Literature Report IV

Carbonyl Catalysis Enables a Biomimetic Asymmetric Mannich Reaction

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Checker: Chang-Bin Yu
Date: 2018-10-15

Guo, Q,-X. *et al. Chem. Sci.* **2014**, *5*, 1988.
Zhao, B. *et al. Science* **2018**, *360*, 1438.

CV of Professor Baoguo Zhao

Background:

- **1992-1996** B.S. in Wuhan University;
- **1999-2002** M.S. in Nanjing University;
- **2002-2006** Ph.D. in SIOC, CAS;
- **2006-2011** Postdoctoral, Colorado State University;
- **2011-Now** Professor, Shanghai Normal University

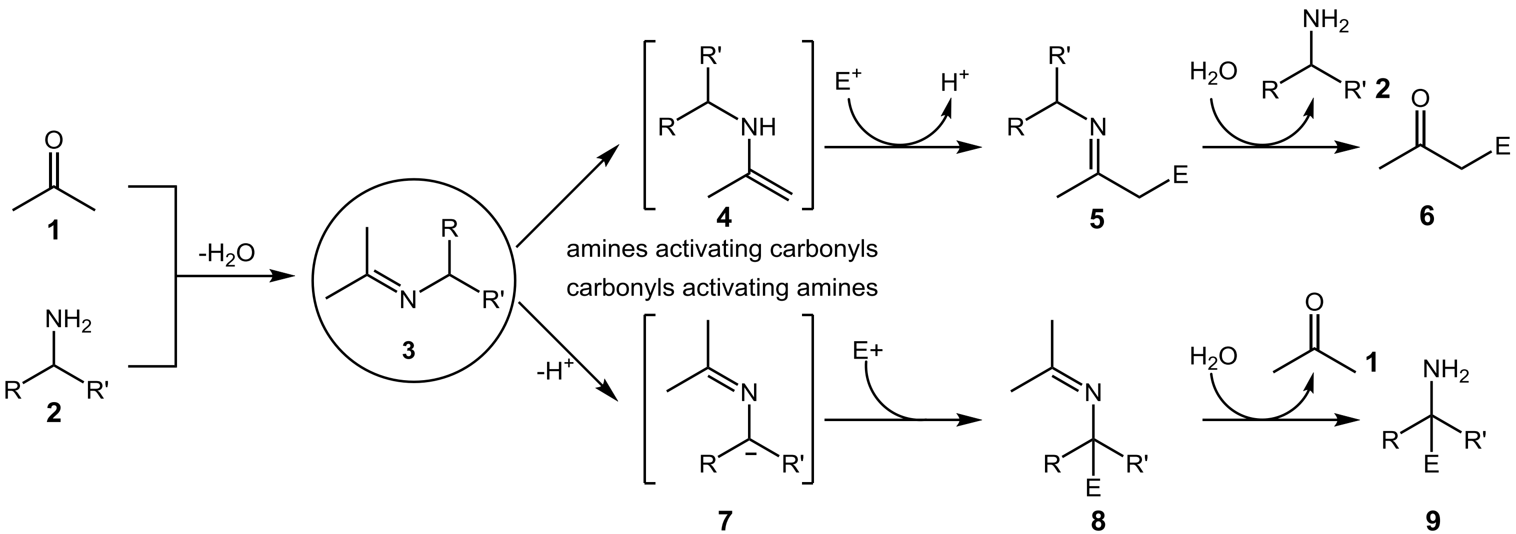
Baoguo Zhao

Research:

- Biomimetic Asymmetric Catalysis;
- Biomimetic Total Synthesis

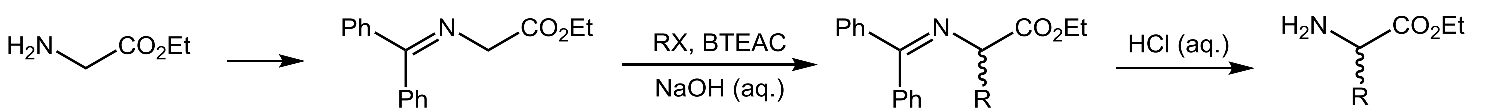
Contents

Introduction



High atomic economy

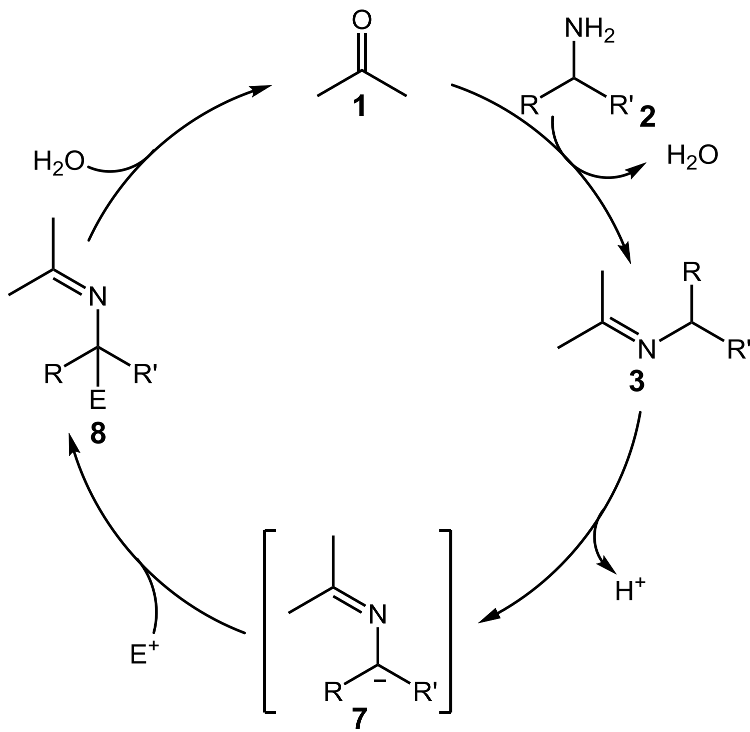
The first synthesis of racemic α-amino acids



PKa = 18.7 BTEAC = Benzyltriethylammonium chloride

O'Donnell, M. J. *et al. Tetrahedron Lett*.**1978**, *47*, 4625.
O'Donnell, M. J. *Acc. Chem. Res*. **2004**, *37*, 506.
List, B. *et al. Chem. Rev.* **2007**, *107*, 5413.

Carbonyl Catalysis



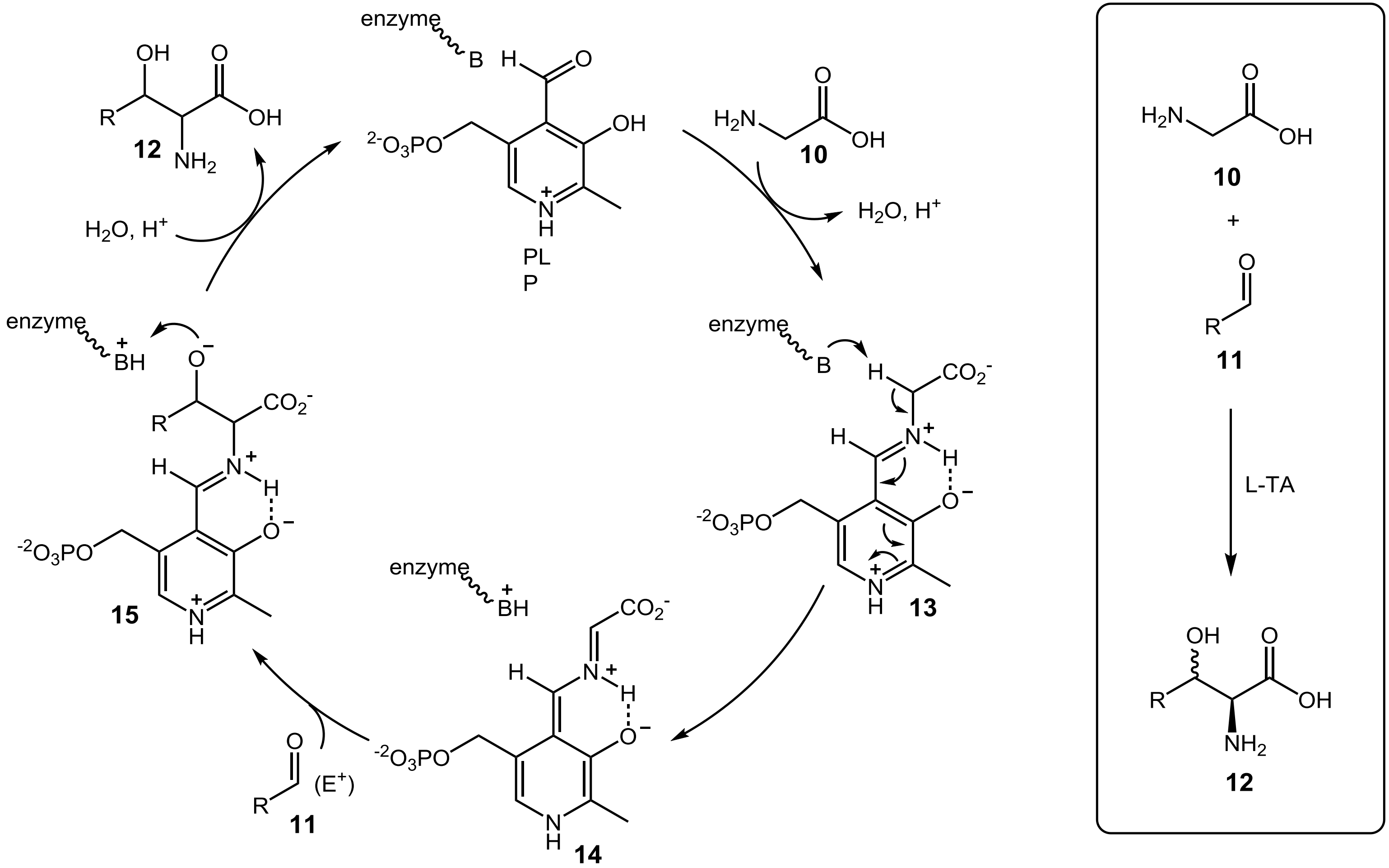
An ideal reaction should meet the following requirements:

a) Carbonyl catalyst **1** must be electron-withdrawing enough to promote deprotonation to form *α*-amino anion **7** for further reaction with an electrophile;

b) Both the carbonyl catalyst **1** and the imine intermediate **3** should be much less reactive than the electrophile in competition for the active *α*-amino anion **7** under the reaction conditions;

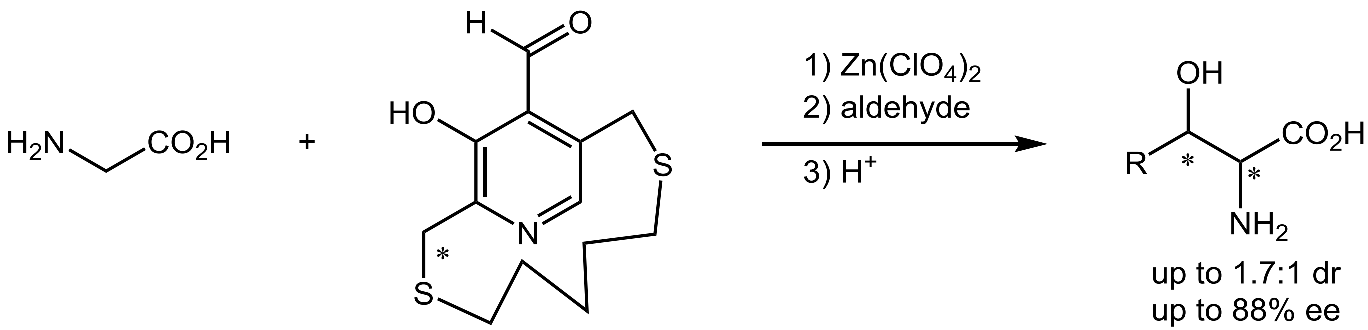
c) For an asymmetric version, carbonyl catalyst **1** should control positioning of the incoming electrophile.

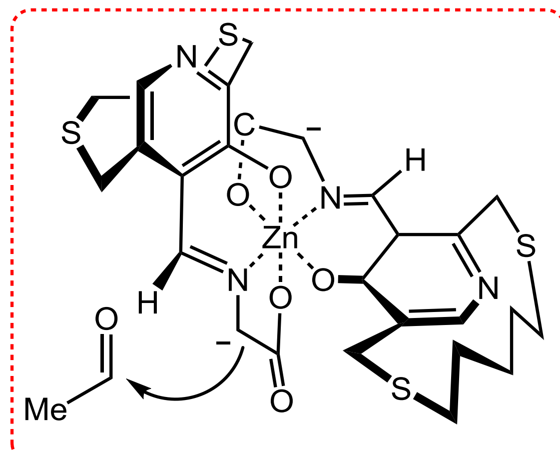
Carbonyl Catalysis in Biological Systems



Kimura, T. *et al*. *J. Am. Chem. Soc.* **1997**, *119*, 11734.
Vivoli, M. *et al. FEBS J*. **2014**, *281*, 129.

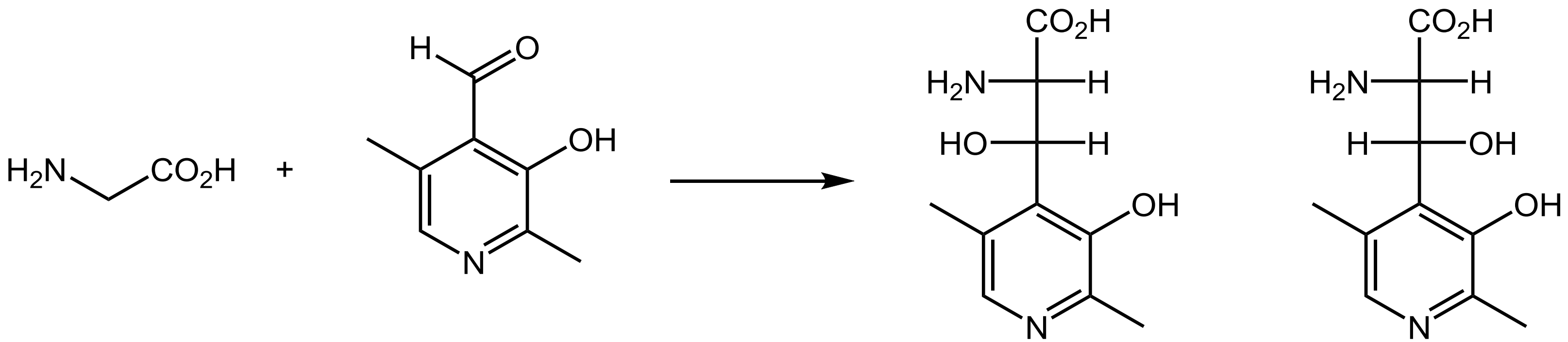
Studies on Imitating the Biological Process





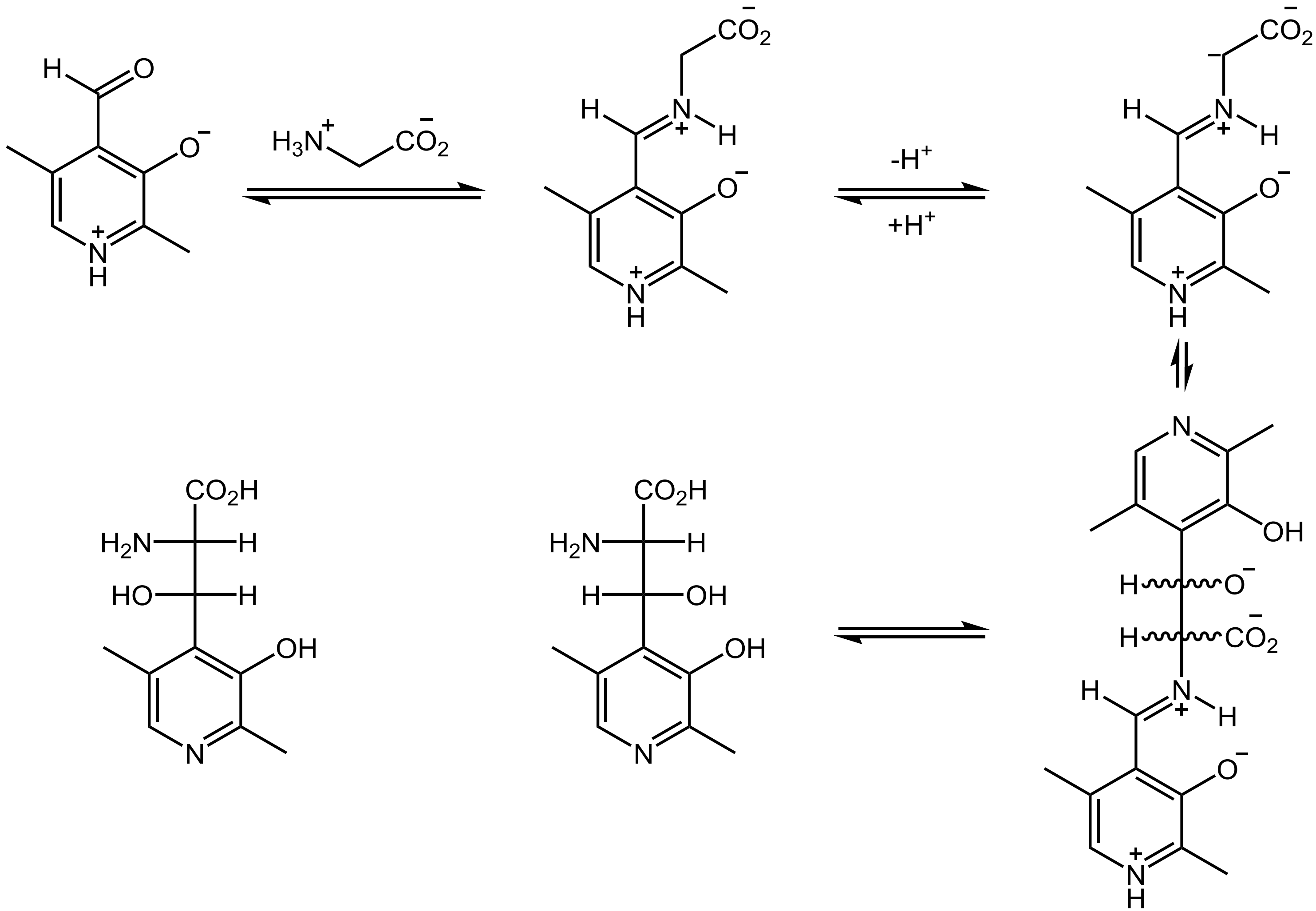
Kuzuhara, H. *et al. J. Chem. Soc. Chem. Commun*. **1987**, *2*, 95.

Claisen-Type Addition of Glycine to Pyridoxal



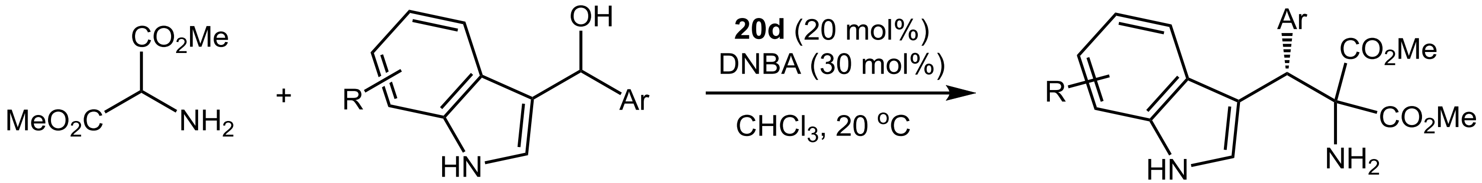
Richard, J. P. G. *et al. J. Am. Chem. Soc.* **2004**, *126*, 10538.

Claisen-Type Addition of Glycine to Pyridoxal

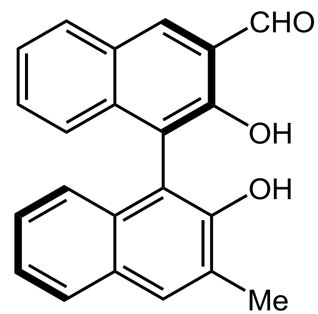


Richard, J. P. G. *et al. J. Am. Chem. Soc.* **2004**, *126*, 10538.

Chiral Aldehyde Catalyzed *α*-Alkylation Reaction



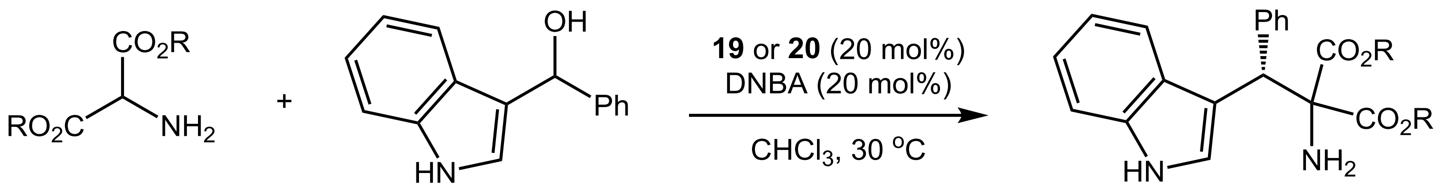
16 **17** **18** 33-88% yield
77-98% ee



20d

Guo, Q,-X. *et al. Chem. Sci.* **2014**, *5*, 1988.

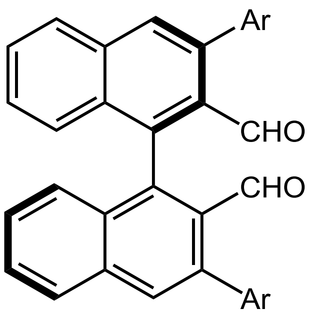
Optimization of Reaction Conditions



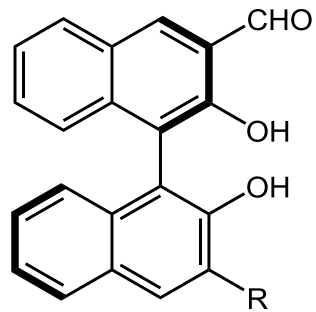
16a: R = Et
16b: R = Me

17a

18a: R = Et
18b: R = Me



19a: Ar = Ph
19b: Ar = 2-naphthyl
19c: Ar = 4-^{t}Bu
19d: Ar = 3,5-$F_2C_6H_3$



20a: R = H
20b: R = Ph
20c: R = 9-Anthracene
20d: R = Me
20e: R = Et

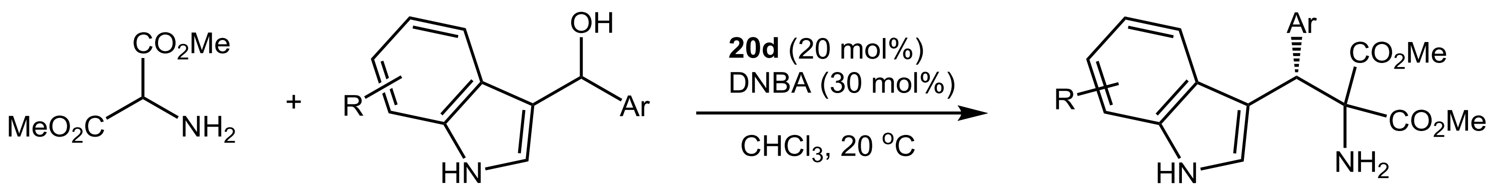
Entry[a]	Cat.	**16**	Time (h)	Yield (%)[b]	Ee (%)[c]
1	**19a**	**16a**	24	24	50
2[d]	-	**16a**	12	0	-
3	**19b**	**16a**	30	37	55
4	**19c**	**16a**	40	42	64
5	**19d**	**16a**	30	32	66

Optimization of Reaction Conditions

Entry	Cat.	**16**	Time (h)	Yield (%)[b]	Ee (%)[c]
6	**20a**	**16a**	4	66	71
7	**20b**	**16a**	6	57	81
8	**20c**	**16a**	5	61	77
9	**20b**	**16b**	4	57	82
10	**20b**	**16b**	4	65	84[e]
11	**20e**	**16b**	6	60	84[e]
12	**20d**	**16b**	6	77	86[e]
13	**20d**	**16b**	6	72	87[e,f]
14	**20d**	**16b**	9	68	86[e,g]
15	**20d**	**16b**	12	55	85[e,h]

[a] Entries 1-4: **16** (0.2 mmol), **17a** (0.1 mmol), **19** or **20** (0.02 mmol), $CHCl_3$ (1 mL), 30 ^oC; 5–15: **16** (0.4 mmol), **17a** (0.2 mmol), **19** or **20** (0.04 mmol), $CHCl_3$ (2 mL), 30 ^oC. [b] Isolated yield. [c] Determined by HPLC. [d] No catalyst added. [e] At 20 ^oC. [f] Using 50 mol% DNBA. [g] Using 15 mol% **20d**. [h] Using 10 mol% **20d**.

Substrate Scope



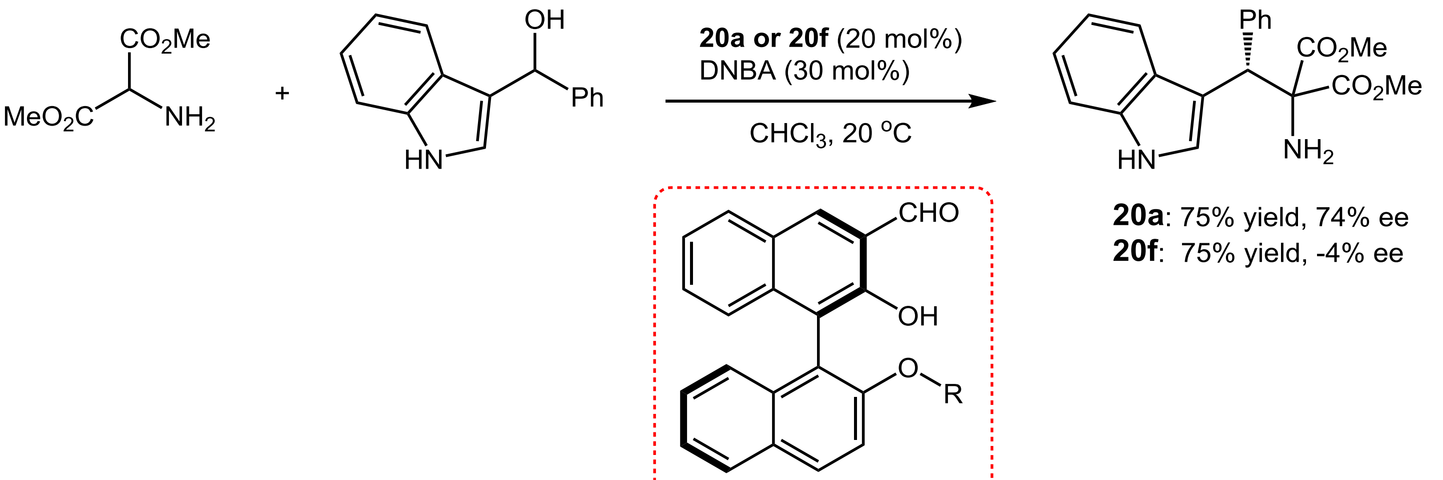
Entry[a]	**18**	Ar	R	Time (h)	Yield (%)[b]	Ee (%)[c]
1	**18b**	Ph	H	6	77	86
2	**18c**	2-ClC_6H_4	H	48	68	92
3	**18d**	2-BrC_6H_4	H	24	64	96
4	**18e**	2-FC_6H_4	H	24	62	91
5	**18f**	2-$O_2NC_6H_4$	H	120	49	95
6	**18g**	2-$MeOC_6H_4$	H	7	59	82
7	**18h**	3-FC_6H_4	H	5	88	87
8	**18i**	3-MeC_6H_4	H	18	42	84
9	**18j**	3-$MeOC_6H_4$	H	6	77	87
10	**18k**	4-MeC_6H_4	H	7	53	77

Substrate Scope

Entry	**18**	Ar	R	Time (h)	Yield (%)[b]	Ee (%)[c]
11	**18l**	4-BrC_6H_4	H	13	76	87
12	**18m**	4-$CF_3C_6H_4$	H	24	76	88
13	**18n**	1-Naphthyl	H	20	67	89
14	**18o**	2-Naphthyl	H	6	88	80
15	**18p**	1-Naphthyl	5-Br	10	86	82
16	**18q**	1-Naphthyl	5-Cl	10	84	79
17	**18r**	1-Naphthyl	6-F	21	49	94
18	**18s**	1-Naphthyl	7-Me	21	33	92
19	**18t**	1-Naphthyl	7-Me	41	43	98[d]
20	**18u**	1-Naphthyl	7-Me	15	67	95[d]

[a] **1** (0.4 mmol), **2** (0.2 mmol), **5d** (0.04 mmol), DNBA (0.06 mmol), $CHCl_3$ (2 mL), 20 °C. [b] Isolated yield. [C] Determined by HPLC. [d] At 40 °C.

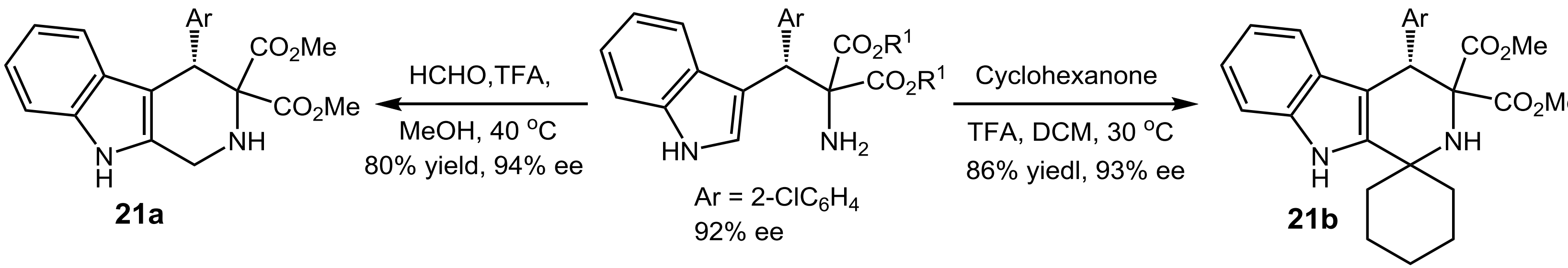
Control Experiment



20a: R = H
20f: R = Me

20a: 75% yield, 74% ee
20f: 75% yield, -4% ee

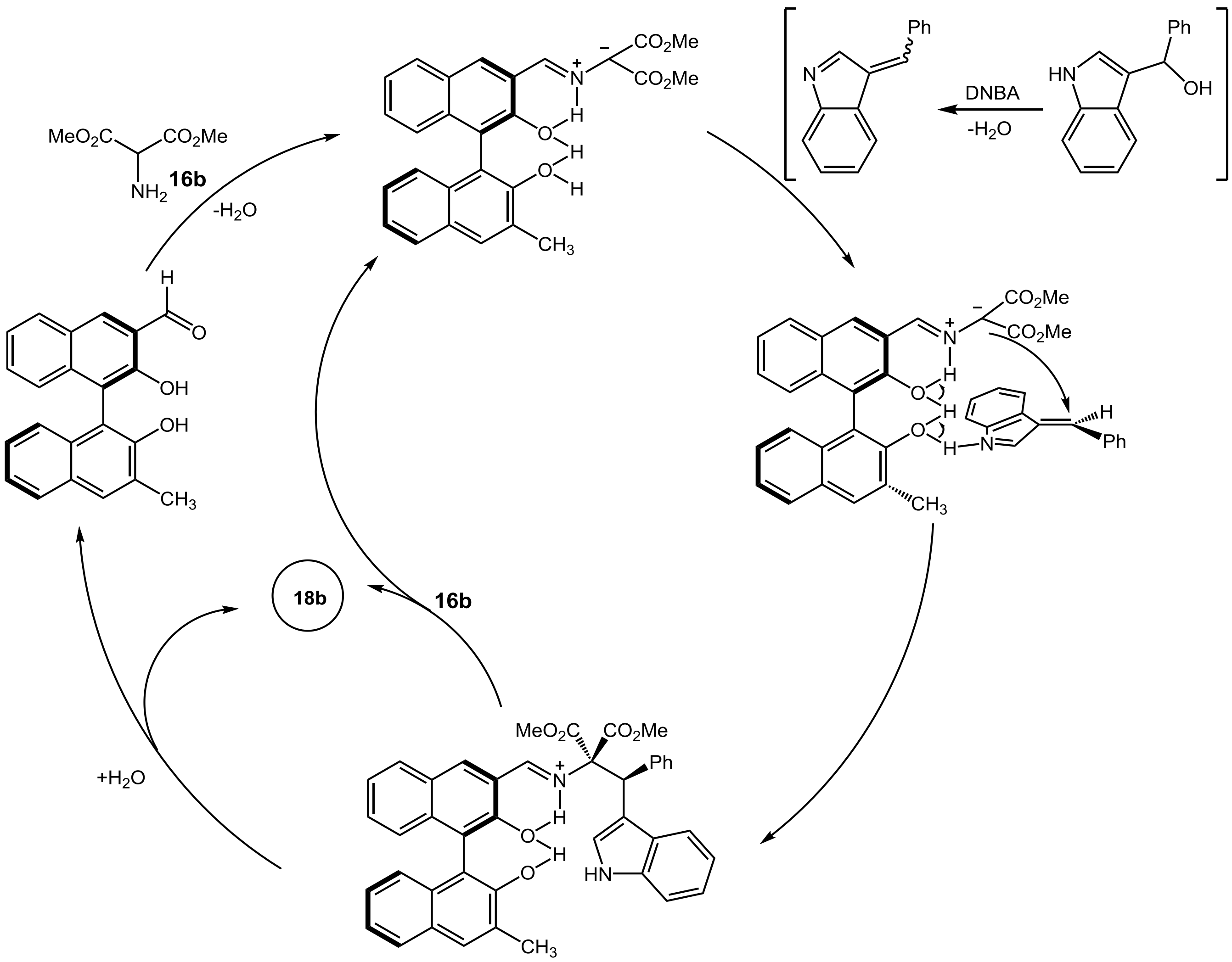
Product Conversion



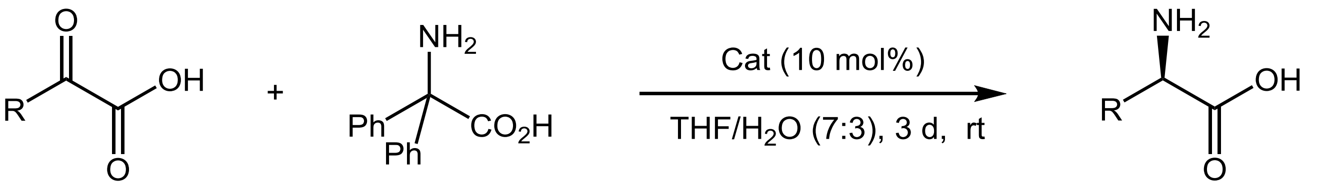
21a

21b

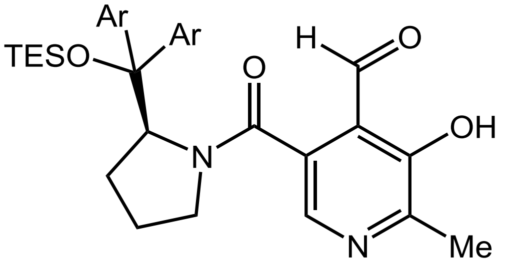
Proposed Catalytic Cycle



Chiral Pyridoxal-catalyzed Transamination



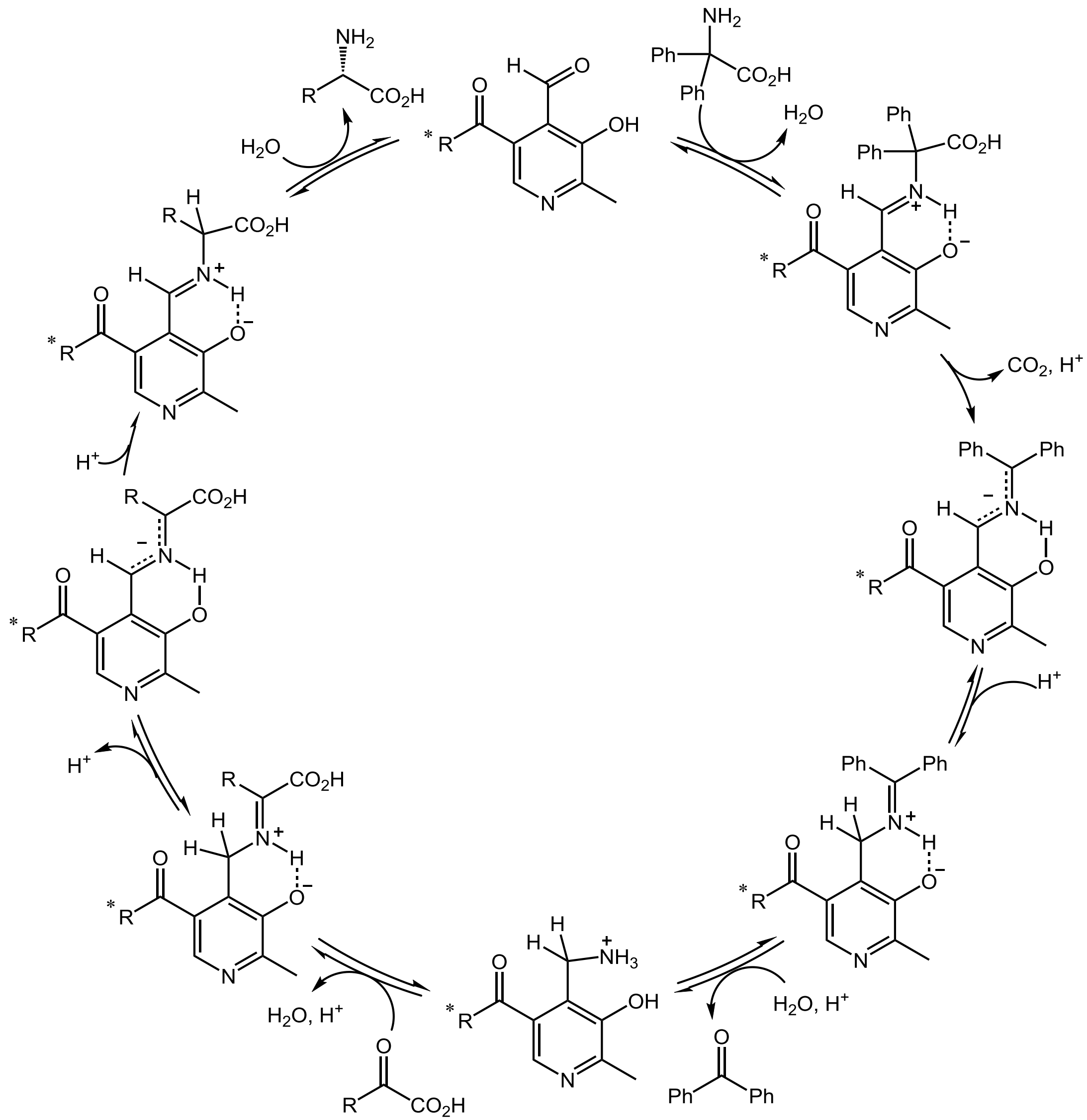
up to 85% yield
up to 80% ee



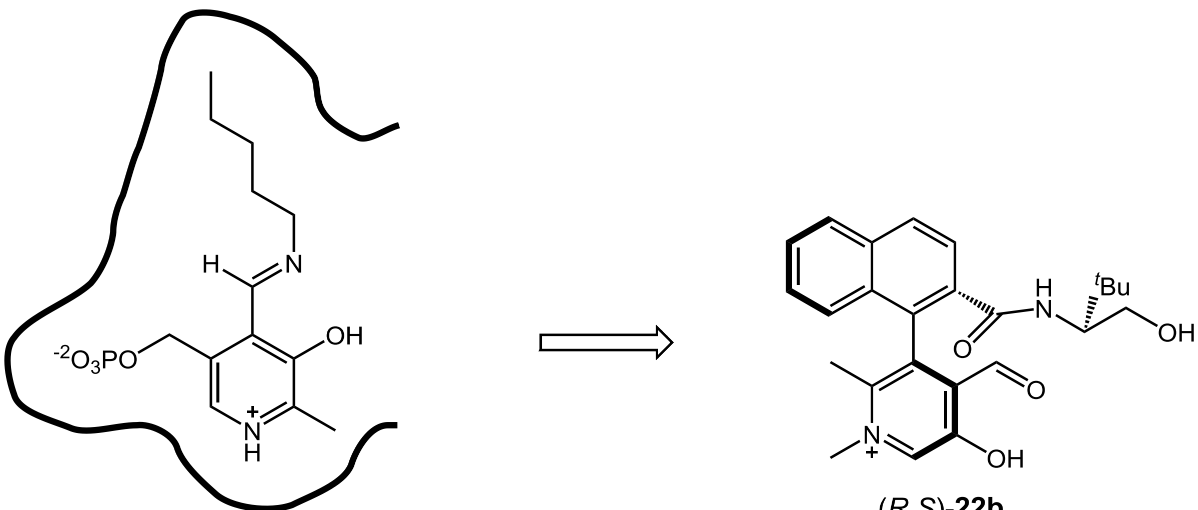
Cat: Ar = 3,5-$Ph_2C_6H_3$

Zhao, B. *et al. Org. Lett.* **2015**, *17*, 5784.

Proposed Mechanism

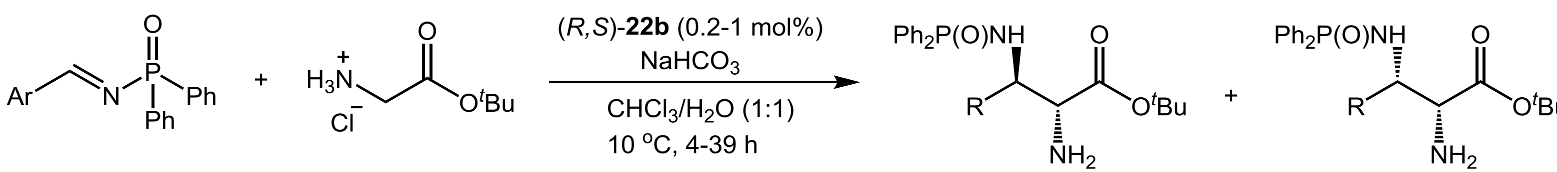


Asymmetric Mannich Reaction



pyridoxal-dependent aldolase

(*R*,*S*)-**22b**



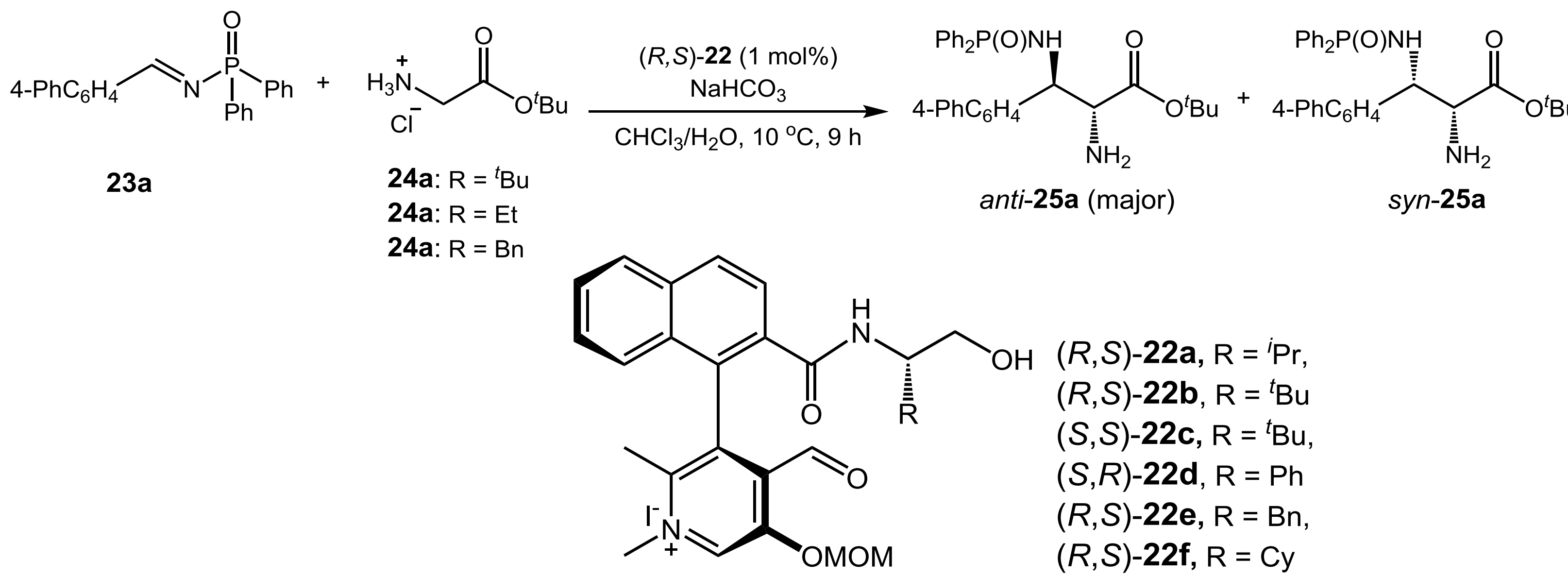
23 **24**

anti-**25** (major)
54-94% yield
>20:1 dr, 94-99% ee

syn-**25**

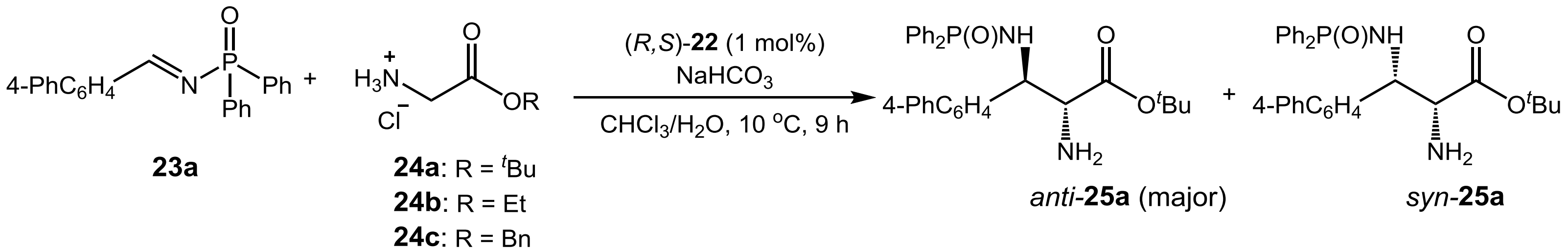
Zhao, B. *et al. Science* **2018**, *360*, 1438.

Optimization of Reaction Conditions



Entry[a]	Cat.	**24**	$CHCl_3/H_2O$	Yield (%)[b]	dr[c]	Ee (%)[d]
1	(*R*,*S*)-**22a**	**24a**	1:1	79	18:1	95
2	(*R*,*S*)-**22b**	**24a**	1:1	90	>20:1	99
3	(*S*,*S*)-**22c**	**24a**	1:1	41	5:1	16
4	(*S*,*R*)-**22d**	**24a**	1:1	84	>20:1	-97
5	(*R*,*S*)-**22e**	**24a**	1:1	73	>20:1	94
6	(*R*,*S*)-**22f**	**24b**	1:1	76	>20:1	95

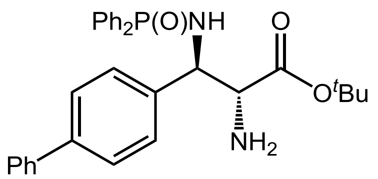
Optimization of Reaction Conditions



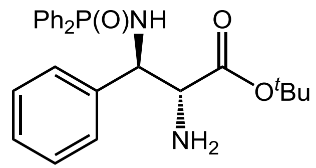
Entry[a]	Cat.	**24**	$CHCl_3/H_2O$	Yield (%)[b]	dr[c]	Ee (%)[d]
7	none	**24a**	1:1	0	-	-
8	(*R*,*S*)-**22b**	**24a**	3:7	82	>20:1	98
9	(*R*,*S*)-**22b**	**24a**	7:3	76	>20:1	98
10	(*R*,*S*)-**22b**	**24a**	9:1	74	>20:1	97
11	(*R*,*S*)-**22b**	**24a**	10:0	47	>20:1	97
12	(*R*,*S*)-**22b**	**24b**	1:1	65	>20:1	99
13	(*R*,*S*)-**22b**	**24c**	1:1	64	>20:1	99

[a] All reactions were carried out with **23a** (0.10 mmol), **24** (0.15 mmol), **22** (0.0010 mmol), and $NaHCO_3$ (0.25 mmol) in solvent (0.30 mL) at 10 °C unless otherwise stated. For entry 2, the reaction was carried out in double scale. [b] Isolated yield based on imine **23a**. [c] The dr (*anti/syn*) values were determined by ^1H NMR analysis of the crude reaction mixtures after the reaction was quenched by treatment with hydroxylamine hydrochloride (1.0 equiv). [d] The ee values were determined by HPLC analysis after the product **25a** was converted to the corresponding *N*-benzoy derivative.

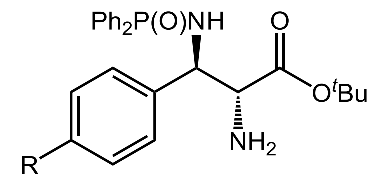
Substrate Scope



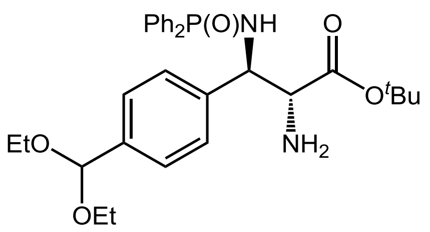
25a: (1 mol%): 90%, >20:1 dr, 99% ee
25a: (0.1 mol%): 89%, >20:1 dr, 99% ee



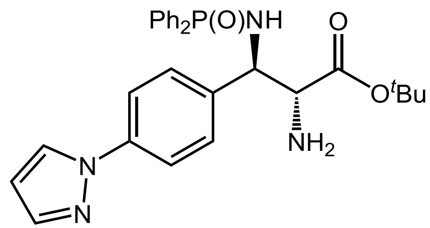
25b: 93%, >20:1 dr, 98% ee



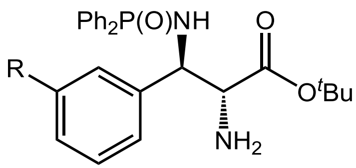
25c: (R = Me): 83%, >20:1 dr, 99% ee
25d: (R = MeO): 62%, >20:1 dr, 99% ee
25e: (R = F): 84%, >20:1 dr, 96% ee
25f: (R = CN): 76%, >20:1 dr, 95% ee



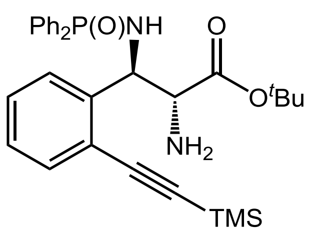
25g: 77%, >20:1 dr, 98% ee



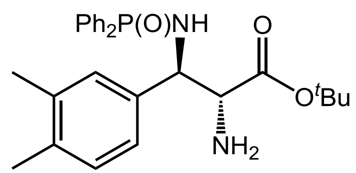
25h: 92%, >20:1 dr, 95% ee



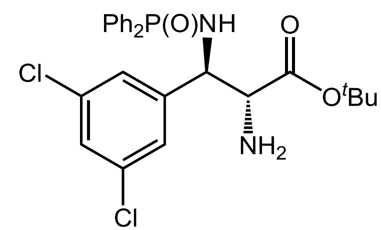
25i: (R = Me): 78%, >20:1 dr, 99% ee
25j: (R = MeO): 92%, >20:1 dr, 99% ee
25k: (R = Cl): 76%, >20:1 dr, 96% ee
25l: (R = CF_3): 78%, >20:1 dr, 95% ee



25m: 54%, >20:1 dr, 99% ee

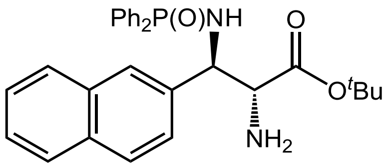


25n: 87%, >20:1 dr, 99% ee

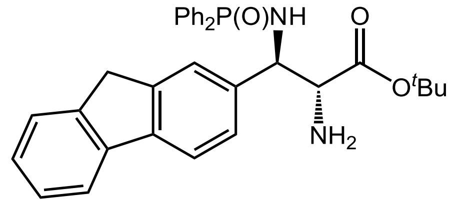


25o: 82%, >20:1 dr, 94% ee

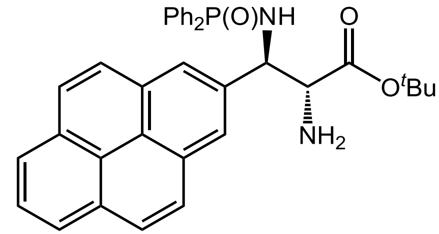
Substrate Scope



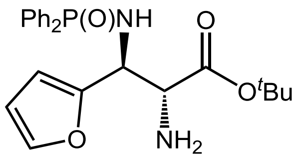
25p: 66%, >20:1 dr, 99%ee



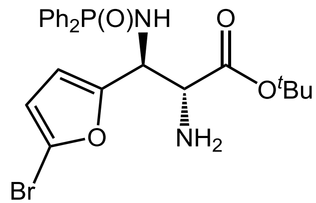
25q: 74%, >20:1 dr, 99%ee



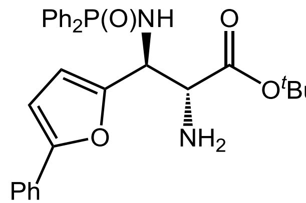
25r: 77%, >20:1 dr, 98%ee



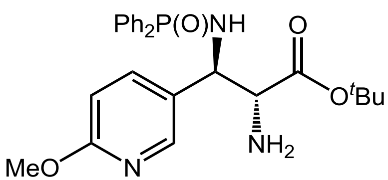
25s: 92%, >20:1 dr, 99%ee



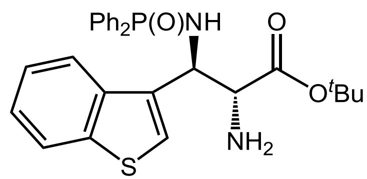
25t: 91%, >20:1 dr, 98%ee



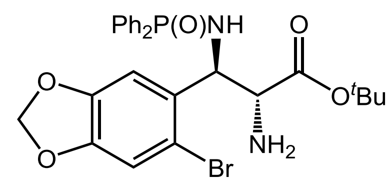
25u: 94%, >20:1 dr, 98%ee



25v: 74%, >20:1 dr, 99%ee

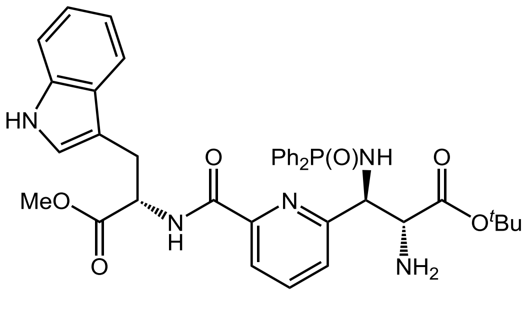


25w: 67%, >20:1 dr, 98%ee

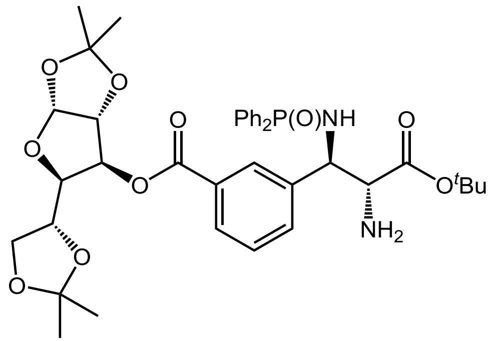


25x: 84%, >20:1 dr, 99%ee

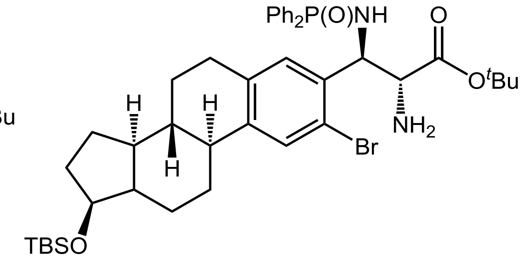
Substrate Scope



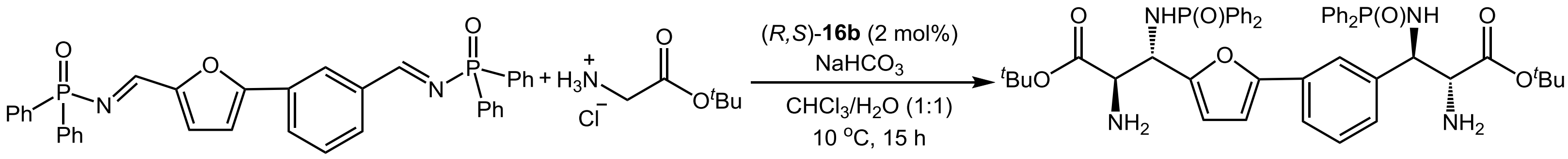
25y: 83%, 17:1 dr



25z: 78%, >20:1 dr

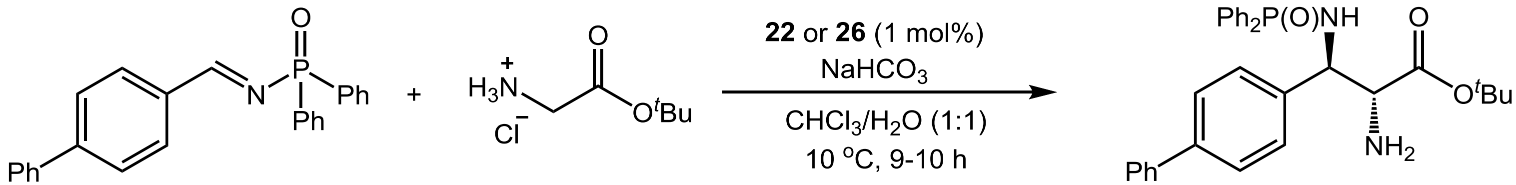


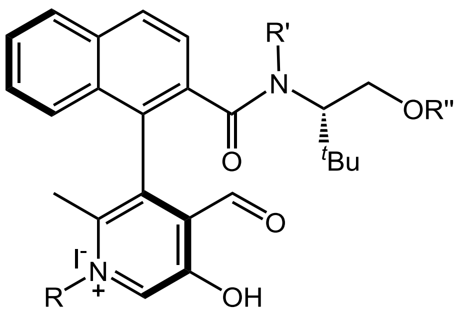
25aa: 62%, >20:1 dr



25ab: 69%, 99% ee

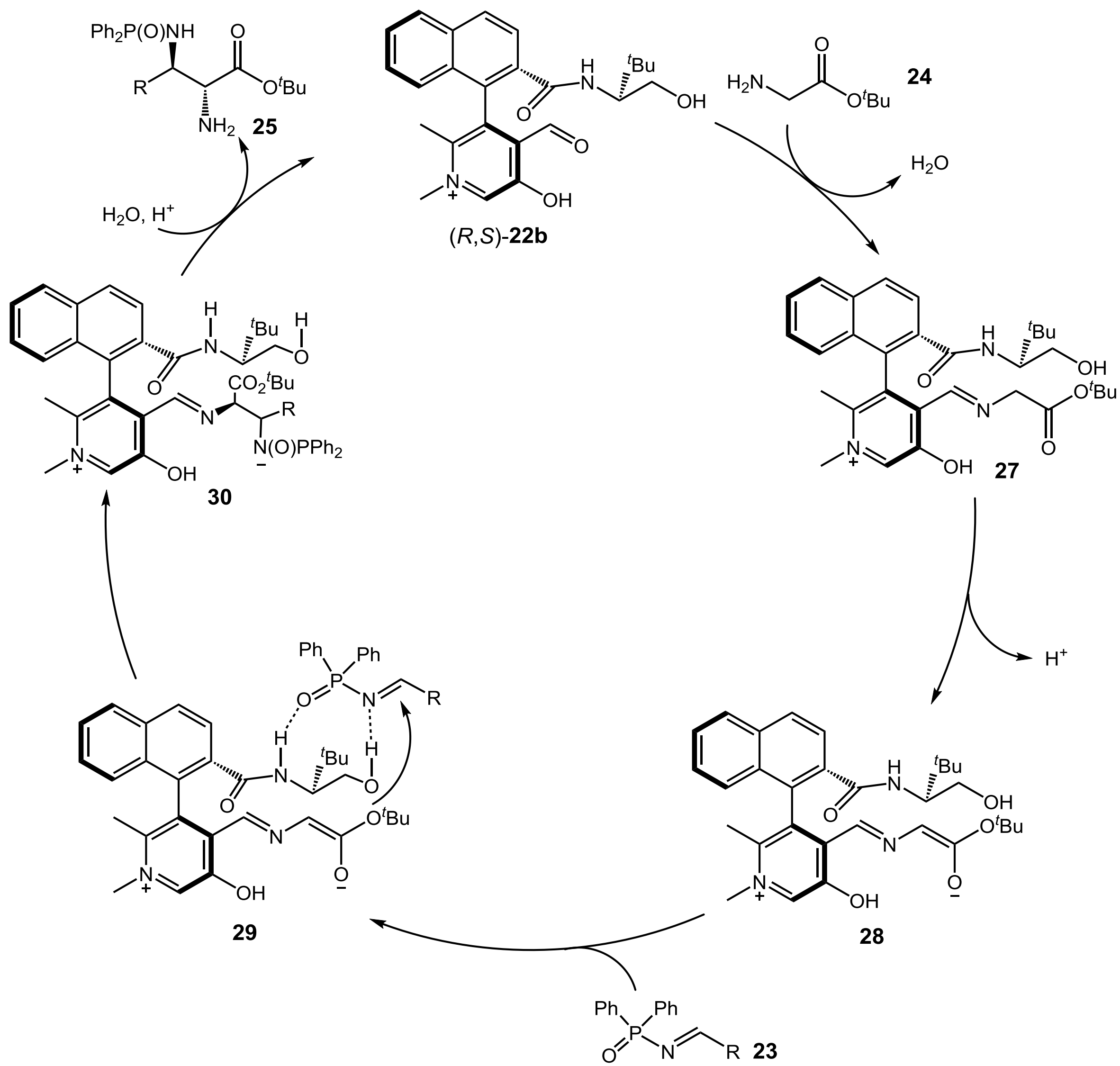
Control Experiments



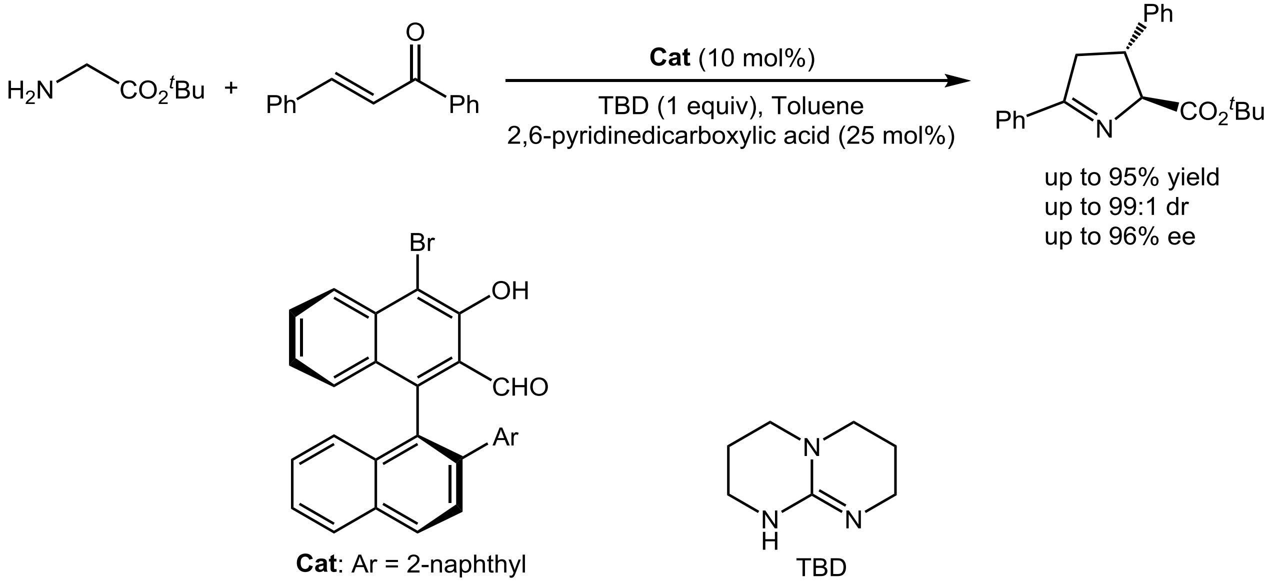


(*R*,*S*)-**22b**, (R = Me, R' = H, R'' = H): 90%, >20:1 dr, 99% ee
(*R*,*S*)-**22b**, (R = Me, R' = H, R'' = Me): 27%, 12:1 dr, -31% ee
(*R*,*S*)-**22b**, (R = Me, R' = Me, R'' = H): 9%, 1:1 dr, -87% ee
(*R*,*S*)-**26**, (R = none, R' = H, R'' = H): 0%

Proposed Mechanism

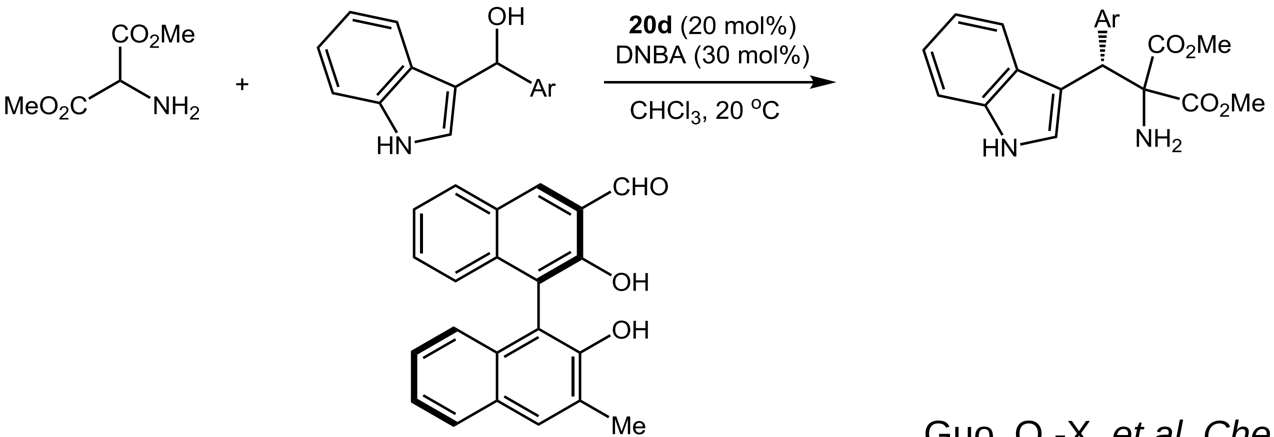


Chiral Aldehyde Catalysis



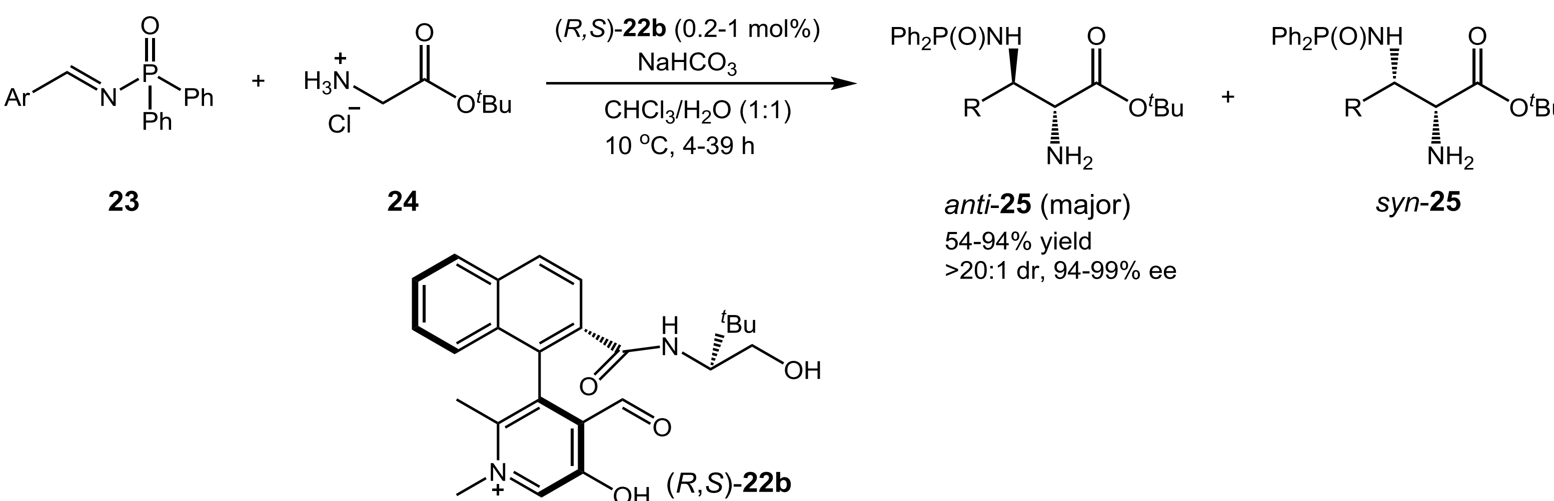
Guo, Q,-X. *et al. J. Am. Chem. Soc.* **2018**, *140*, 9774.

Summary



20d

Guo, Q,-X. *et al. Chem. Sci.* **2014**, *5*, 1988.



Zhao, B. *et al. Science* **2018**, *360*, 1438.

The First Paragraph

Enamine catalysis is a powerful activation mode in organocatalysis. The process involves conversion of carbnyl compound into enamine through imine intermediate **3** (an iminium intermediate if a secondary amine is applied) and is catalyzed by amine **2**. Nucleophilic addition of the activated enamine to an electrophile can proceed to yield substituted carbonyl **6**. On the other hand, the formation of imine **3** also increases the α-H acidity of amine **2** to facilitate formation of the α-amino carbanion **7**, which can also react with an electrophile to produce **8**. If the product **8** can be hydrolyzed under the reaction conditions to regenerate **1**, it would be possible to use the carbonyl compound **1** as a catalyst to promote α-functionalization of amine **2**.

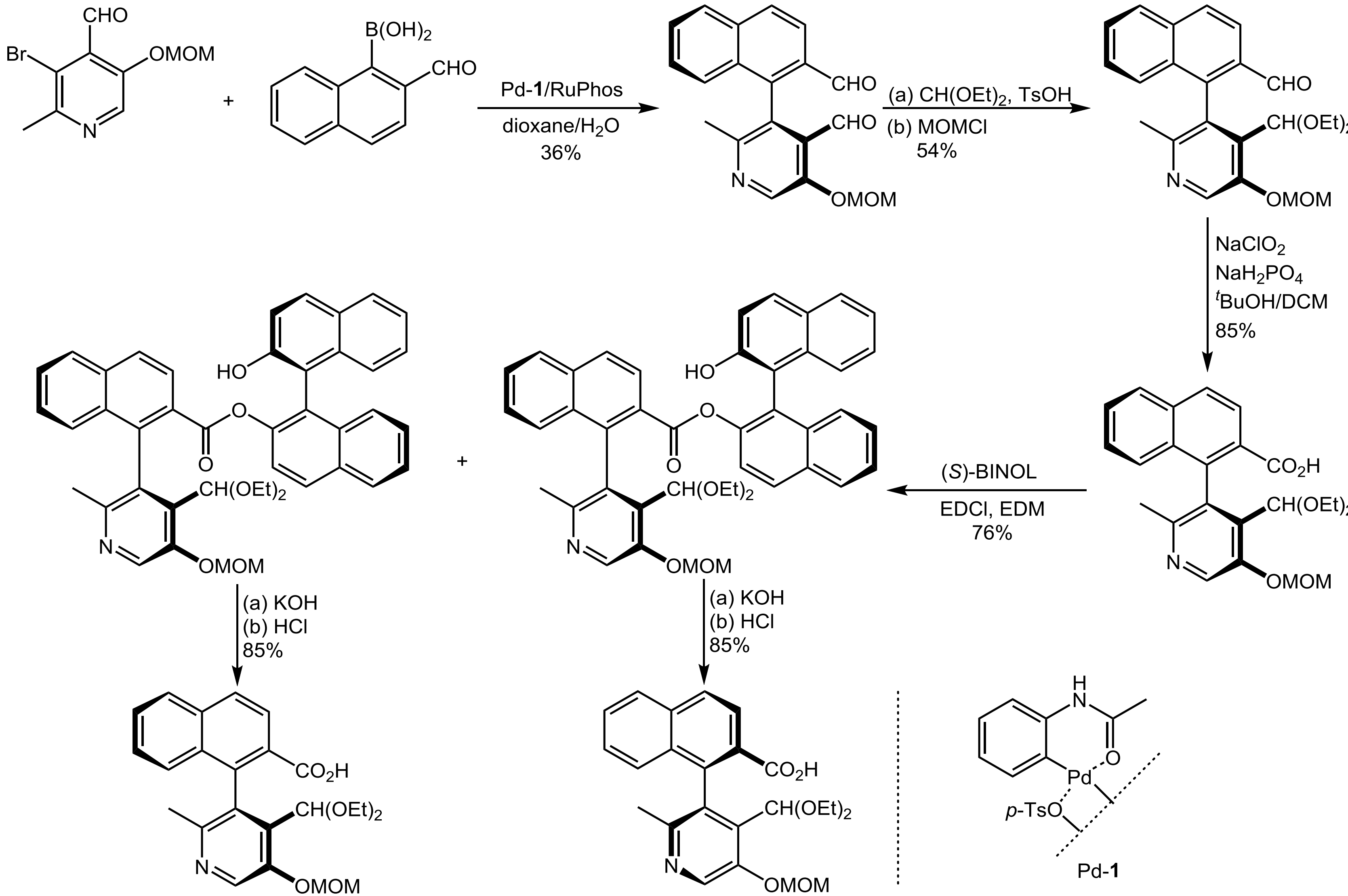
The Last Paragraph

The side chain of catalysts influences activity and selectivity. To explain the side-chain effect as well as the origin of chirality, we propose the orientation for the addition of carbanion to imine. As glycinate is deprotonated to yield the delocalized carbanion, imine is also activated by the side chain through hydrogen bonds with the N–H and O–H moieties. We thus propose that the catalyst not only activates both of the substrates but, similar to an enzyme, also orients the addition by bringing the two reactants together with a specific spatial arrangement. This cooperative bifunctional activation mode leads to product with excellent selectivities. The proposed transition state is further supported by control experiments. Methylation of the N–H or O–H group of the side chain led to decreases in activity and in diastereo and enantioselectivities, likely because the methylation weakens or eliminates the hydrogen bond with the imine.

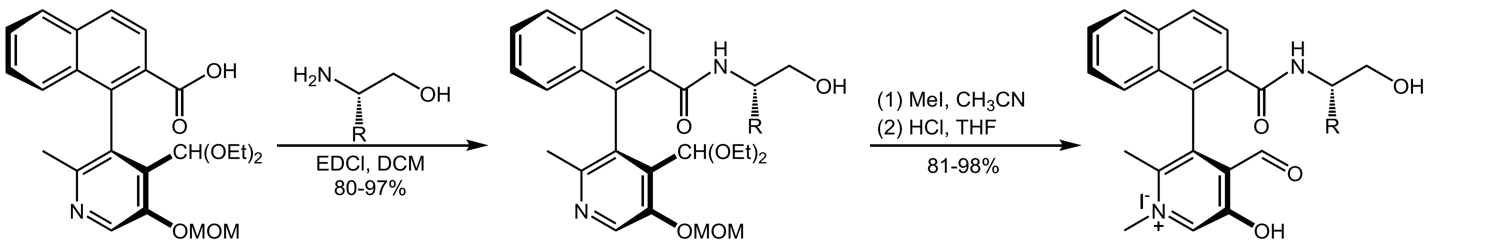
Acknowledgement

Thanks
for your attention

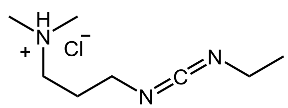
Synthesis of Catalysts



Synthesis of Catalysts



(*R*,*S*)-**16a,** R = ^{i}Pr, (*S*,*S*)-**16c,** R = ^{t}Bu, (*R*,*S*)-**16e,** R = Bn
(*R*,*S*)-**16b**, R = ^{t}Bu, (*R*,*S*)-**16d**, R = Ph, (*R*,*S*)-**16f,** R = Cy



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