activation

- Indirect α-Allylation of Ketones
  - Enolates
  - Phase Transfer Catalysts

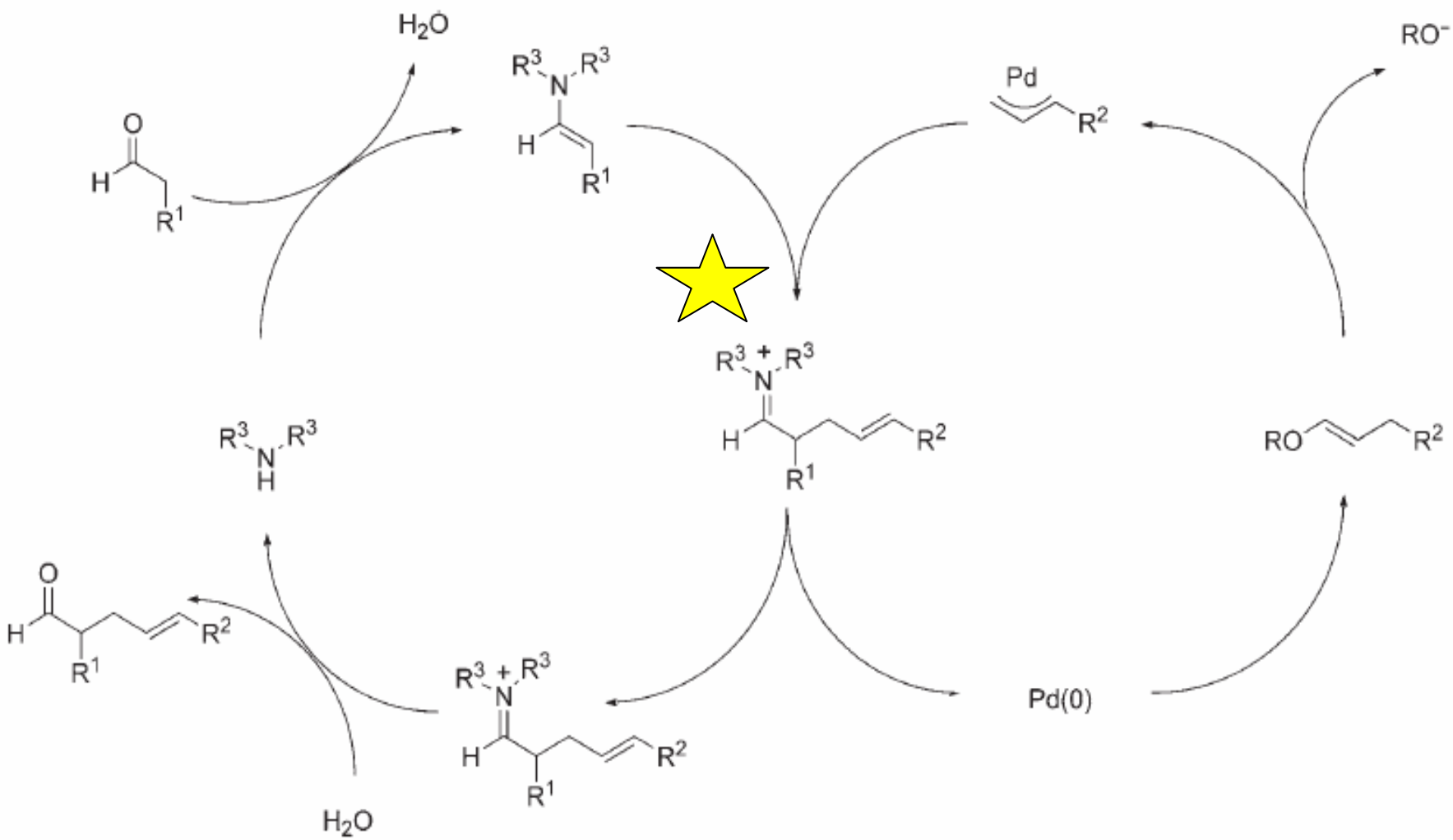
Basis for Direct α-Allylation of Aldehydes



Direct catalytic intermolecular α-alkylation of aldehydes by combination of transition metal and organocatalysis

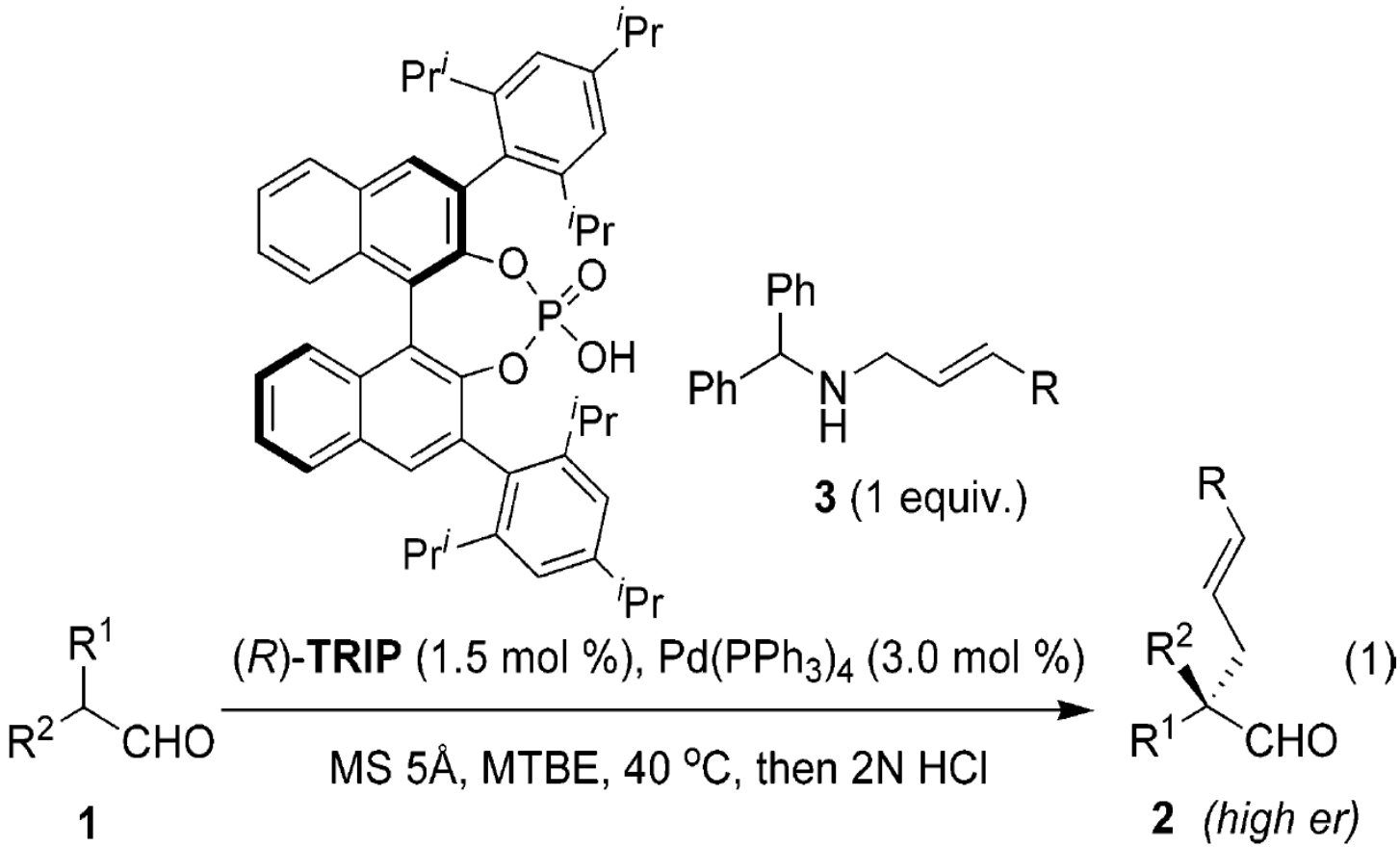
Ibrahem, I.; Cordova, A. Angew. Chem. Int. Ed. 2006, 45, 1952.

Basis for Direct α-Allylation of Aldehydes



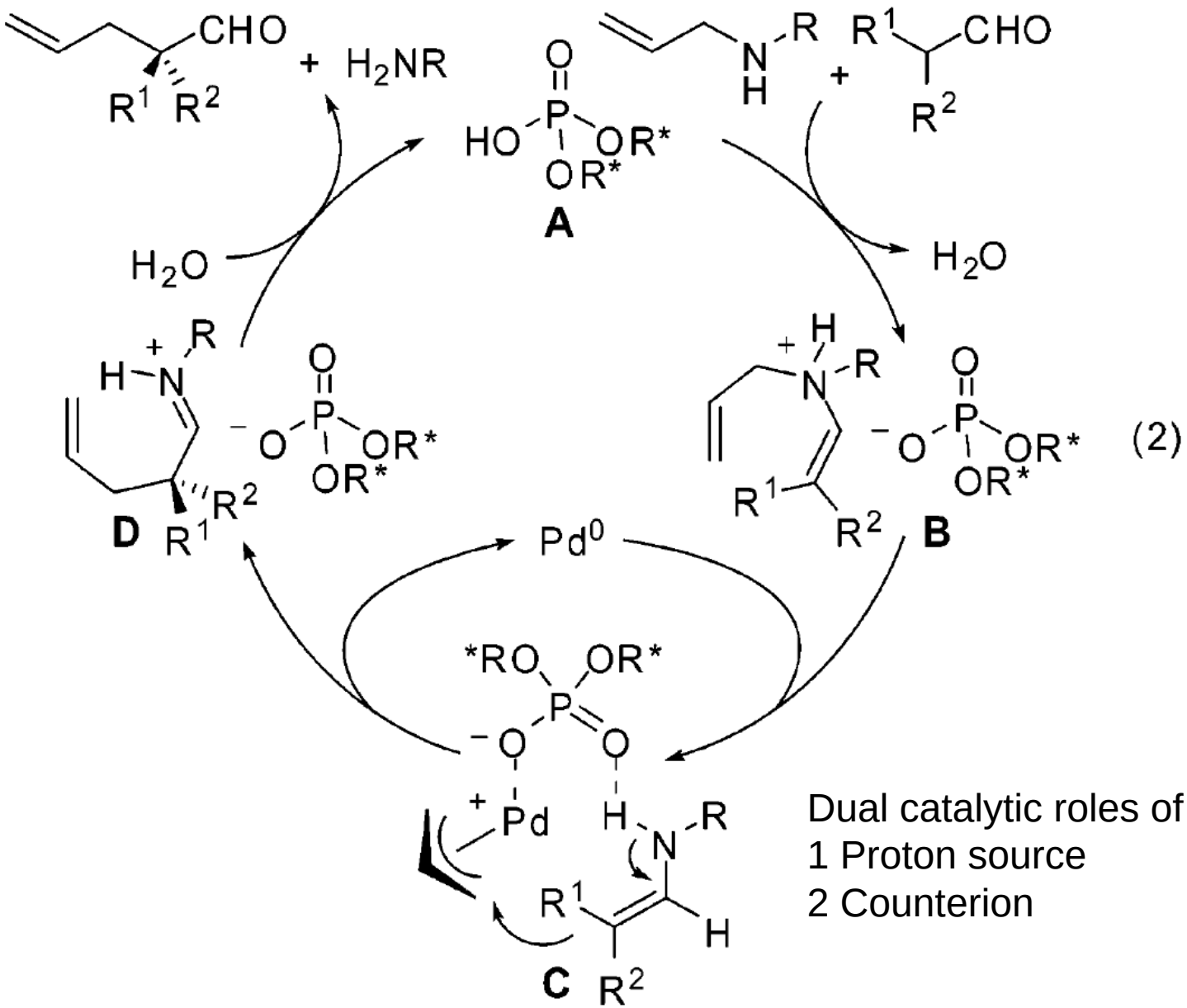
Ibrahem, I.; Cordova, A. Angew. Chem. Int. Ed. 2006, 45, 1952.

ACDC in Transition Metal Catalysis



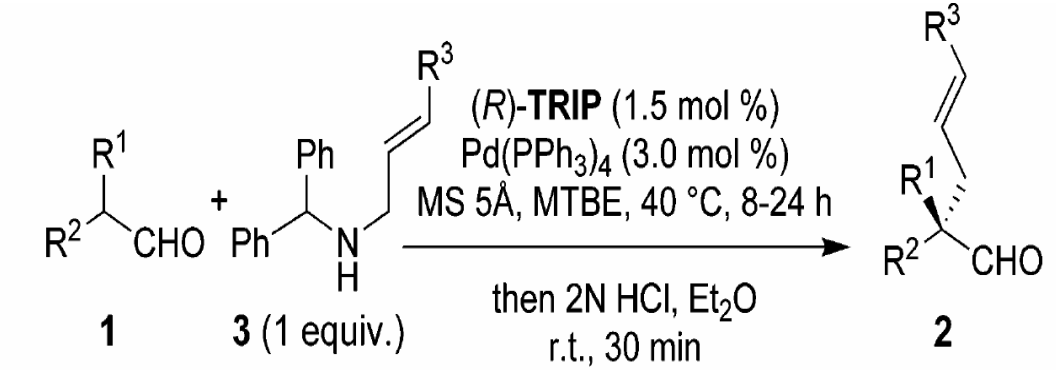
Mukherjee, S.; List, B. J. Am. Chem. Soc. 2007, 129, 11336.

Mechanism for the Reaction

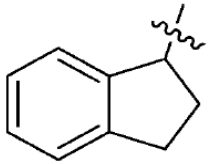


Dual catalytic roles of TRIP
1 Proton source
2 Counterion

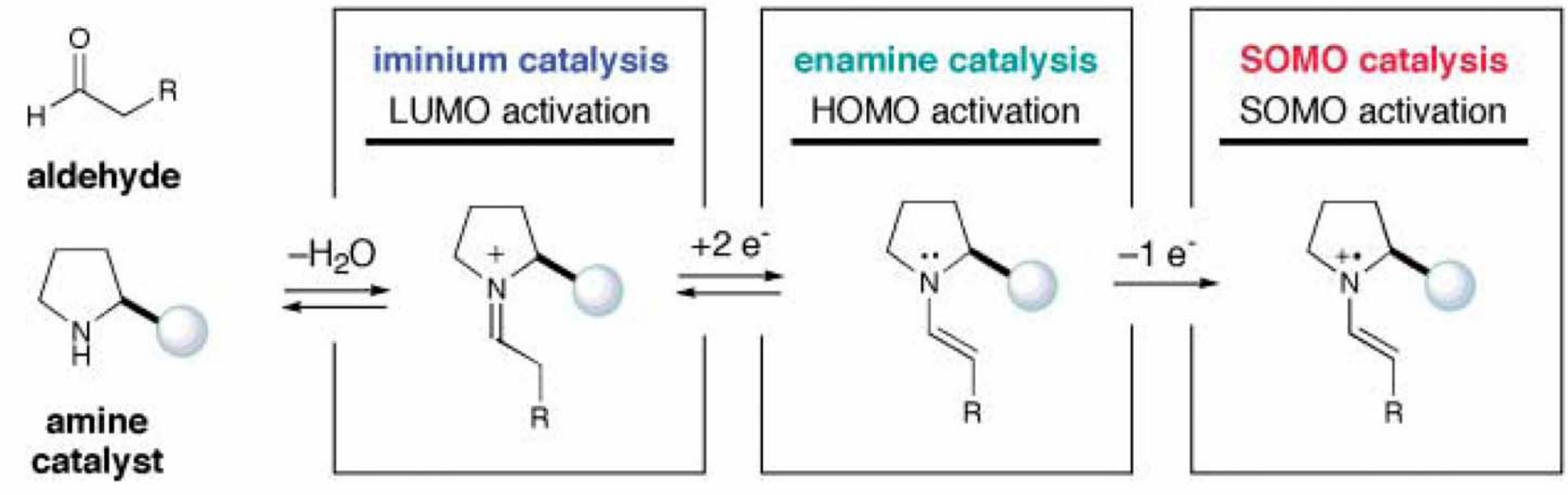
Substrate Scope



1 **3** (1 equiv.) **2**

entry	R^1	R^2	R^3		yield (%)	er[a]
1	Me	Ph	H	**2a**	85	98.5:1.5
2	Me	4-Me-C_6H_4	H	**2b**	89	97:3
3	Me	3-Me-C_6H_4	H	**2c**	84	98:2
4	Me	3-F-C_6H_4	H	**2d**	85	98:2
5[b]	Me	2-F-C_6H_4	H	**2e**	74	97:3
6	Me	4-*i*-Bu-C_6H_4	H	**2f**	76	97.5:2.5
7	Me	2-naph	H	**2g**	71	97:3
8	Me	2-thiophenyl	H	**2h**	80	93:7
9			H	**2i**	45	95:5
10[c]	Me	*c*-hex	H	**2j**	65	85:15
11[d,e]	Me	Ph	Me	**2k**	40	96:4
12[d,e]	Me	Ph	Ph	**2l**	82	91:9

Organocatalysis Using SOMO Activation

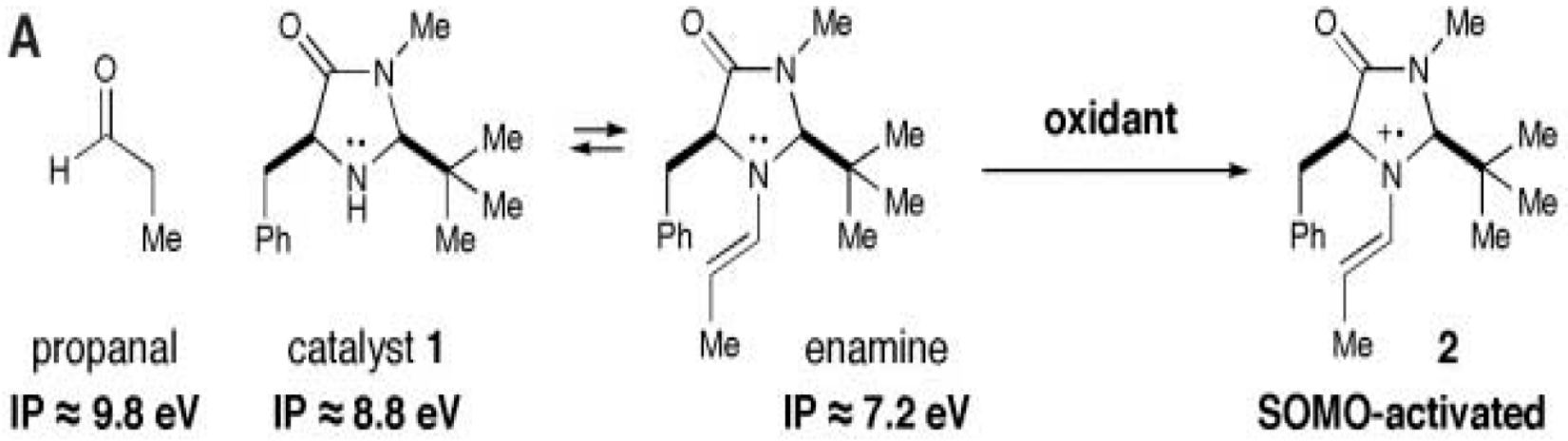


SOMO: a singly occupied molecular orbital

Beeson, T. D.; Mastracchio, A.; Hong, J-B.; Ashton, K.; MacMillan, W. C. Science, 2007, 316, 582-585.

SOMO Activation

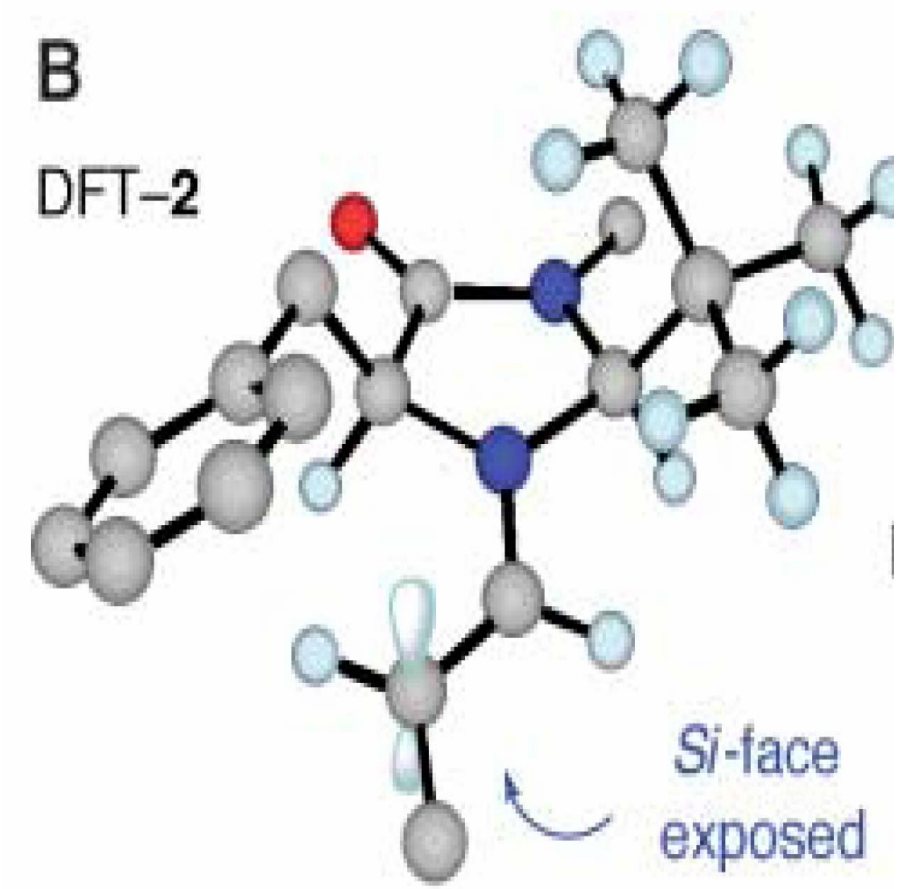
Key elements to support the proposal

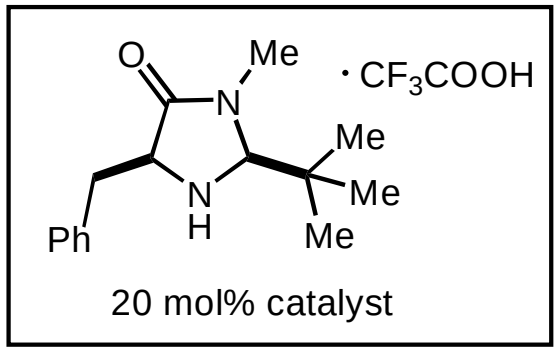


The transient enamine component to be sufficiently more susceptible to oxidation than the accompanying reaction partners.

SOMO Activation

Key elements to support the proposal

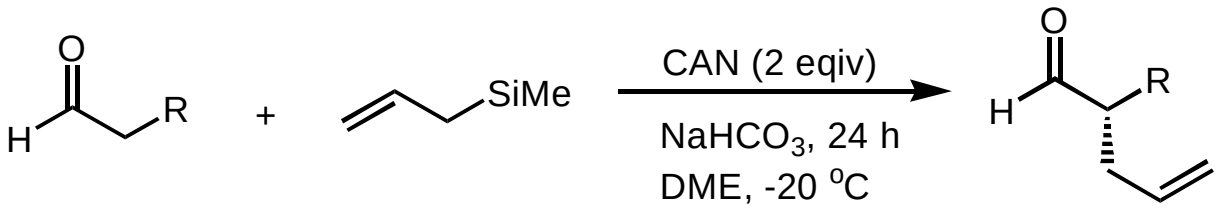


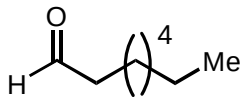
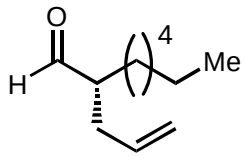
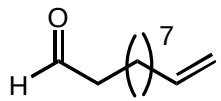
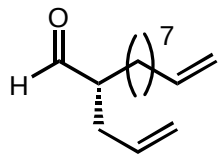
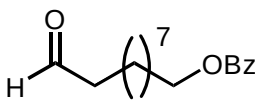
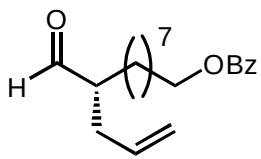
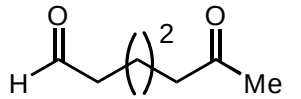
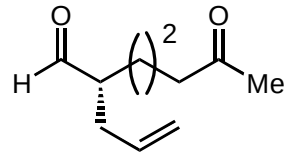
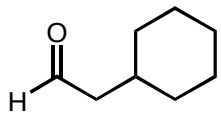
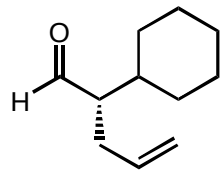
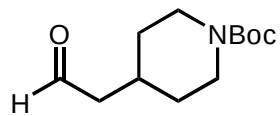
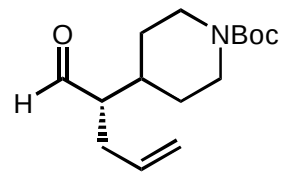


✓Three π electron system away from the bulky t-Bu group

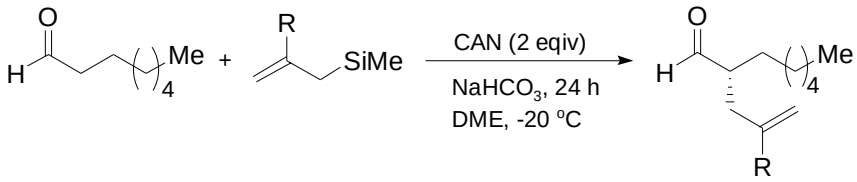
✓Radical-centered carbon selectively populates an E configuration to minimize nonbonding interactions with the ring

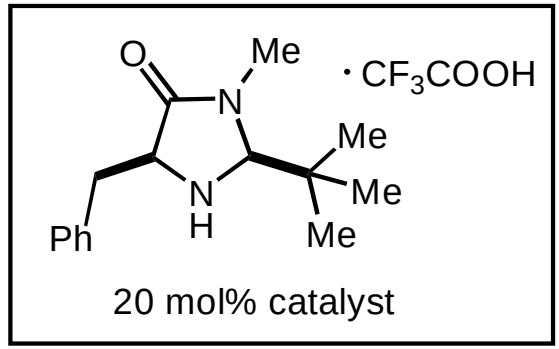
Enantioselective Aldehyde α-Allylation

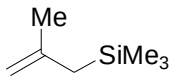
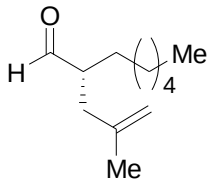
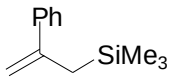
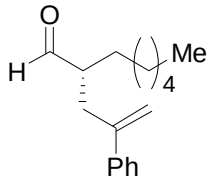


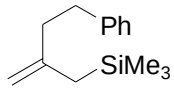
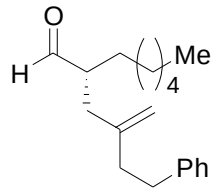
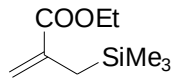
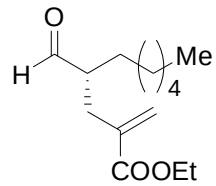
Aldehyde	Product	Yield / *ee*
		Yield: 81% *ee*: 91%
		Yield: 75% *ee*: 92%
		Yield: 72% *ee*: 95%
		Yield: 72% *ee*: 87%
		Yield: 75% *ee*: 94%
		Yield: 70% *ee*: 93%

Enantioselective Aldehyde α-Allylation

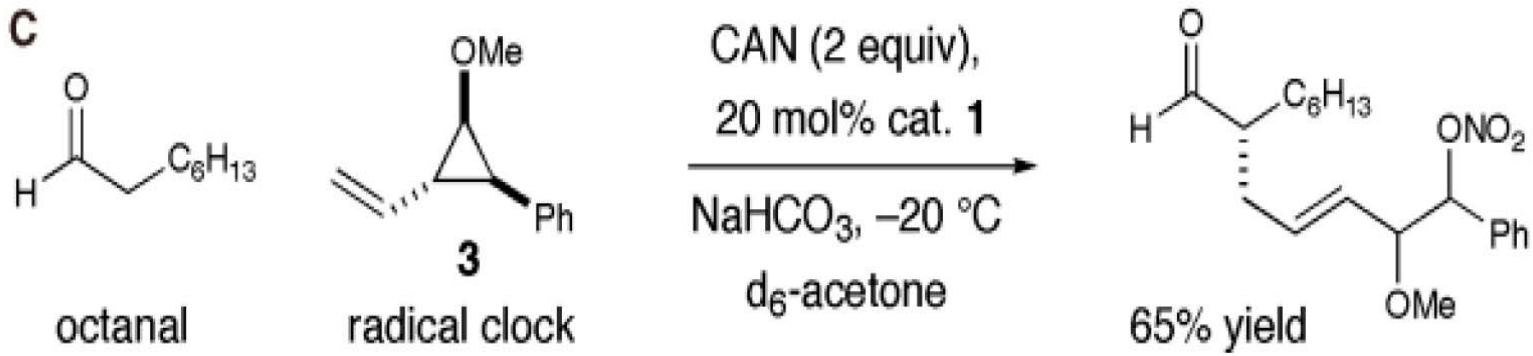




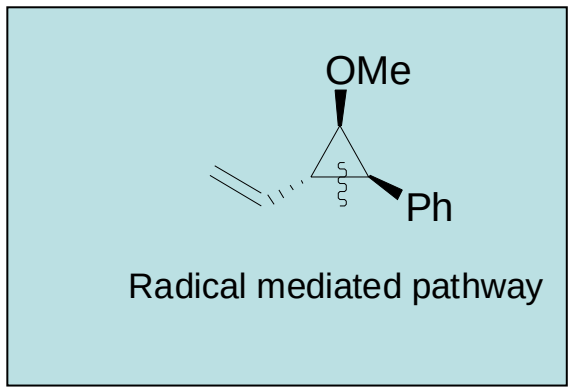
Allylsilane	Product
 Yield: 88% *ee*: 91%	
 Yield: 87% *ee*: 90%	

Allylsilane	Product
 Yield: 77% *ee*: 88%	
 Yield: 81% *ee*: 90%	

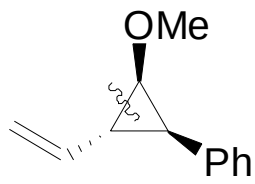
Evidence for SOMO



octanal radical clock 65% yield



Radical mediated pathway



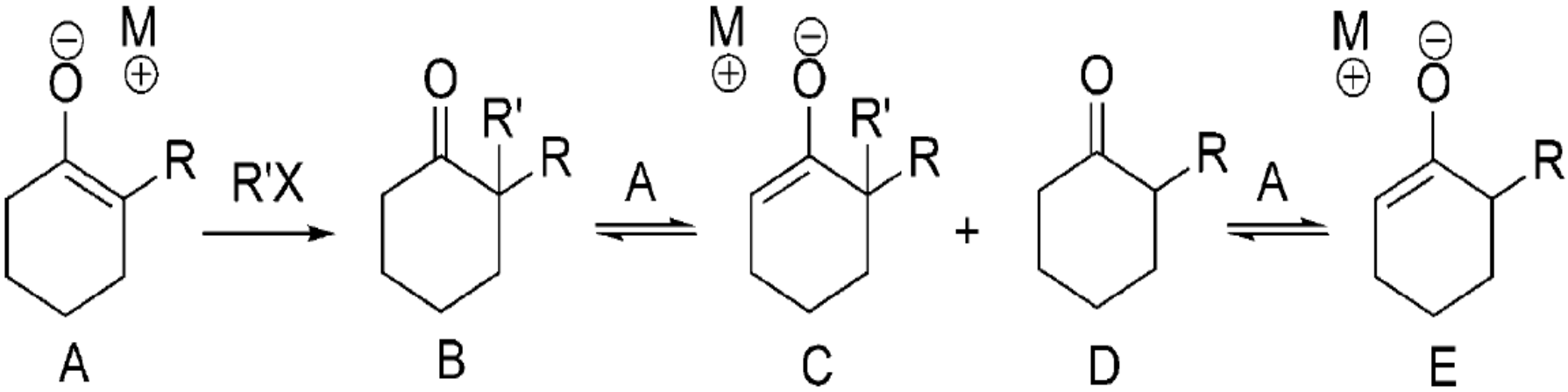
Cationic pathway

Outline

- Direct α-Allylation of Aldehydes
  - Using ACDC
  - Using SOMO Activation

- Indirect α-Allylation of Ketones
  - Enolates
  - Phase Transfer Catalysts

Enantioselective Allylation of ketones

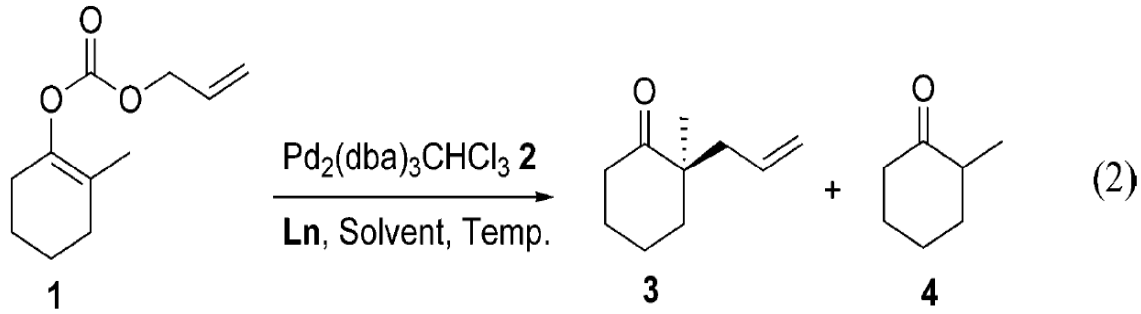


Problems:
Enolate equilibrium can lead to loss of regioselectivity (A and E)
R = H, the chiral product is subjected to racemization

Neutral condition
Low concentration of enolate

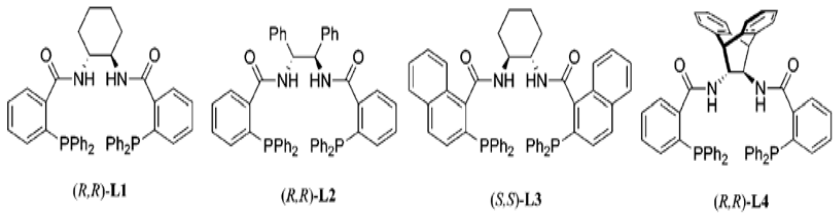
Trost, B. M.; Xu, J. J. Am. Chem. Soc. 2005, 127, 2846.

Enantioselective Pd-Catalyzed Allylation

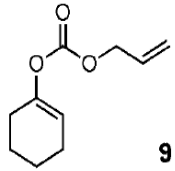
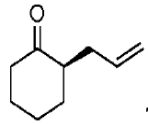
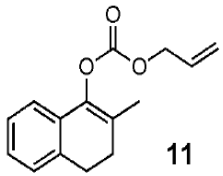
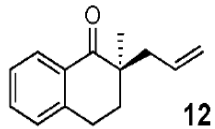
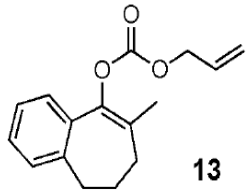
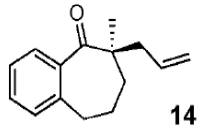
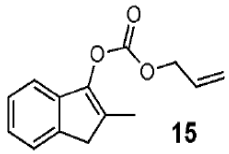
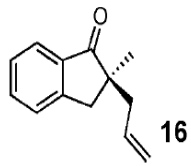
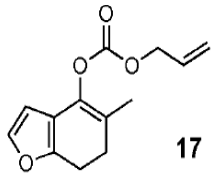
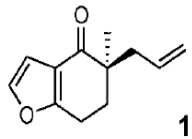
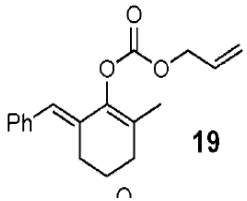
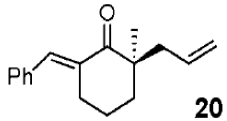


(2)

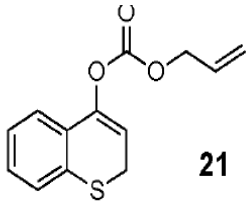
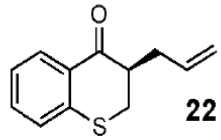
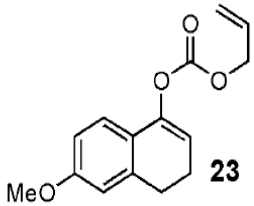
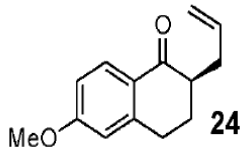
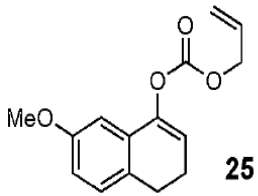
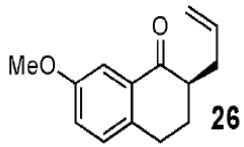
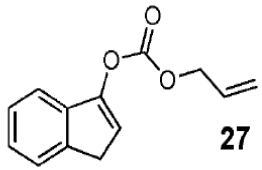
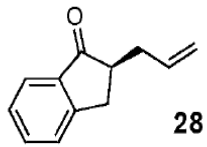
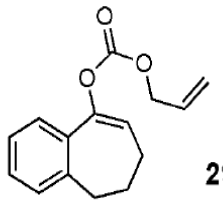
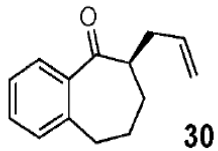
entry	ligand	solvent	ee[b]	yield[c] of **3**	yield[c] of **4**
1	**L1**	DME	66	81	8
2	**L3**	DME	76	87	2
3	**L1**	toluene	31	73	0
4	**L2**	toluene	61	73	2
5	**L3**	toluene	60	85	1
6	**L4**	toluene	85	88	0
7	**L4**	CH_2Cl_2	84	64	26
8	**L4**	dioxane	80	99	0
9	**L4**	DME	84	87	7
10	**L4**	THF	81	85	1
11	**L4**	DME (1%H_2O)	NA	20	3.7
12	**L3**	DME (1%H_2O)	NA	1.5	0



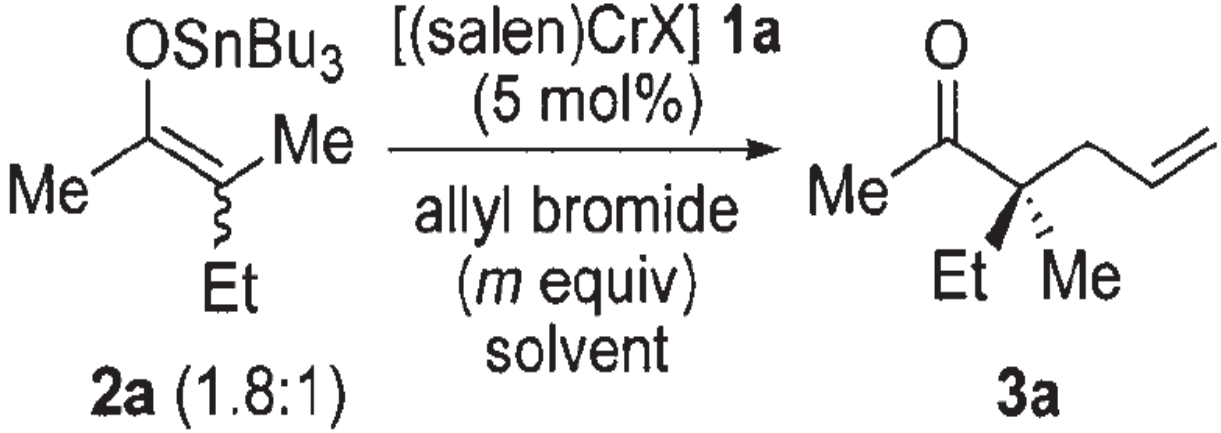
Substrate Scope

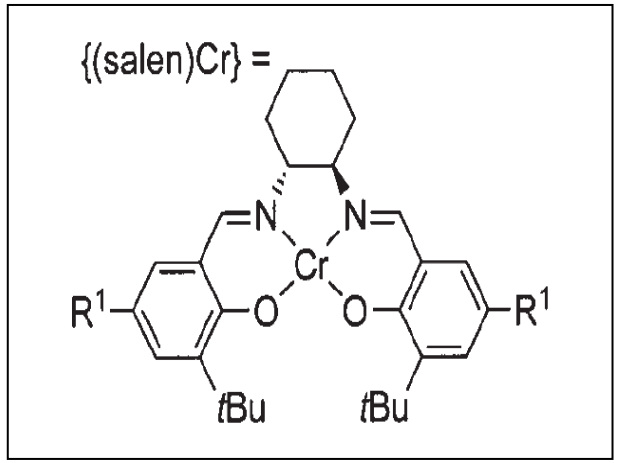
entry	substrate	product	yield[b]	ee[c]
1[d]	 9	 10	78%	78%[e]
2[d]	 11	 12	88%	>99%
3	 13	 14	94%	91%[e]
4[b]	 15	 16	98%	76%
5	 17	 18	64%	82%
6	 Ph 19	 Ph 20	99%	95%

Substrate Scope

7	 **21**	 **22**	89%	93%
8[f]	 **23**	 **24**	90%	>99%
9[f]	 **25**	 **26**	97%	97%
10	 **27**	 **28**	87%	81%
11[f]	 **29**	 **30**	93%	99%

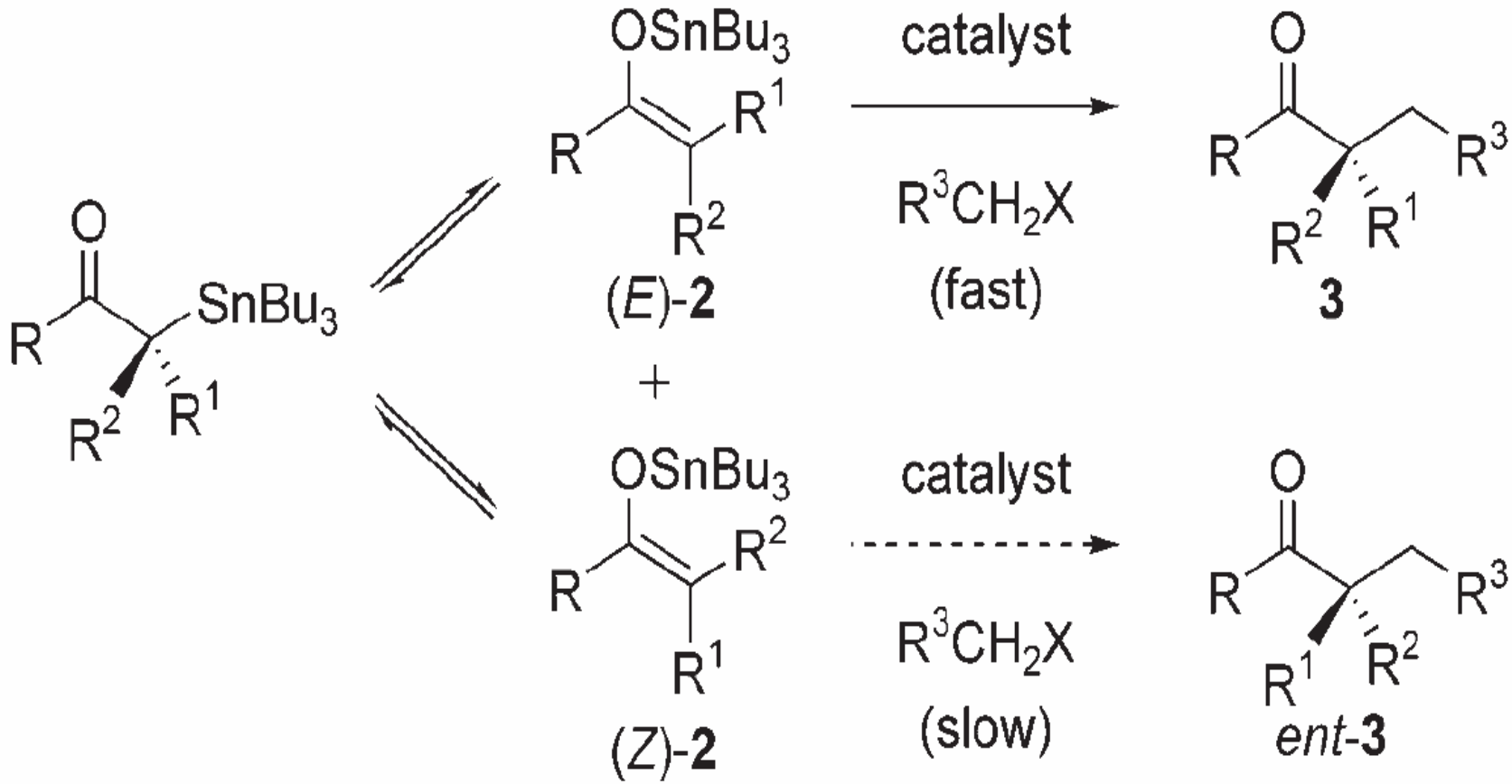
Enantioselective Allylation of Acyclic α,α-Disubstituted Tributyltin Enolates





Doyle, A. G.; Jacobsen, E. N. Angew. Chem. Int. Ed. 2007, 46, 3701-3705

How could they come up with the idea?

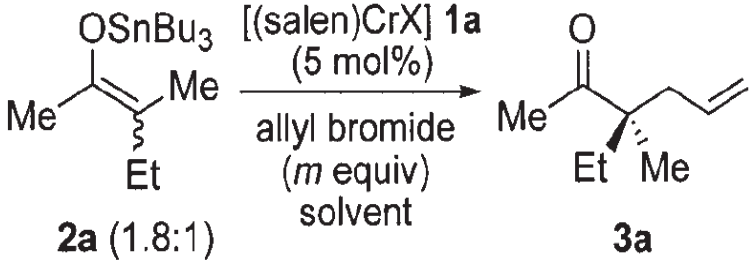


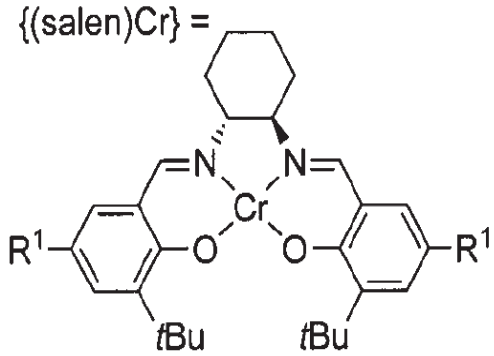
Tin enolates are known to undergo tautomerization between their O-stannyl and C-stannyl forms in solution

The mixture of acyclic tin enolates might undergo reaction selectively through one geometric isomer

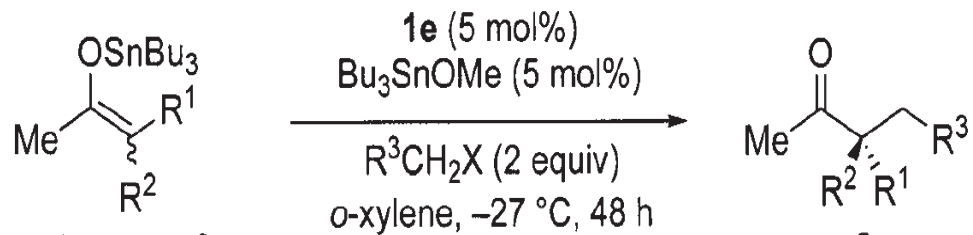
Dynamic control

Catalyst Screening



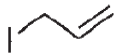
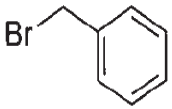
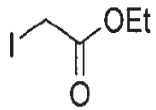
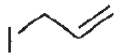
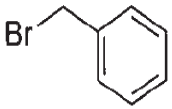
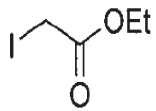


Entry	Catalyst	X	R^1	Solvent	*m* [equiv]	*T* [°C]	Yield [%][b]	*ee* [%][c]
1	**1a**	Cl	*t*Bu	benzene	4	4	80	21
2	**1b**	Cl	OTIPS	benzene	4	4	84	36
3	**1c**	Br	OTIPS	benzene	4	4	90	49
4	**1d**	I	OTIPS	benzene	4	4	93	56
5	**1d**	I	OTIPS	benzene	2	4	90	60
6[d]	**1d**	I	OTIPS	*o*-xylene	2	4	95	65
7[d]	**1e**	I	$OSiThMe_2$	*o*-xylene	2	4	94	68
8[d]	**1e**	I	$OSiThMe_2$	*o*-xylene	2	−27	94	79

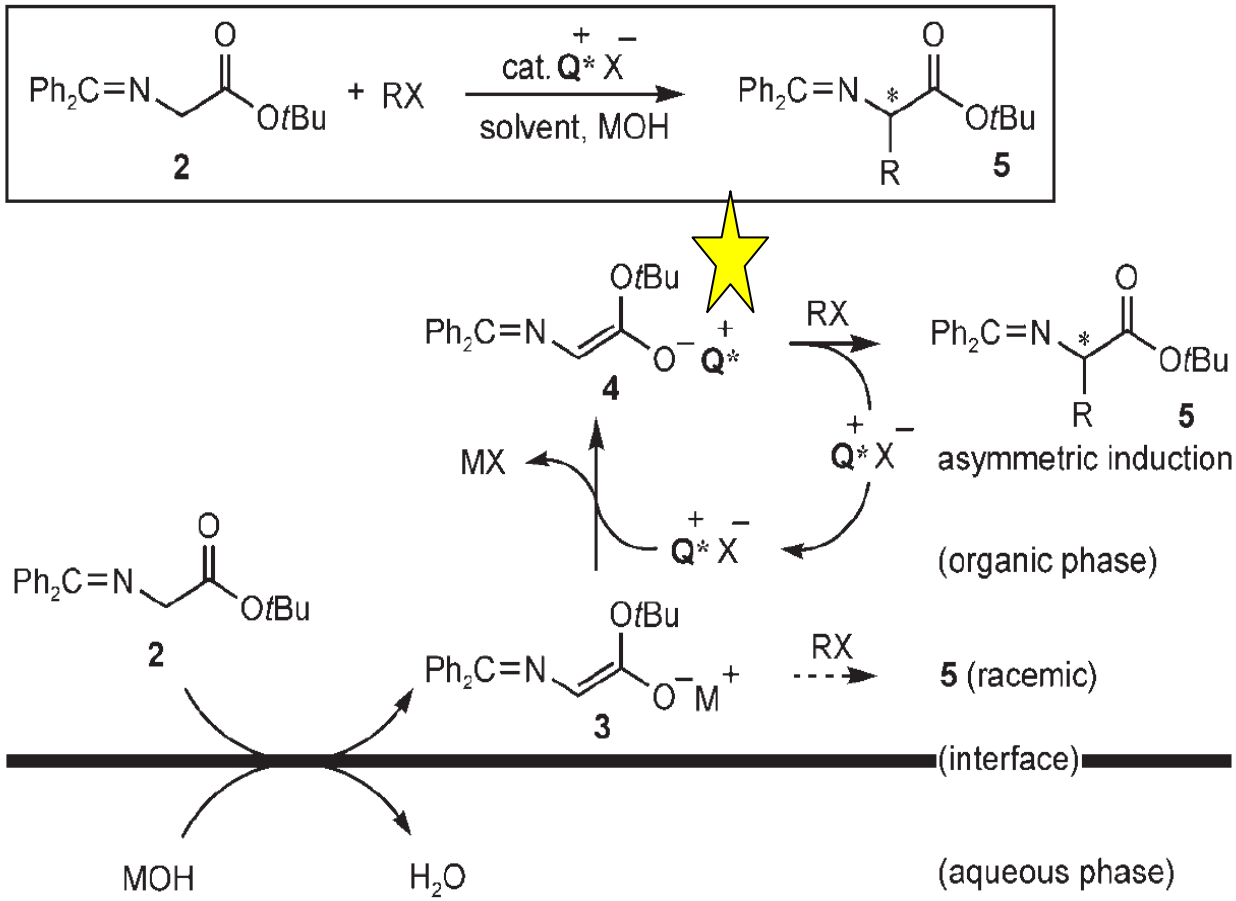


2a: R^1 = Me, R^2 = Et
2b: R^1 = Me, R^2 = *n*Bu

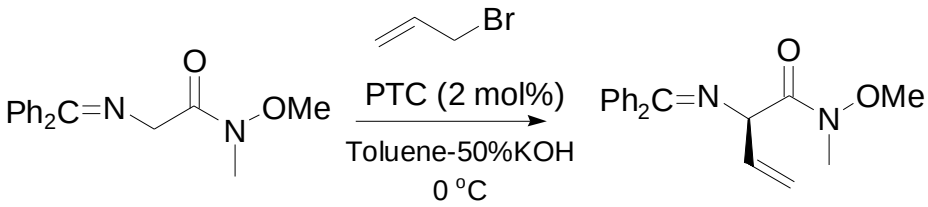
3

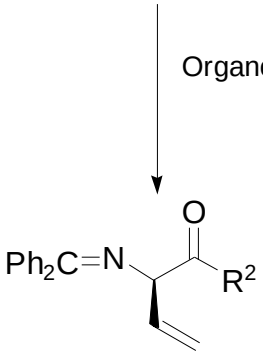
Entry	Tin enolate (*E*/*Z* ratio)	R^3CH_2X	Adduct	Yield [%][a]	*ee* [%][b]
1	**2a** (1.8:1)		**3a**	80	79
2			**3a**	83	82
3			**3b**	86	81
4			**3c**	73	76
5	**2b** (1.5:1)		**3d**	92	87
6			**3e**	83	86
7			**3f**	77	84[c]
8			**3g**	97	78[d]

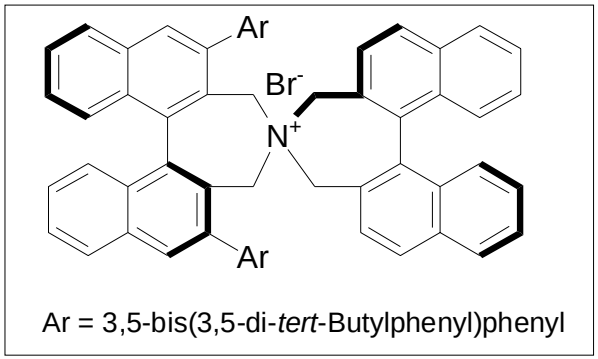
Allylation Using Phase Transfer Catalysts



One Example







Ooi, T.; Takeuchi, M.; Kato, D.; Uematsu, Y.; Tamaya, E.; Sakai, D.; Maruoka, K. J. Am. Chem. Soc. 2005, 127, 5073.

Conclusions

- There are more than one way to get to the destination.

- How you get there really matters.

One shortcut