Catalytic, Enantioselective β-Protonation through a Cooperative Activation Strategy

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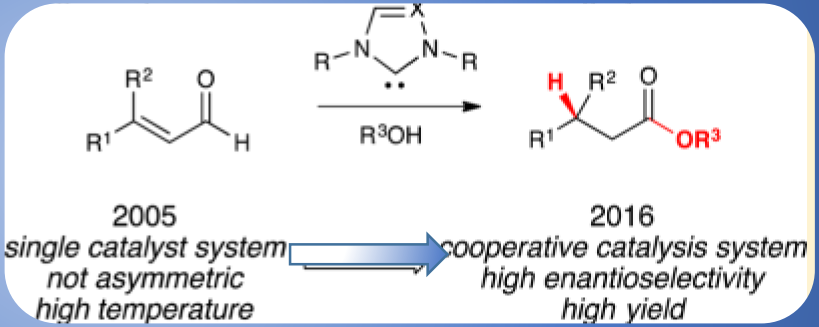
Content:


R³OH
2005
single catalyst system
not asymmetric
high temperature
2016
cooperative catalysis system
high enantioselectivity
high yield

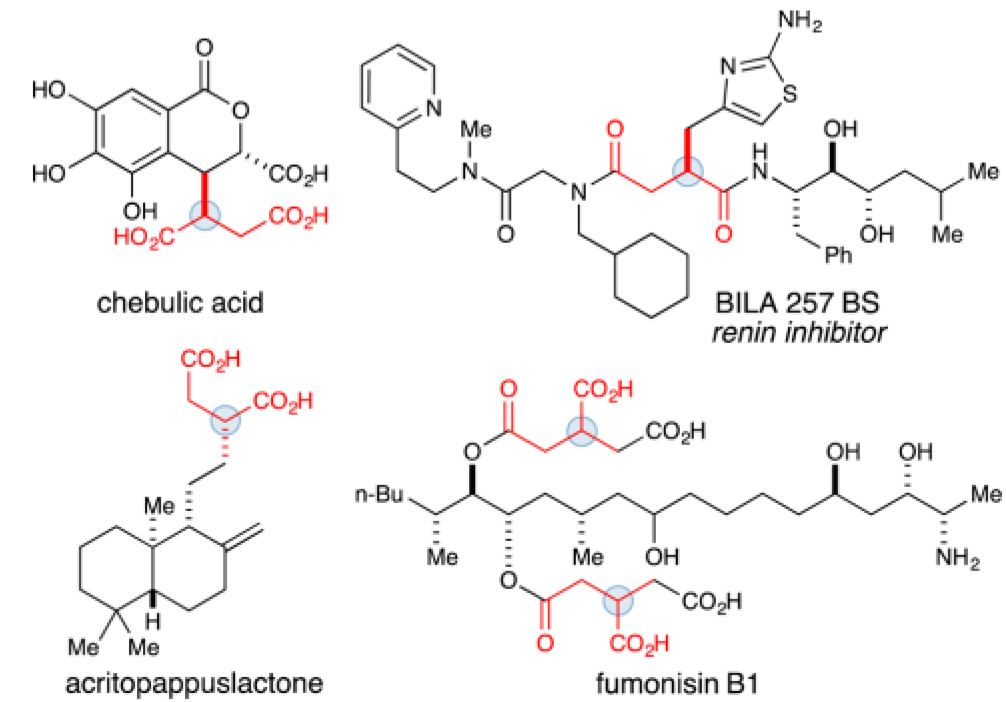
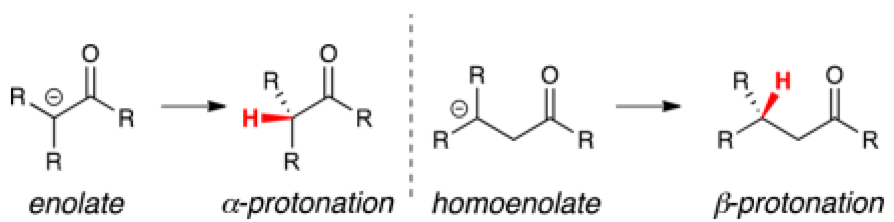


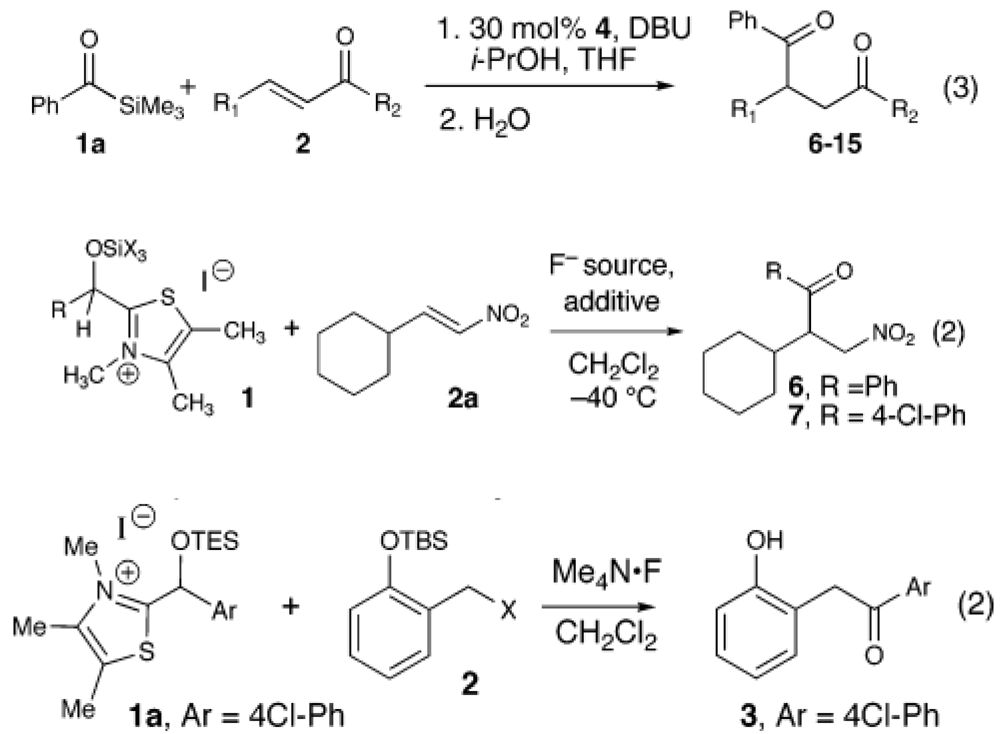
Figure 1. Natural products and bioactive molecules with *α*-stereocenters.



Scheme1. α-Protonaton versus β-protonnation

The difficulties of β-protonation

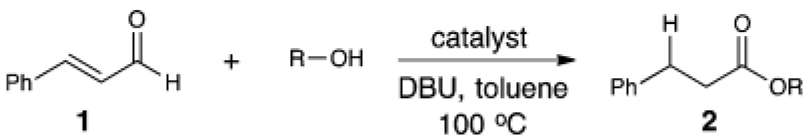
- generating the required homoenolate under catalytic conditions.
- imparting significant enantioinduction at a remote site from the carbonyl.



Scheme 1. NHC catalysis investigations with acylsilanes for carbonyl anion generation

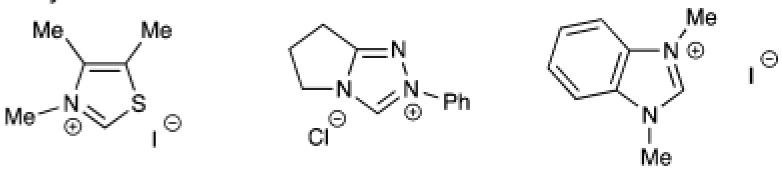
Scheidt, K. A. et al. *J. Am. Chem. Soc.* **2004**, *126*, 2314.
Scheidt, K. A. et al. *Org. Lett.* **2004,** 6, 4363.
Scheidt, K. A. et al. *J. Am. Chem. Soc.* **2006,** *128,* 4932.
Scheidt, K. A. et al. *J. Org. Chem.* **2006**, *71,* 5715.
Scheidt, K. A. et al. *J. Am. Chem. Soc.* **2007**, *129*, 4508.

Table 1. Initial Screen for *β*-Protonation



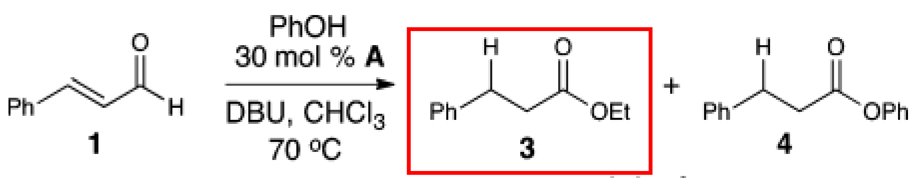
entry	ROH	pK_a(H_2O)	catalyst (mol %)	additive	yield (%)
1	EtOH	16	**A** (30 mol %)		30
2	CF_3CH_2OH	12	**A** (30 mol %)		17
3	PhOH	10	**A** (30 mol %)		42
4	4-NO_2-PhOH	7	**A** (30 mol %)		0
5	BnOH	15	**A** (30 mol %)	PhOH	58
6	BnOH	15	**B** (10 mol %)	PhOH	47
7	BnOH	15	**C** (20 mol %)	PhOH	82
8	BnOH	15	**C** (5 mol %)	PhOH	83

catalyst:



A **B** **C**

Scheme 2. Fortuitous Results



$CHCl_3$ is stabilized by EtOH **1:1 mixture**

The reason for the decreased yield:

- Decreased nucleophilicity for the regeneration of the catalyst
- Higher acidity could suppress the amount of carbine generated in situ

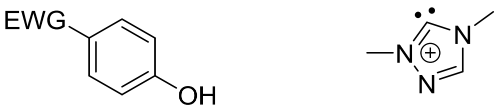
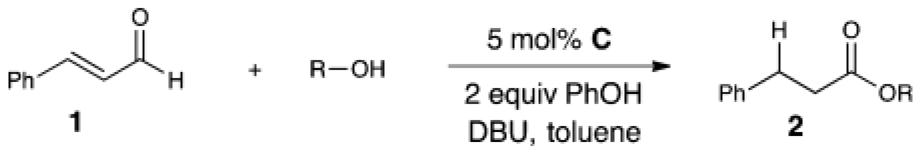
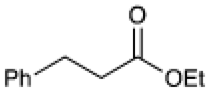
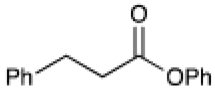
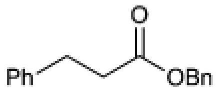
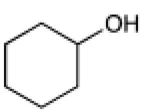
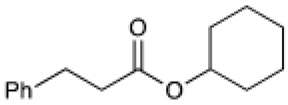
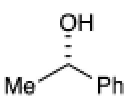
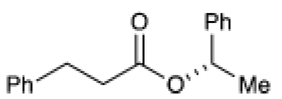
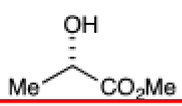
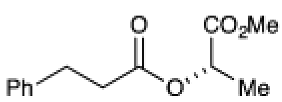
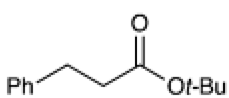
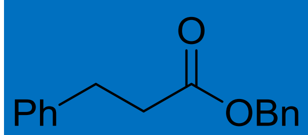


Table 2. Survey of Alcohols

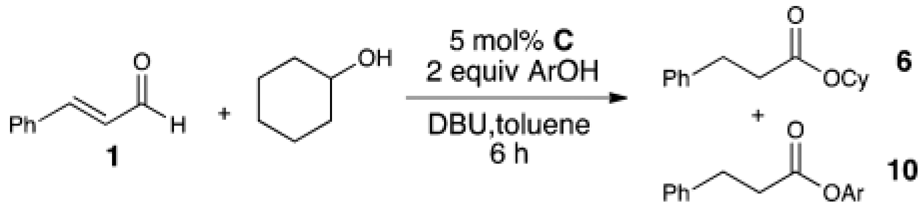


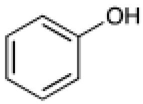
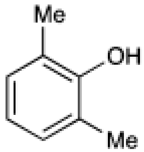
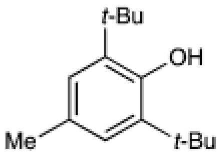
entry	ROH	time (h)	product		yield (%)
1	EtOH	4		**3**	72
2	PhOH	6		**4**	56
3	BnOH	2		**5**	82
4		6		**6**	57
5		6		**7**	77
6		6		**8**	61
7	*t*-BuOH	6		**9**	0



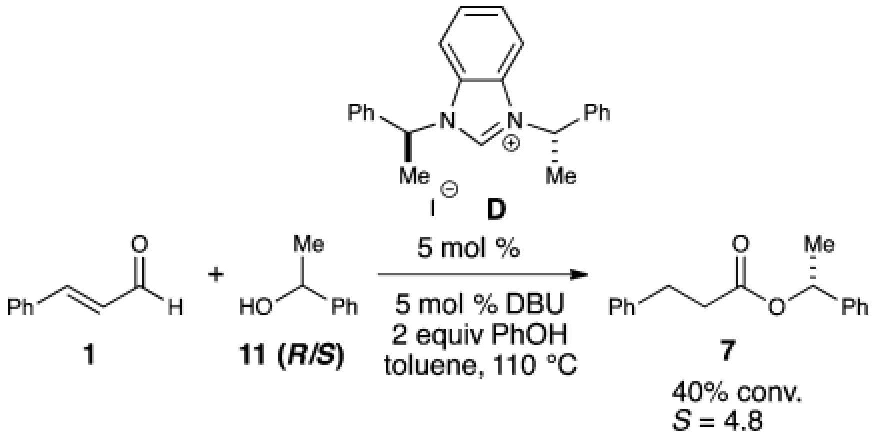
Byproduct

Table 3. Compatibility of Sterically Hindered Phenols



entry	ArOH	yield (%) of **6**	yield (%) of **10**
1		57	26
2		58	20
3		65	0

Scheme 3. Kinetic Resolution of Secondary Alcohols



Scheme 4. Amines as Turnover Reagents

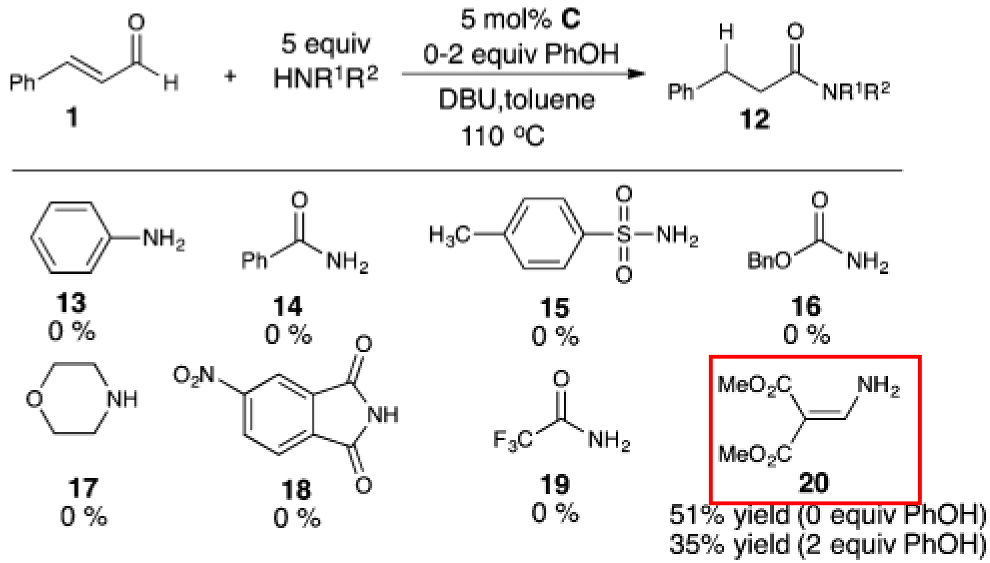
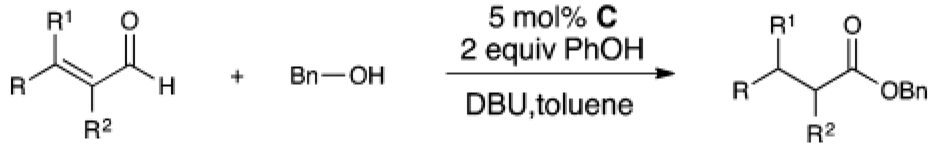
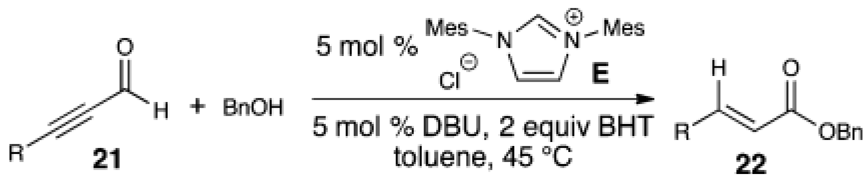


Table 4. Optimized NHC-Catalyzed β-Protonation



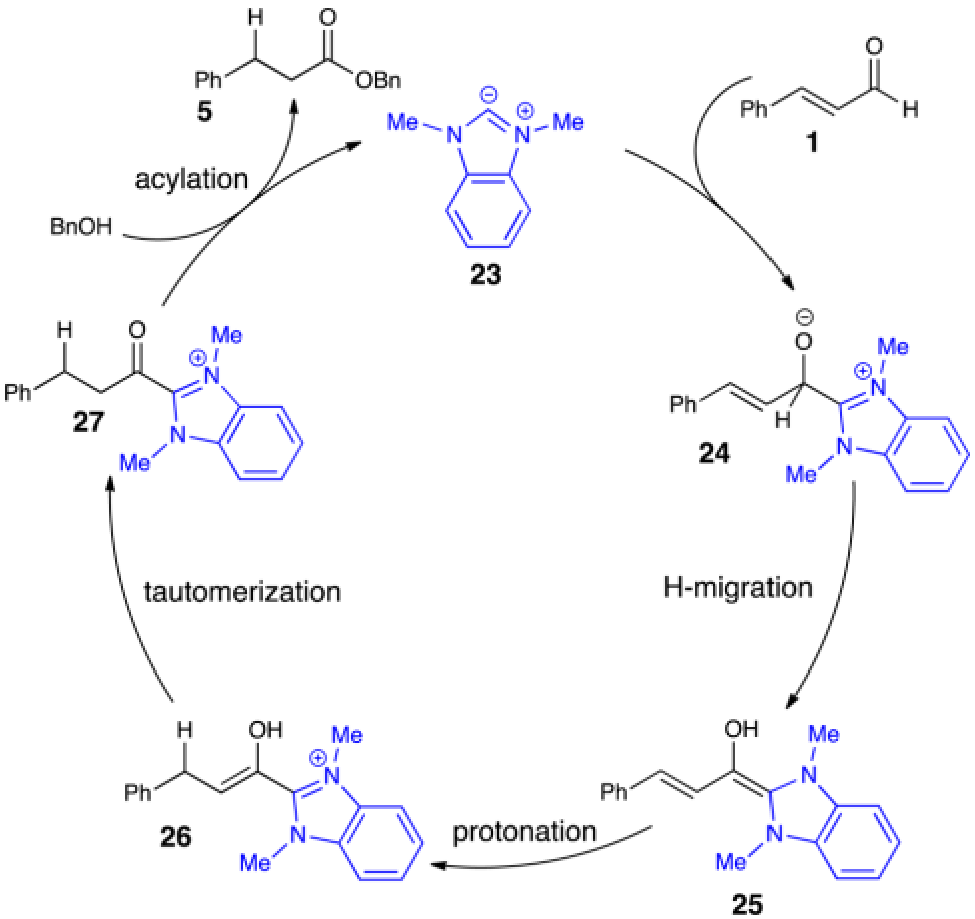
entry	R	R¹	R²	yield (%)
1	Ph	H	H	82
2	4-MeO-Ph	H	H	76
3	4-Cl-Ph	H	H	71
4	*n*-propyl	H	H	90
5	$H_3C(CH{=}CH)$	H	H	70
6	Ph	H	CH_3	82
7	Ph	Ph	H	82
8	4-Cl-Ph	Ph	H	86
9	CH_3	CH_3	H	NR

Table 5. β-Protonation of Ynals

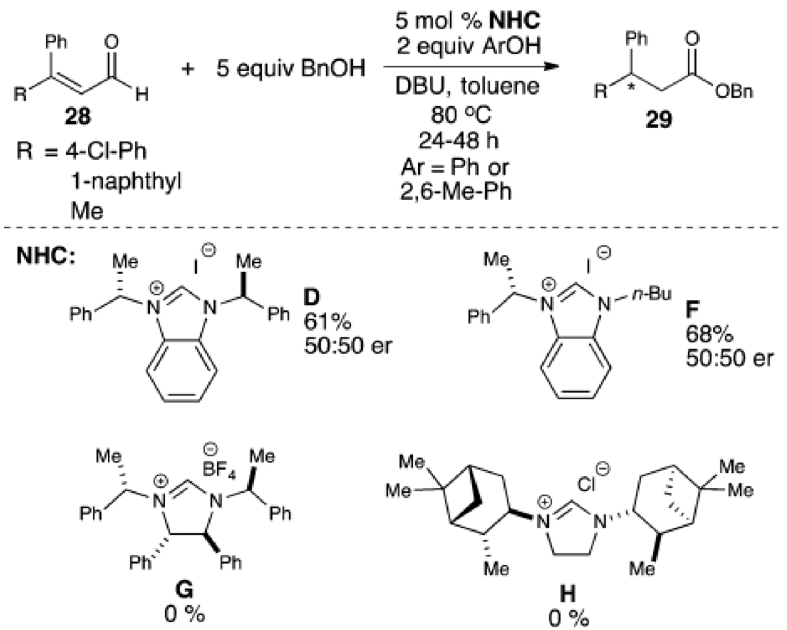


entry	R	NHC	yield (%)	*E*/*Z*
1	Ph	**C**	65	3:1
2	Ph	**E**	67	>20:1
3	4-Cl-Ph	**C**	56	3:1
4	4-Cl-Ph	**E**	59	>20:1
5	4-MeO-Ph	**C**	10	4:1
6	$TBSO(CH_2CH_2)$	**C**	0	

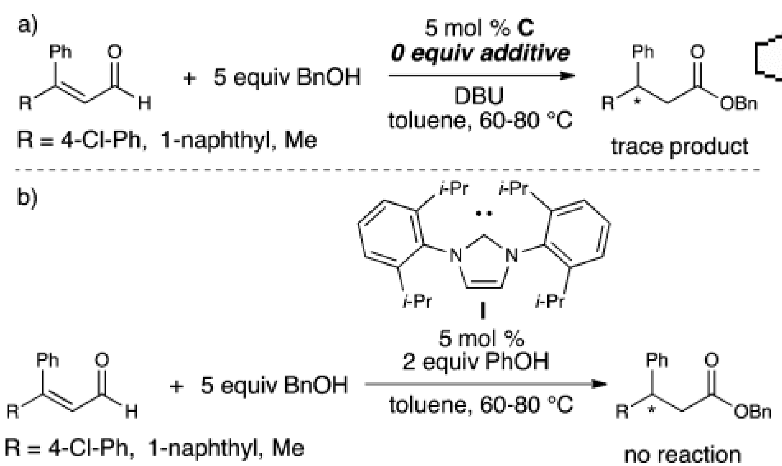
Scheme 5. Proposed Mechanism for *β*-Protonation



Scheme 6. Exploration of Chiral NHCs for Asymmetric β-Protonation



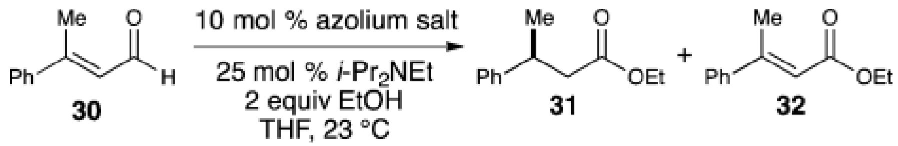
Scheme 7. Control Experiments



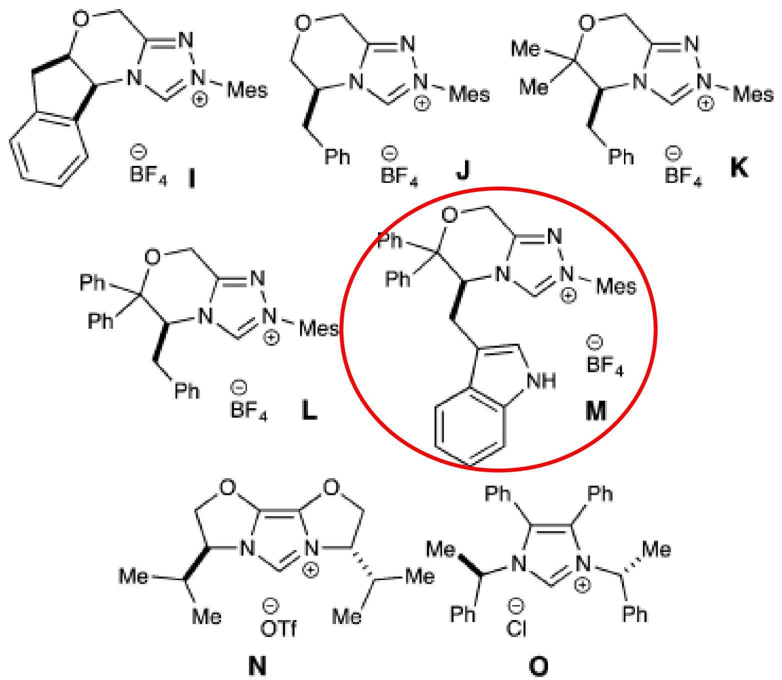
BINOL and TADDOL in place of BHT with NHC precatalyst C led to only trace amounts of product.

Simpkin's base derivatives, sparteine, and cinchona alkaloid derivatives funished racemic products.

Table 6. Asymmetric Protonation of Homoenolate Equivalents



entry	azolium salt	yield (%) of **31** + **32**	er of **31**
1	**I**	51	67:33
2	**J**	trace	55:45
3	**K**	trace	62:38
4	**L**	58	78:22
5	**M**	45	80:20
6	**N**	0	
7	**O**	0	



Scheme 8. Proposed Mechanism for Oxidative Pathway

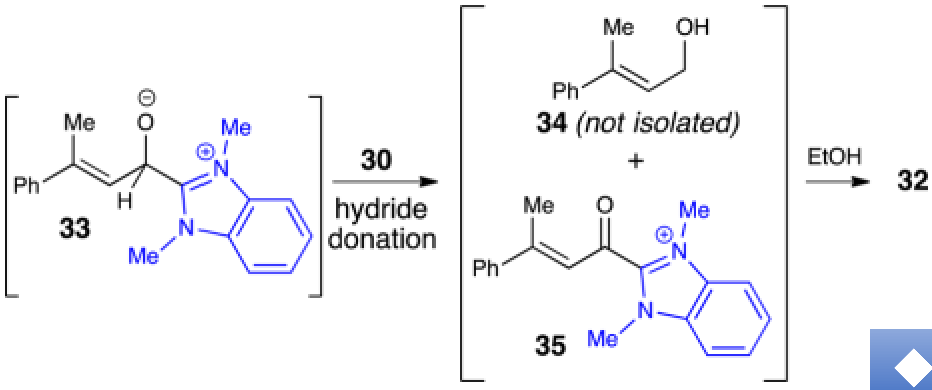
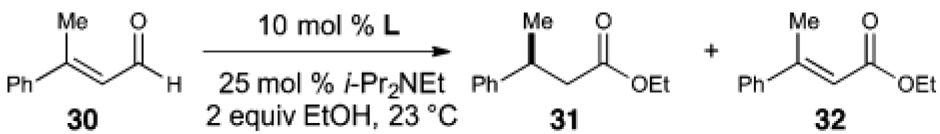


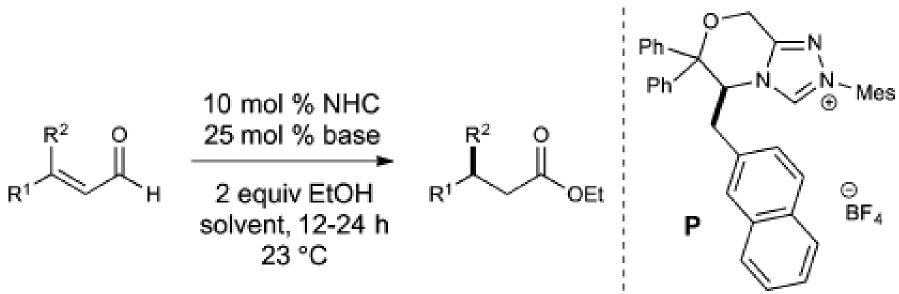
Table 7. Solvent Effect on β-Protonation



entry	solvent	yield (%, **31** + **32**)	ratio **31**:**32**	er of **31**
1	THF	**58**	3:1	78:22
2	toluene	**81**	13:1	77:23

- The divergent pathways of β-protonation
- Oxidation

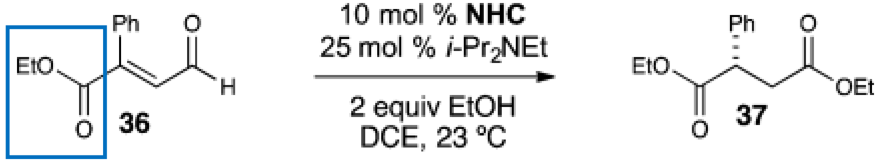
Table 8. New Solvent for Asymmetric β-Protonation



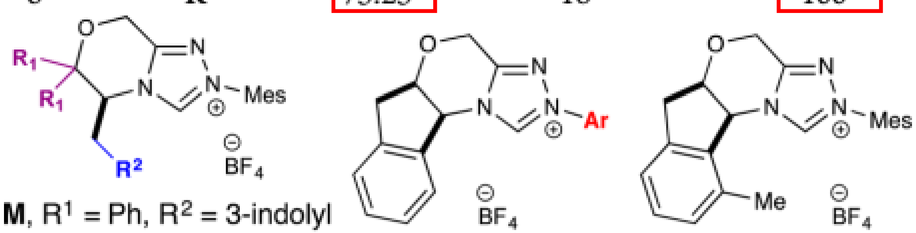
The yield was still low

entry	R^1	R^2	NHC	base	solvent	yield (%)	er
1	Ph	Me	**P**	*i*-Pr_2NEt	DCE	48	92:8
2	Ph	$-CH_2CH_2O-$	**L**	*i*-Pr_2NEt	DCE	66	85:15
3	Ph	*i*-Pr	**L**	K_3PO_4	EtOAc	51	78:22
4	4-MeO-Ph	Me	**L**	*i*-Pr_2NEt	DCE	30	85:15
5	4-CF_3-Ph	Me	**M**	K_3PO_4	EtOAc	39	80:20
6	2-F-Ph	Me	**L**	*i*-Pr_2NEt	DCE	43	68:32

Table 9. Catalyst Screen



entry	NHC	er	time (h)	conversion (%)
1	M	55:45	18	100
2	L	58:42	12	100
3	K	66:34	2	100
4	I	57:43	12	100
5	Q	58:42	18	100
6	R	75:25	18	100

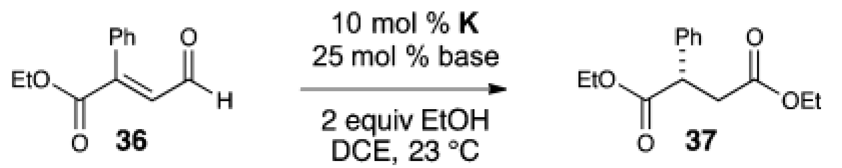


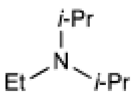
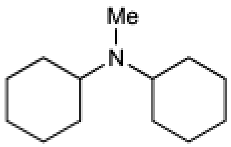
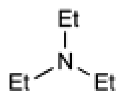
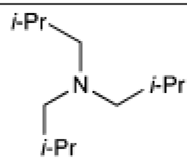
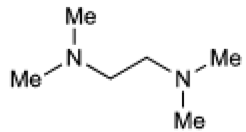
M, R^1 = Ph, R^2 = 3-indolyl
L, R^1 = Ph, R^2 = Ph
K, R^1 = Me, R^2 = Ph

I, Ar = Mes
Q, Ar = 2,6-Et_2-Ph

R

Table 10. Base Screen



				
38	**39**	**40**	**41**	**42**
66:34 er	64:36 er	64:36 er	61:39 er	60:40 er
2 h	2 h	2 h	36 h	2 h

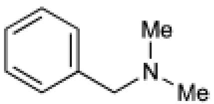
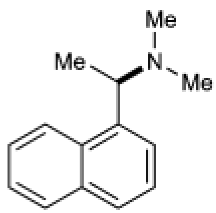
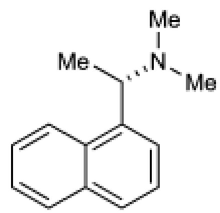
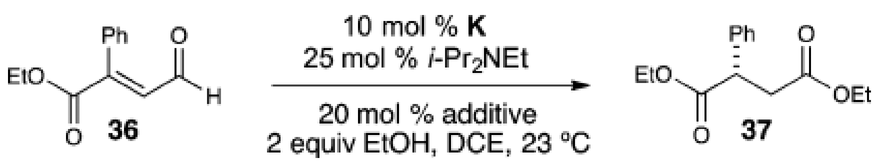
			
43	**44**	**45**	**46**
55:45 er	61:39 er	57:43 er	57:43 er
2 h	2 h	2 h	2 h

Table 11. Lewis Acid Additives



additive	time (h)	conv. (%)	er
none	2	100	66:34
$Mg(Ot\text{-}Bu)_2$	24	50	65:35
$Ti(Oi\text{-}Pr)_4$	16	100	70:30
$Sc(OTf)_3$	18	100	64:36
LiCl	12	100	80:20

Table 12. Effects of HBD Additives

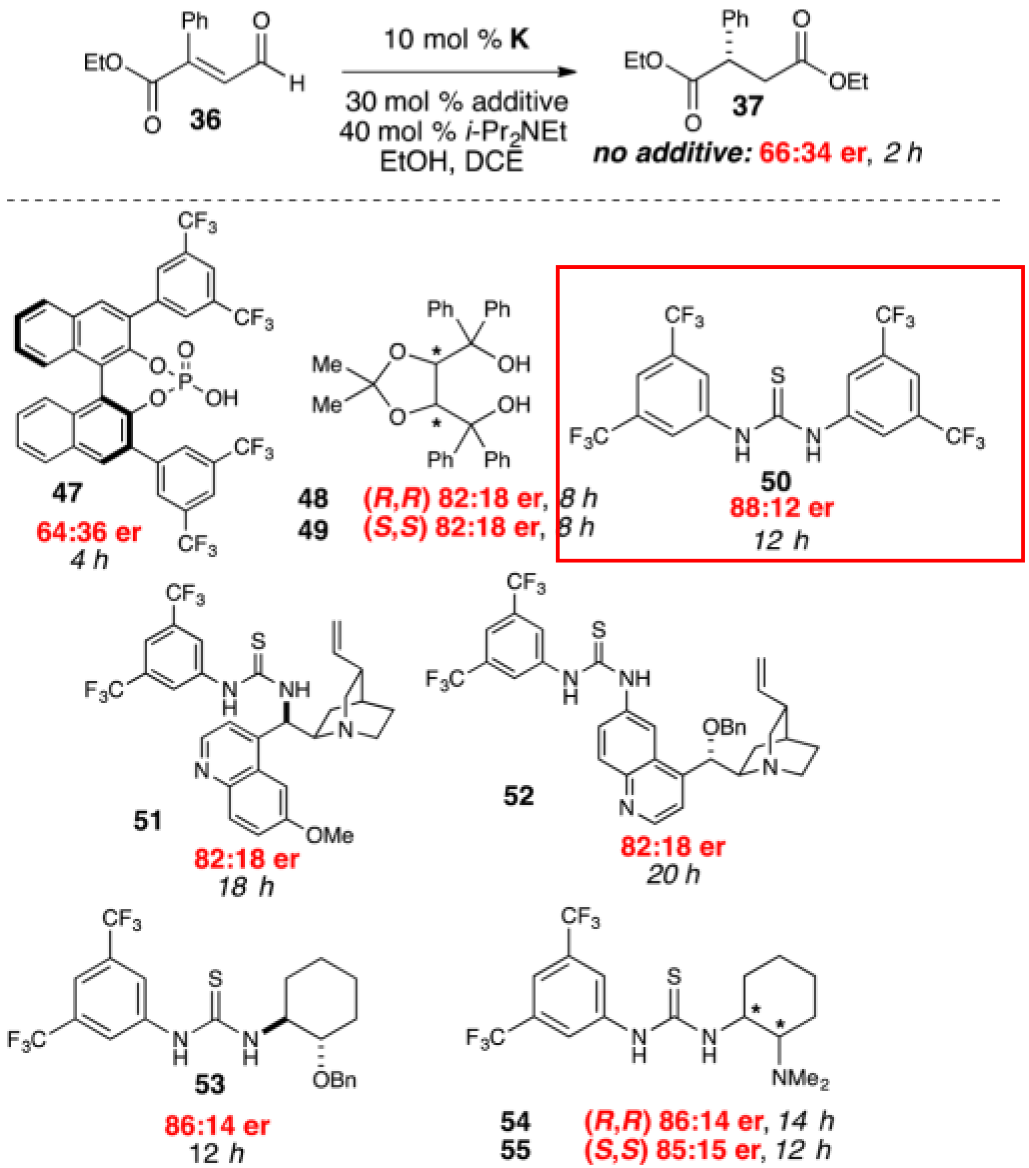
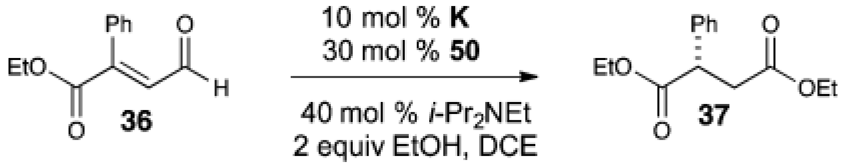


Table 13. Temperature and Additive Effects on β-Protonation



entry	temp (°C)	additive	yield (%)	er
1	45		48	58:42
2	23		44	88:12
3	0		41	93:7
4	0	20 mol % DMAP	69	85:15
5	0	10 mol % DMAP	68	92:8

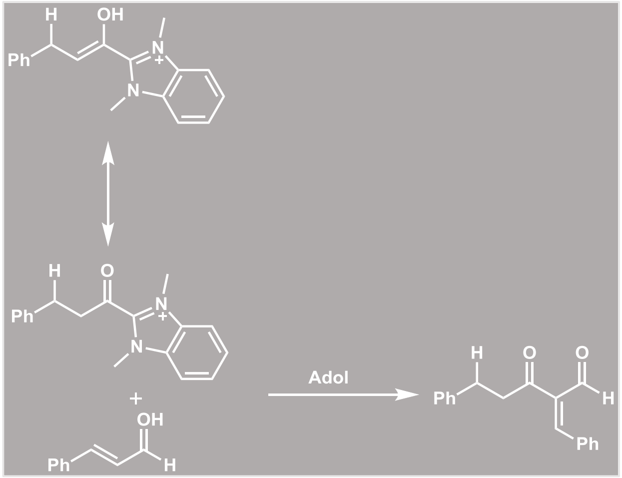
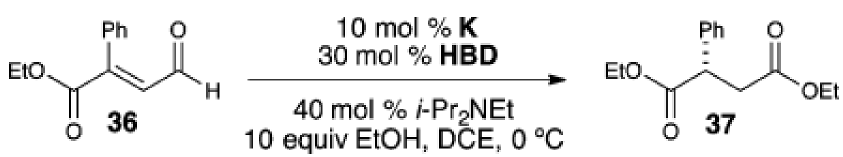
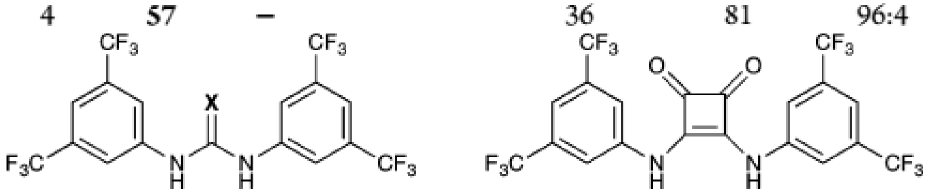


Table 14. Varying the Cocatalysts



entry	HBD	additive	time (h)	yield (%)	er
1	**50**	10 mol % DMAP	18	68	92:8
2	**56**	10 mol % DMAP	24	84	91:9
3	**57**	10 mol % DMAP	24	94	91:9
4	**57**	–	36	81	96:4



50, X = S
56, X = O

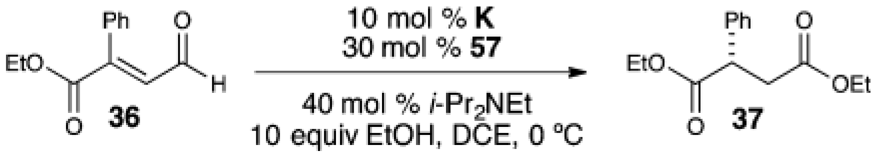
57

Its Solubility in DCE is low

To prevent the Adol reaction:

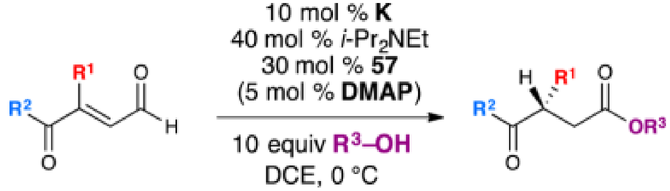
- Use sterically hindered NHCs
- The addition of acyl transfer catalyst : DMAP

Table 15. Impact of H_2O on β-Protonation Selectivity

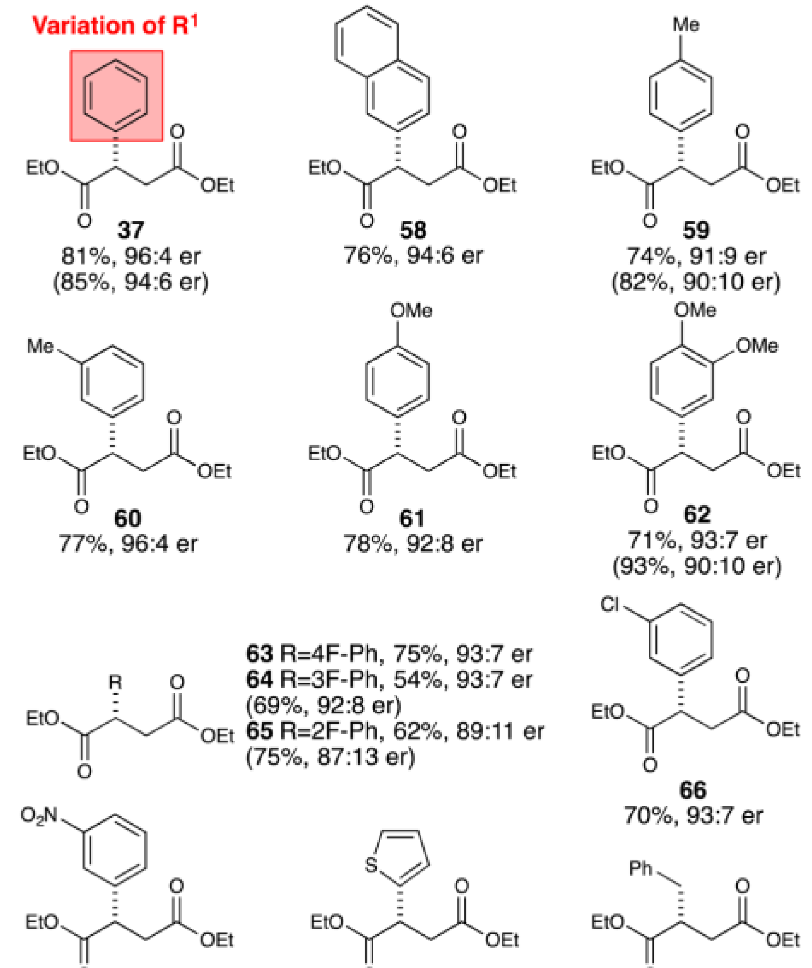


entry	H_2O (equiv)	time (h)	yield (%)	er
1	0	36	80	90:10
2	0.25	30	86	93:7
3	0.5	24	84	95:5
4	1	24	80	90:10

Table 16. Variation of β-Substituent[a]



Variation of R1



37 81%, 96:4 er (85%, 94:6 er)

58 76%, 94:6 er

59 74%, 91:9 er (82%, 90:10 er)

60 77%, 96:4 er

61 78%, 92:8 er

62 71%, 93:7 er (93%, 90:10 er)

63 R=4F-Ph, 75%, 93:7 er
64 R=3F-Ph, 54%, 93:7 er (69%, 92:8 er)
65 R=2F-Ph, 62%, 89:11 er (75%, 87:13 er)

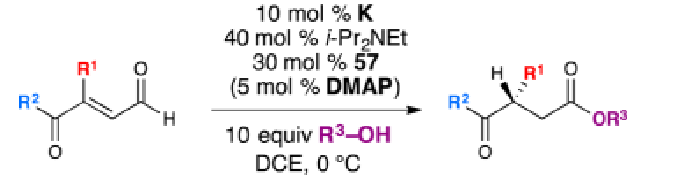
66 70%, 93:7 er

67 57%, 89:11 er (68%, 83:17 er)

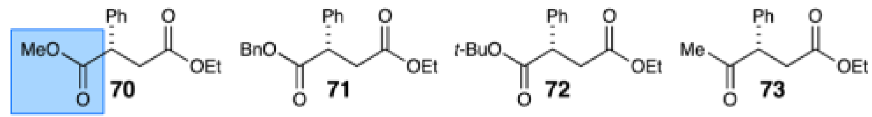
68 61%, 95:5 er (80%, 77:23 er)

69 44%, 92:8 er (57%, 85:15 er)

Table 17. Variation of the Ester[a]



Variation of R2



70 72%, 90:10 er

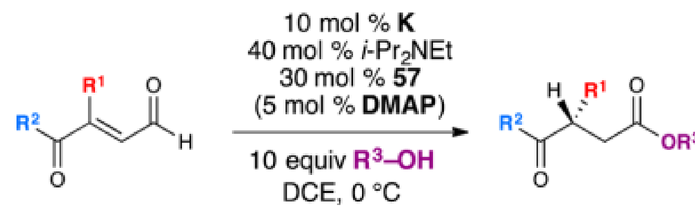
71 69%, 95:5 er

72 76%, 97:3 er

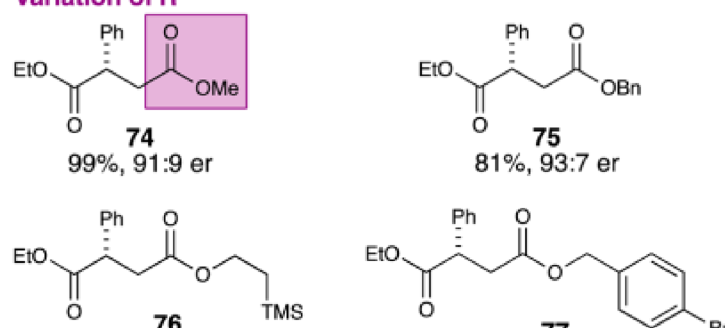
73 62%, 83:17 er

[a]Yields are of isolated product after column chromatography. Enantiomeric ratio (er) was determined by chiral HPLC analysis.

Table 18. Variation of the Alcohol[a]



Variation of R3



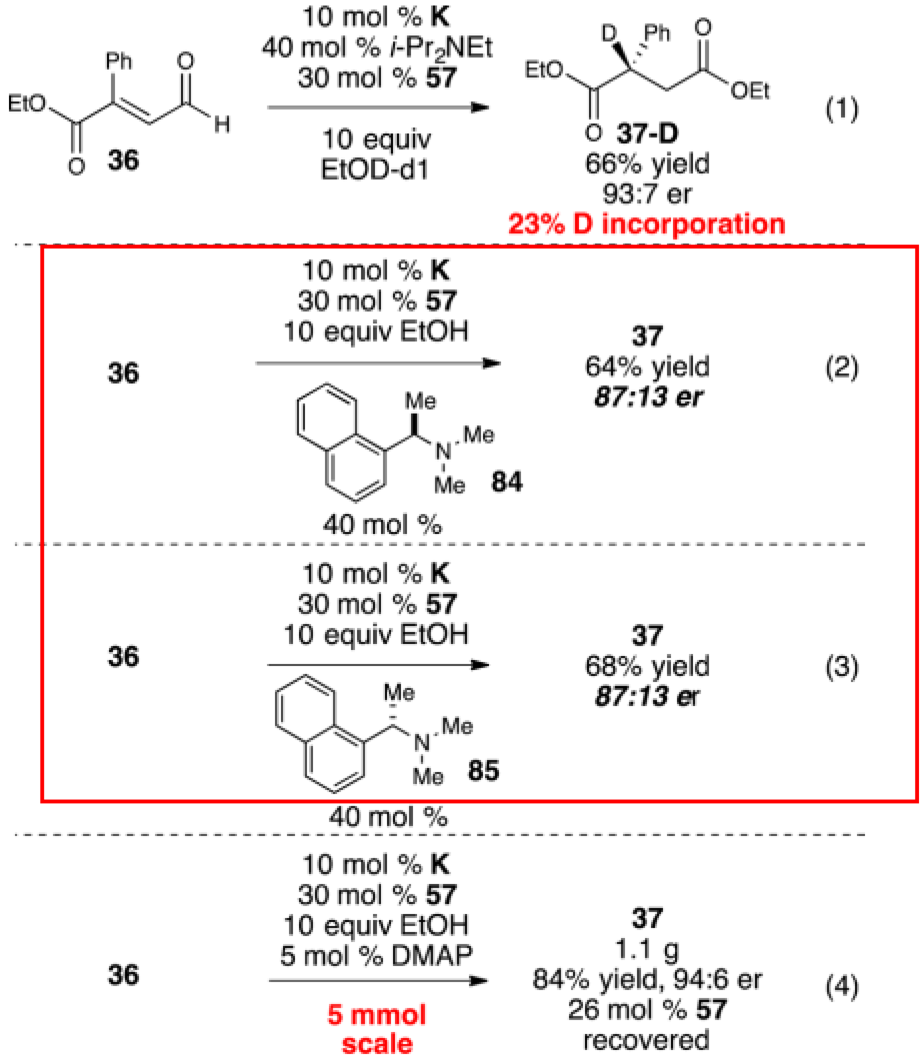
74 99%, 91:9 er

75 81%, 93:7 er

76 62%, 91:9 er

77 71%, 93:7 er
64%, 99:1 after recrystallization

Scheme 10. Control Experiments



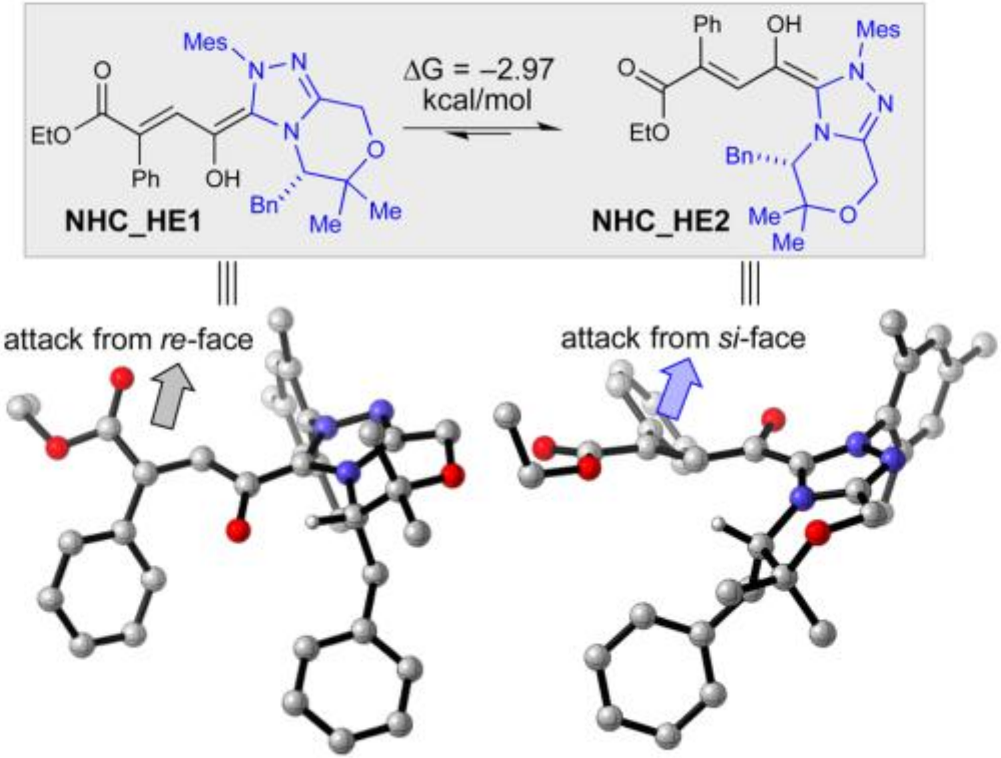


Figure 2. DFT calculations of extended Breslow intermediate.

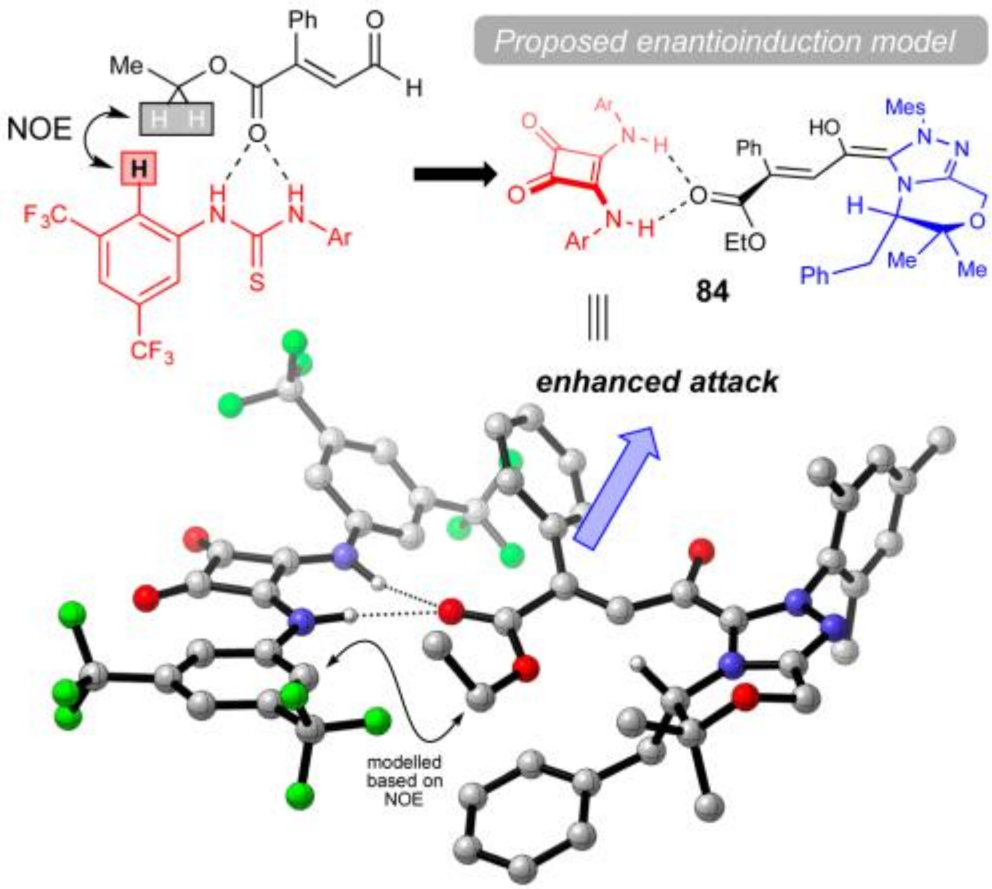
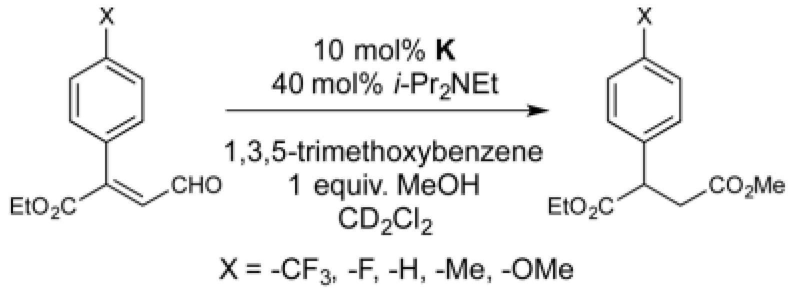
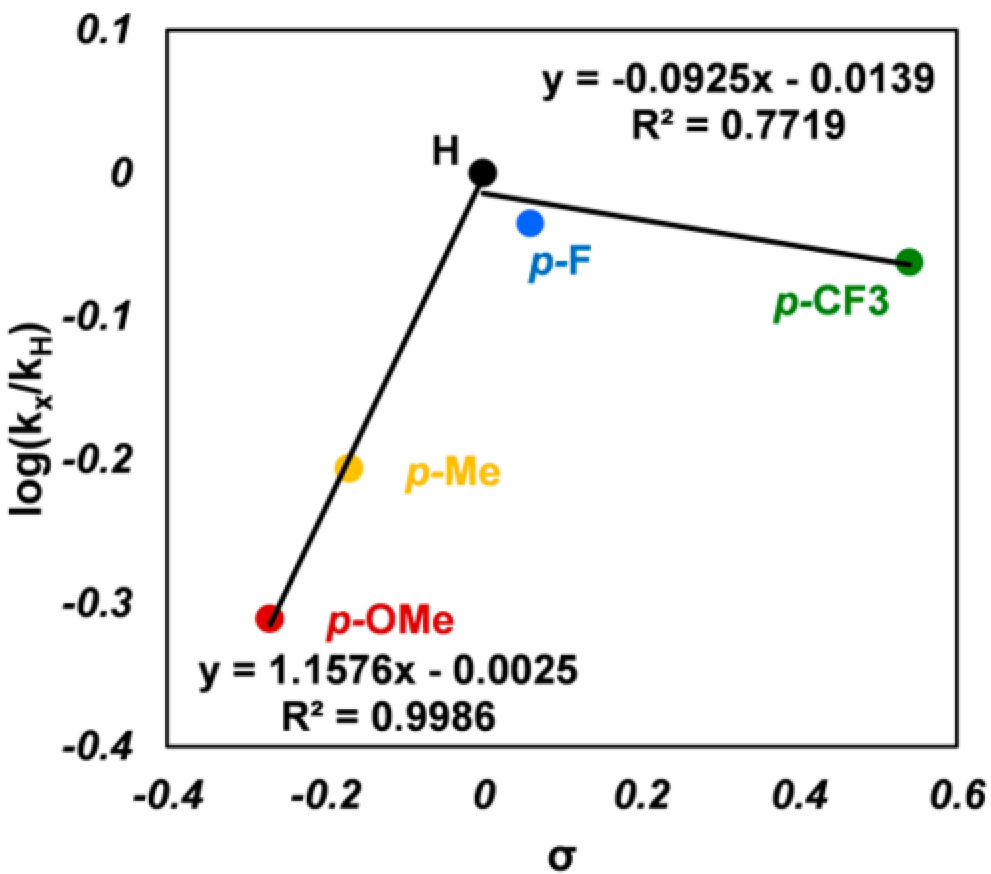


Figure 3. Enantioinduction model.


X
10 mol% K
40 mol% i-Pr2NEt
1,3,5-trimethoxybenzene
1 equiv. MeOH
CD2Cl2
EtO2C
CHO
CO2Me
X = -CF3, -F, -H, -Me, -OMe


y = -0.0925x - 0.0139
R² = 0.7719
H
p-F
p-CF3
p-Me
p-OMe
y = 1.1576x - 0.0025
R² = 0.9986
log(kx/kH)
σ
0.1
0
-0.1
-0.2
-0.3
-0.4
-0.4
-0.2
0
0.2
0.4
0.6

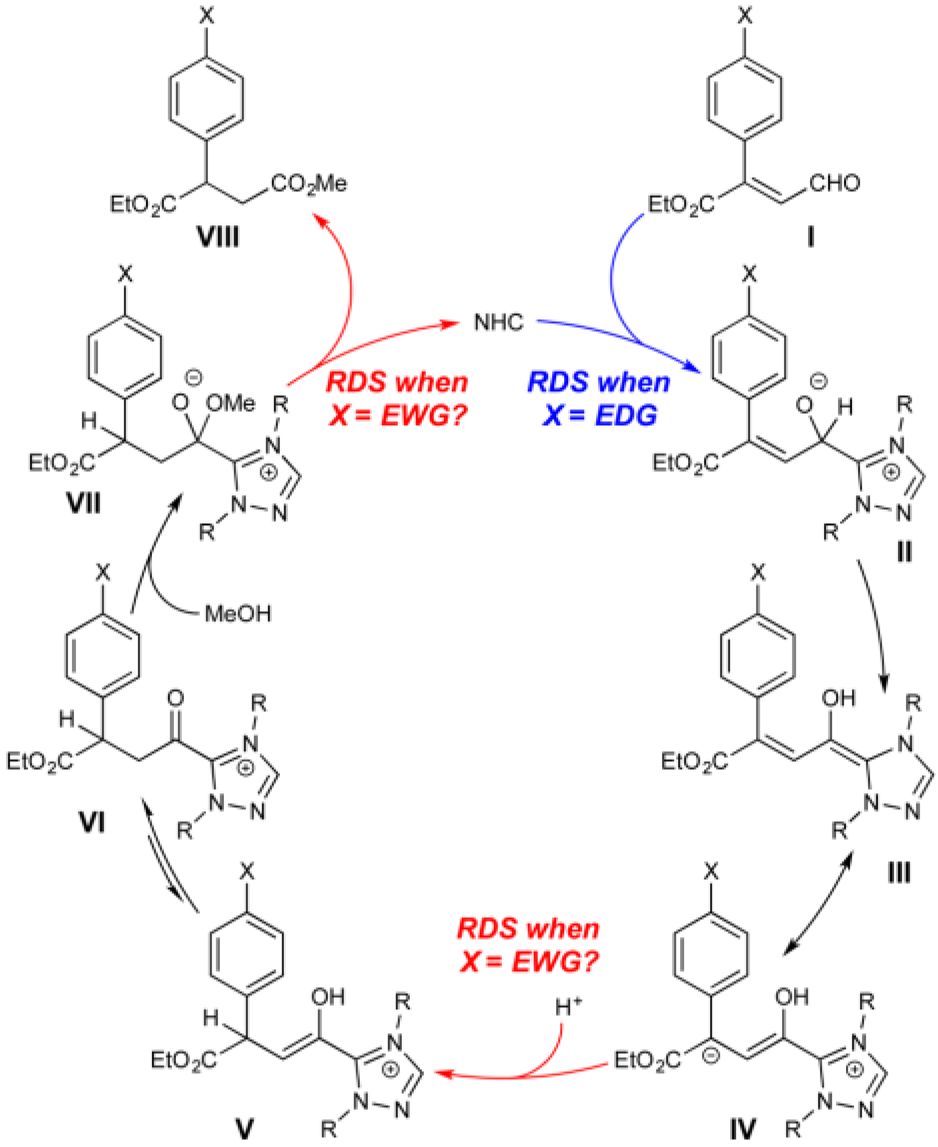
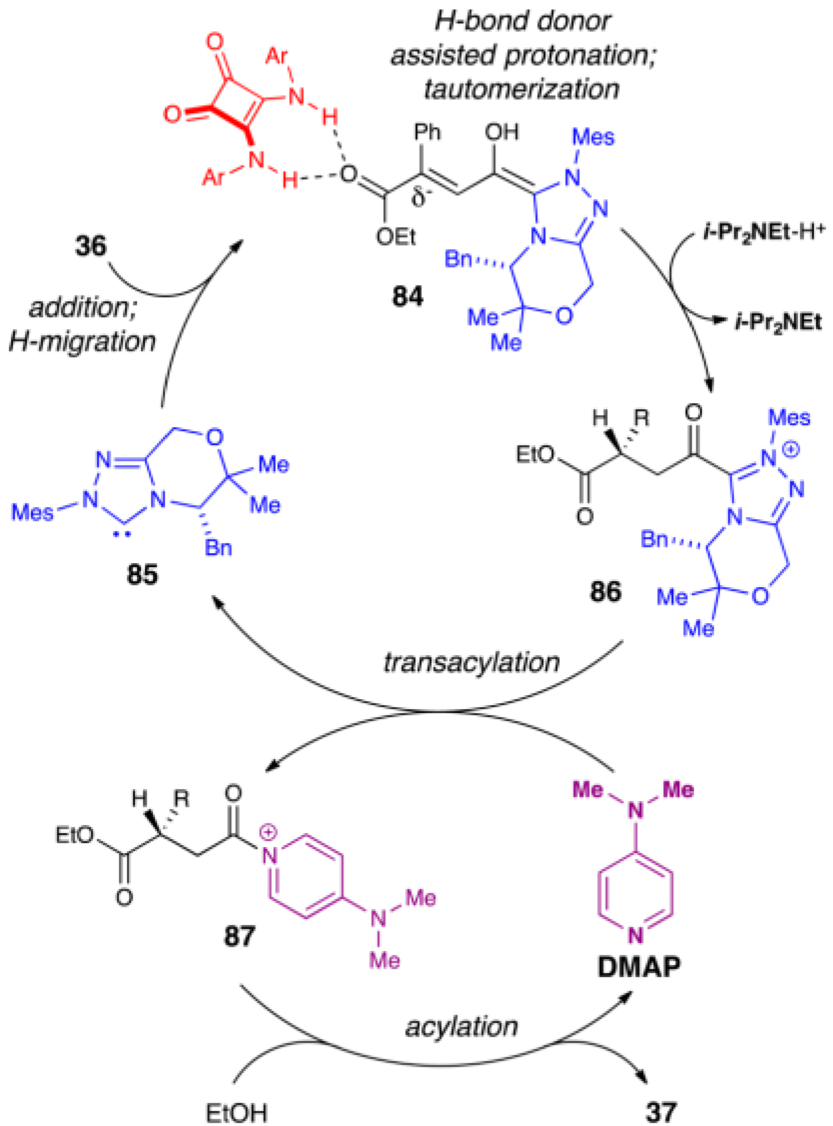
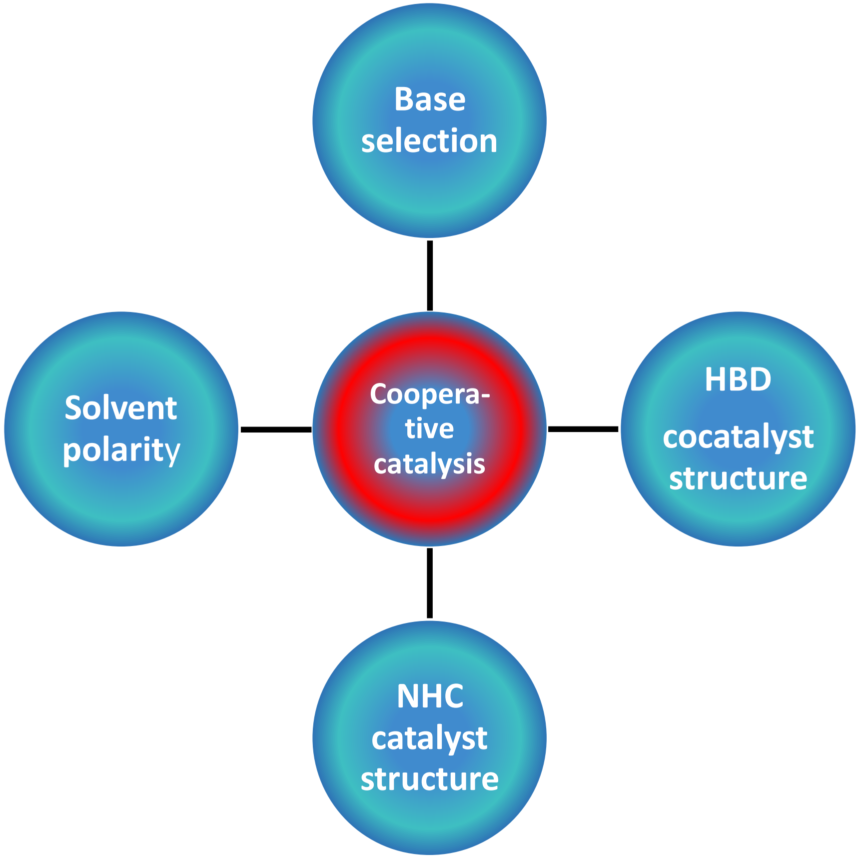


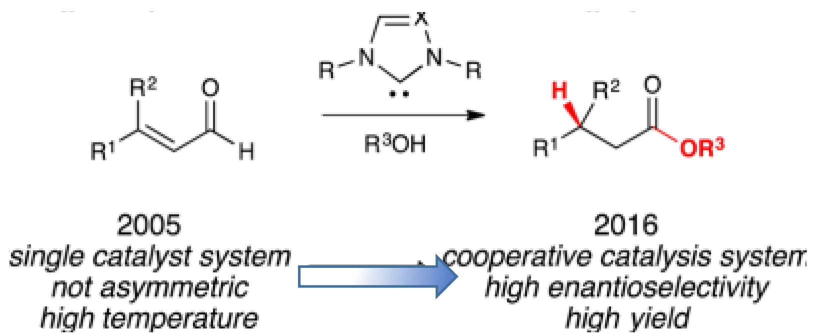
Figure 4. Hammett plot and proposed mechanism.

Scheme 11. Proposed Reaction Pathway

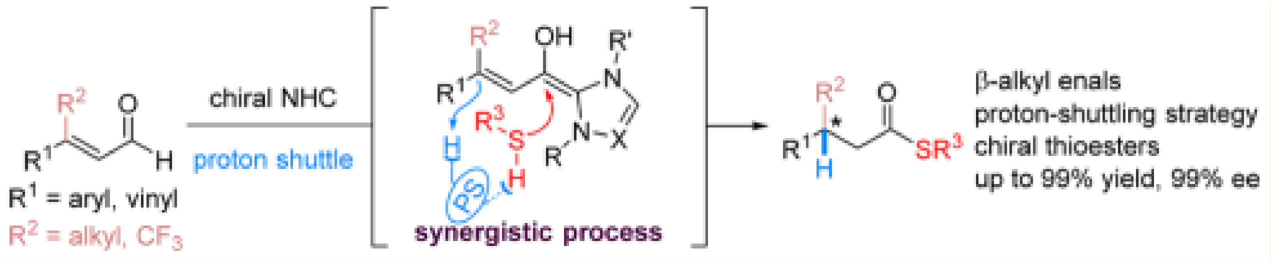


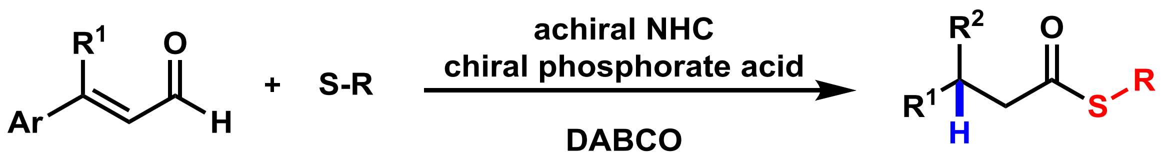
3. Summary and Outlook

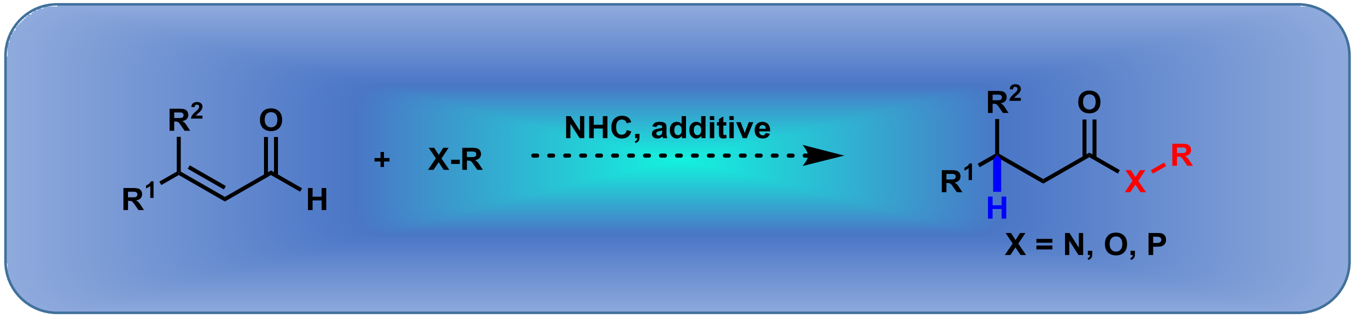




Achieved a high yielding, highly enantioselective NHC-catalyzed β-protonation using a cooperative catalysis approach.







Y. Huang. *J. Am. Chem. Soc.* **2017**, *139*, 7045-7051
J. C., Y. Huang. *ChemComm* . Online.

4. Acknowledgement