Catalytic Arylation of Aldehydes

(Pericas, M. A.; Jimeno, C.; Sayalero, S.; Fjermestad, T.; Colet, G.; Maseras, F. *Angew. Chem. Int. Ed.* **2008**, *47,* 1098-1101)

&

Catalytic vinylation of Iminium Ions

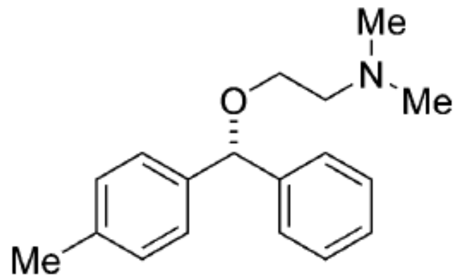
(Schaus, S. E.; Lou, S. *J. Am. Chem. Soc.* **2008**, *130*, 6922-6923)

Anil Kumar Gupta

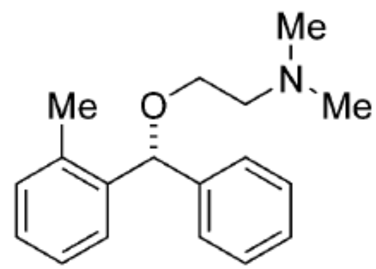
Group Meeting

September 5, 2008

Catalytic Asymmetric Arylation of Aldehydes
Synthesis of Diarylmethanols



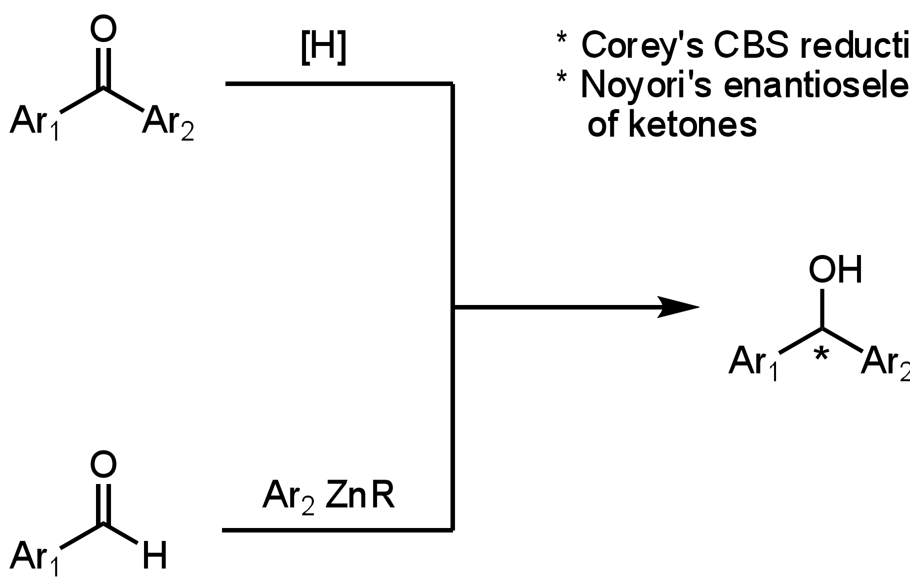
(*R*)-Neobenodine



(*R*)-Orphenadrine

Antihistaminic Agents

- Problem: Ar_1 & Ar_2 are similar in volume and electronic nature

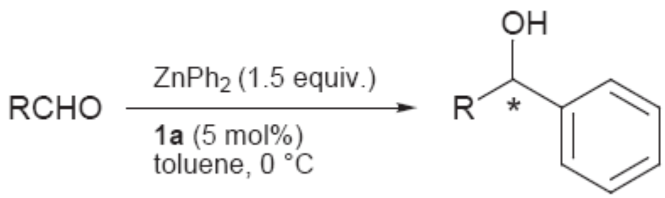


* Corey's CBS reduction methodology
* Noyori's enantioselective hydrogenation of ketones

* Use of Organozinc Compounds

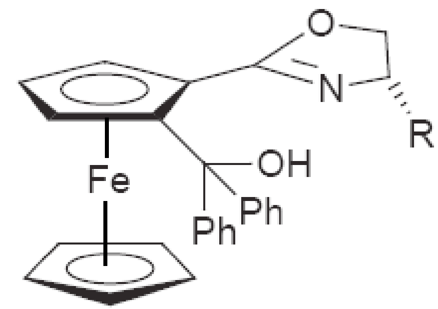
Catalytic Asymmetric Arylation of Aldehydes: Initial Studies

Table 2 Asymmetric addition of diphenylzinc to various aldehydes in the presence of 5 mol% of ferrocene **1a**



Entry	R	*t*/h	Yield[a] (%)	Ee[b] (%)	Configuration[d]
1	4-ClC_6H_4	15	99	82	*R*
2	Ferrocenyl	11	89	⩾96[c]	*R*
3	2-BrC_6H_5	14	98	31	*R*
4	1-Naphthyl	14	99	28	*R*
5	Me	15	94	75	*S*
6	$Ph(CH_2)_2$	10	91	50	*S*
7	Bu^t	16	99	56	*S*
8	2-Pyridyl	12	98	3	*R*

[a] Isolated yield after column chromatography. [b] Determined by chiral HPLC on stationary phase. [c] Determined by ^1H NMR in the presence of $Eu(tfc)_3$. [d] Determined by comparison of the optical rotation with literature values.



1a R = Bu^t
Catalyst

Bolm, C.; Muñiz, K. *Chem. Commun.* **1999**, 1295-1296.

Catalytic Asymmetric Arylation of Aldehydes: Initial Studies

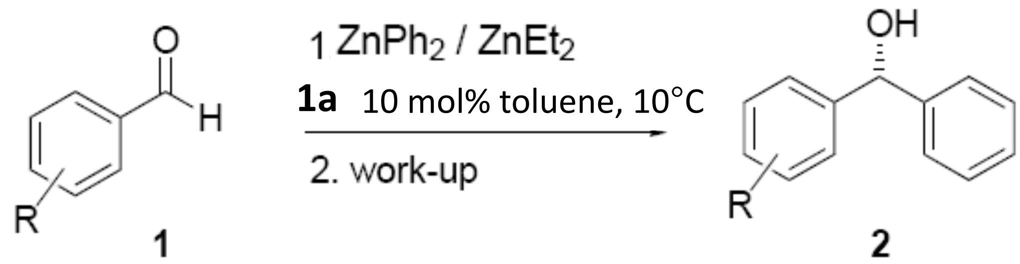
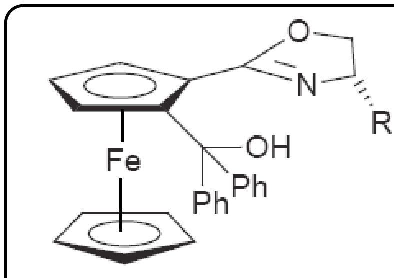


Table 2. Catalyzed phenyl transfer to various aldehydes.[a]

Entry	R in RCHO	Yield [%][b]	*ee* of **2** [%][c,d]	Absololute config.[e]
1	4-Cl-C_6H_4	86	97 (88)	*R*
2	4-H_3CO-C_6H_4	82	98 (87)	*R*
3	3-H_3CO-C_6H_4	99	96	*R*
4	4-H_3C-C_6H_4	86	98 (85)	*R*
5	4-C_6H_5-C_6H_4	98	97 (91)	*R*
6	2-$C_{10}H_9$	70	96 (89)	*R*
7	2-Br-C_6H_4	64	91 (73)	*R*
8	2-Furyl	99	95 (80)	*R*
9	*E*-$C_6H_5CH{=}CH$	97	90 (73)	*S*
10	$C(CH_3)_3$	68	94 (56)	*S*
11	C_6H_5-CH_2	82	83	*S*
12	$CH(CH_3)_2$	75	91	*S*

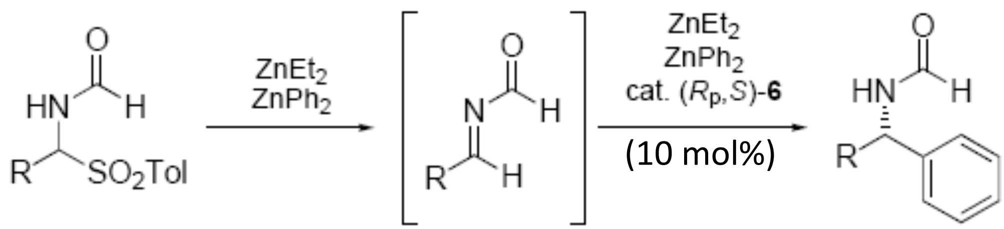


1a R = Bu[t]
Catalyst

Bolm, C.; Hermanns, N. ; Hildebrand, J. P.; Muñiz, K. *Angew. Chem. Int. Ed.* **2000**, *39,* 3465-3467

Catalytic Asymmetric Arylation of Imines

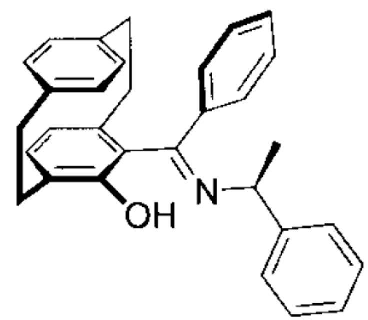
Table 2. Substrate spectrum for the transfer of a phenyl group to imines.[a]



7a-g **8a-g** **9a-g**

Entry	R	Product	(R_p,S)-**6** [mol %]	Yield [%][b]	*ee* [%][c]
1	4-MeC_6H_4	**9a**	10	99 (85)	97 (+)
2	4-MeC_6H_4	**9a**	5	99	94 (+)
3	4-ClC_6H_4	**9b**	10	99 (82)	94 (+)-(*R*)
4	4-ClC_6H_4	**9b**	5	99	81 (+)-(*R*)
5	4-ClC_6H_4	**9b**	1	98	69 (+)-(*R*)
6	4-$MeOC_6H_4$	**9c**	10	99 (75)	97 (+)
7	3-MeC_6H_4	**9d**	10	98	89 (+)
8	2,6-$Cl_2C_6H_3$	**9e**	10	99 (89)	95 (+)
9	4-*t*BuC_6H_4	**9f**	10	98 (81)	96 (+)
10	4-$COOMeC_6H_4$	**9g**	10	99 (80)	95 (−)

[a] Reactions were carried out in toluene at −20 °C for 12 h, 1.5 equiv $ZnPh_2$, 1.5 equiv $ZnEt_2$, with 0.25 mmol of imine precursor **7a–g**. [b] Determined by ^1H NMR spectroscopy. Yields in parenthesis refer to yields after column chromatography. [c] Determined by HPLC on a chiral stationary phase (see Supporting Information).

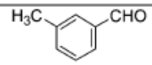
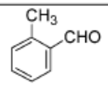
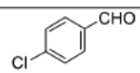
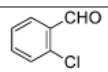
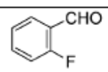
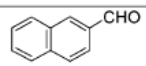
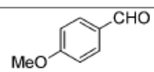
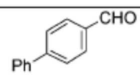
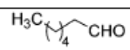
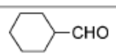
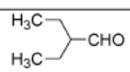
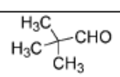


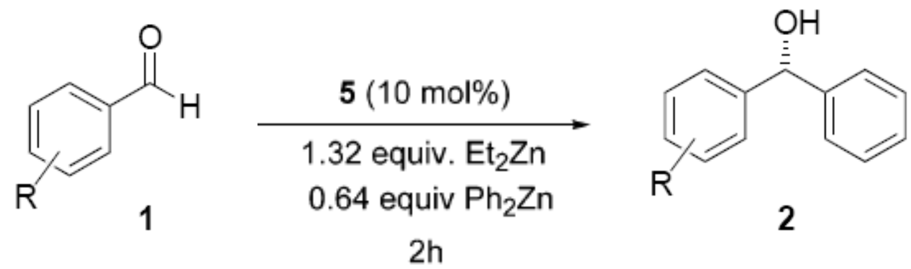
(R_p,S)-**6**
Catalyst

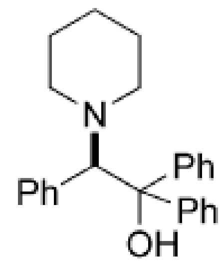
Complex Ligands
upto now

Bolm, C.; Hermanns, N. ; Bräse, S. ; Dahmen, S.
Angew. Chem. Int. Ed. **2002**, *41,* 3692-3694

Catalytic Asymmetric Arylation of Aldehydes: Initial Studies

Entry	R-CHO	Solvent	T (°C)	Yield	ee (%)[b]	Config.
1		hexane	0	99	96	S
2		hexane	0	84	98	S
3		hexane	r.t.	82	95	S
4		hexane	0	91	93	S
5		hexane	0	61	98	S
6		hexane	r.t.	70	96	S
7		hexane	r.t.	91	95	S
8		hexane	0	r.t.	97	S
9		hexane	0	84	63	R
10		hexane	0	96	60	R
11		hexane	0	80	83	R
12		hexane	r.t.	85	92	R
		hexane	0	91	97	





5
Catalyst

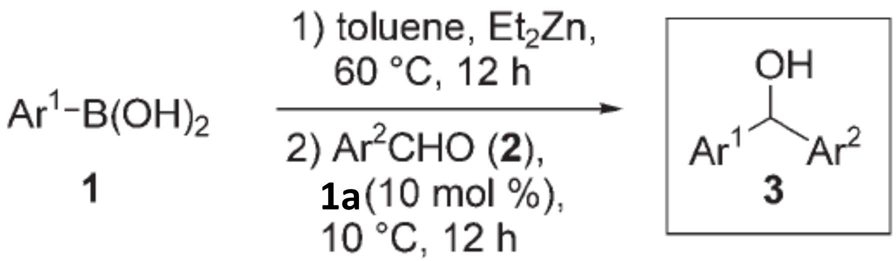
2-Piperidino-1,1,2-triphenylethanol

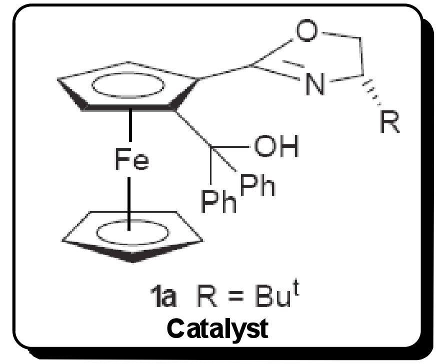
Ph_2Zn = expensive reagent

Fontes, M. ; Verdaguer, X.; Solà, L. ; Pericàs, M. A.; Riera, A.
J. Org. Chem. **2004,** 69, 2532-2543.

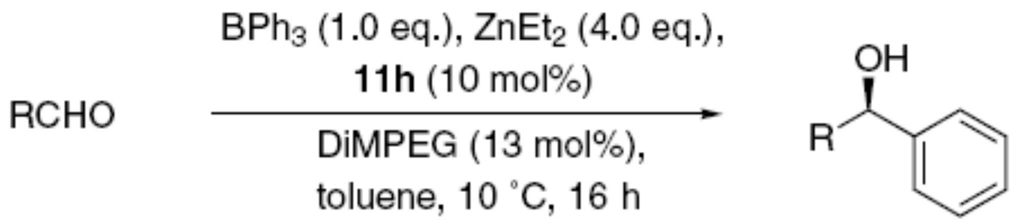
Catalytic Asymmetric Arylation of Aldehydes: Using Boron

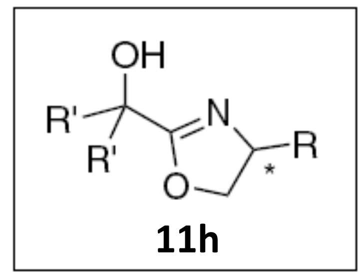
Boronic Acids



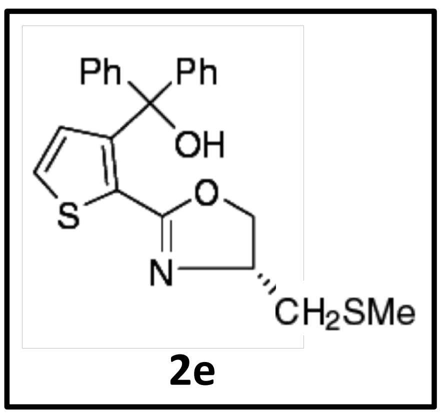


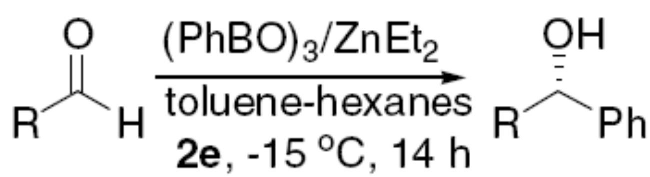
Triphenyl Boranes





Config.	R	R′
S	*t*-Bu	2-Me–Ph





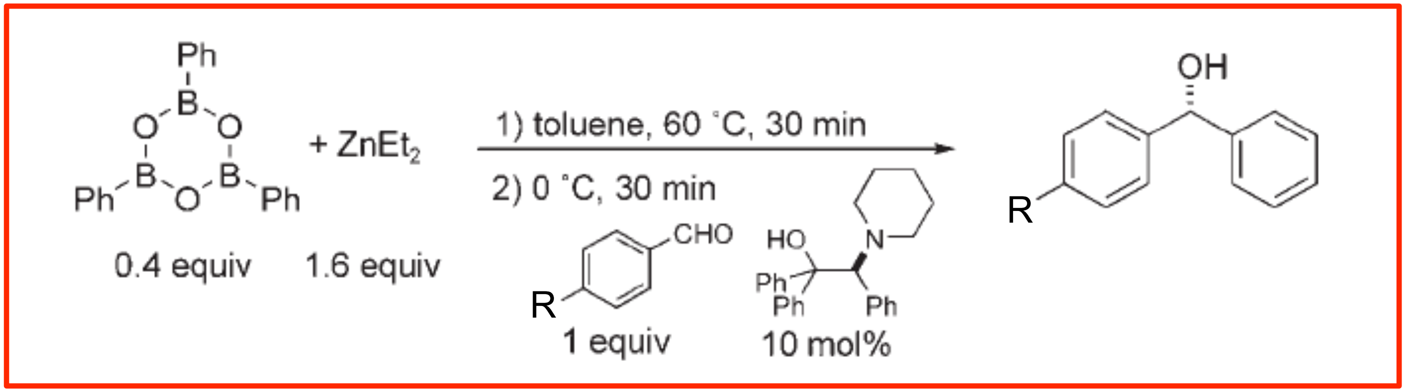
Triphenylboroxines

Schmidt , F.; Rudolph, J.; Bolm, C. *Adv. Synth. Catal.* **2007**, *349,* 703-708

Schmidt , F.; Zani, L.; Bolm, C. *Tetrahedron: Asymmetry* **2005**, *16,* 1367-1376

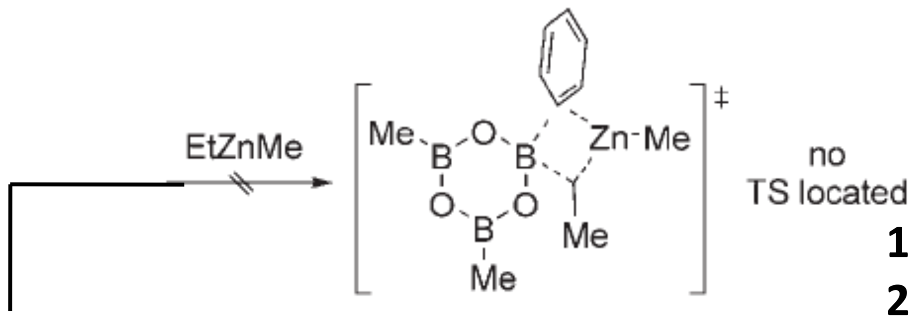
Chai, Z.; Liu, X.; Wu, X.; Zhao, G. *Tetrahedron: Asymmetry* **2006**, *17,* 2442-2447

Catalytic Asymmetric Arylation of Aldehydes



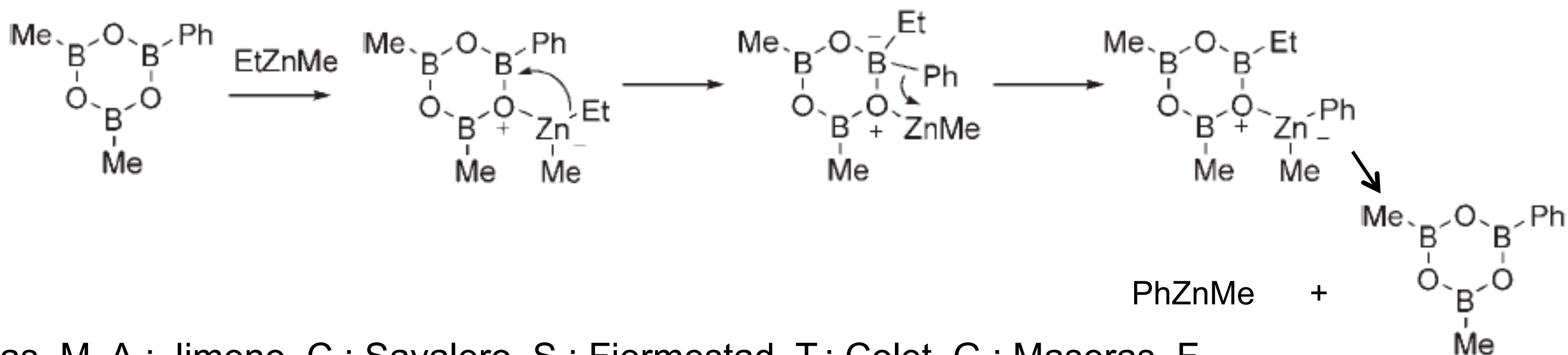
Theoretical Calculations

[B3LYP/6-31 G(d)]



1. Zinc-to-Boron Transmetalation (Et)

2. Boron-to-Zinc Transmetalation (Ph)



Pericas, M. A.; Jimeno, C.; Sayalero, S.; Fjermestad, T.; Colet, G.; Maseras, F.
Angew. Chem. Int. Ed. **2008**, *47,* 1098-1101

Computed Potential-energy profile

Should be fast Step due to low energy barriers even at room temperature

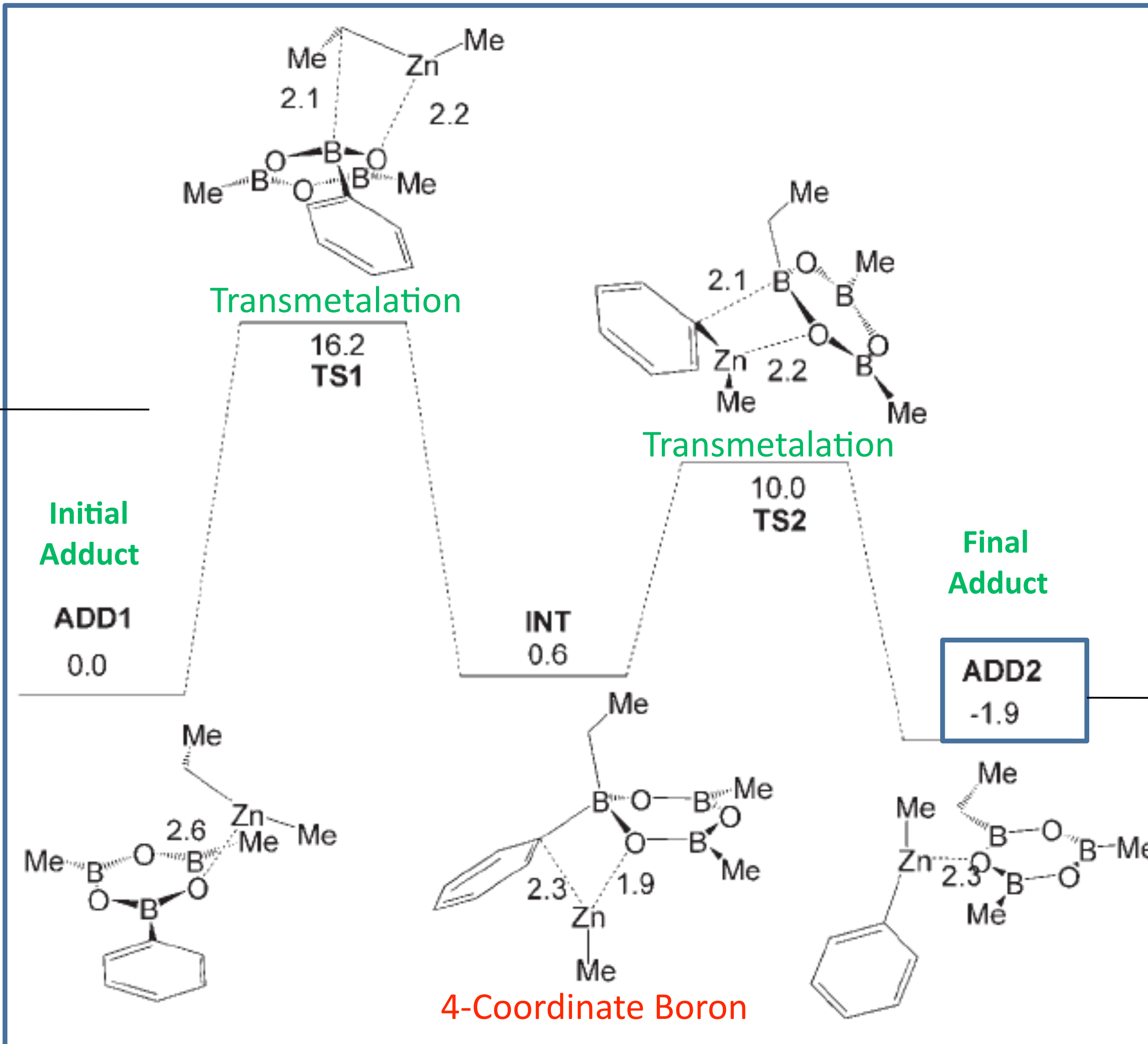


Figure 1. Computed B3LYP/6-31G(d) potential-energy profile [kcal mol^{-1}] for the boroxine system. Interatomic distances are given in [Å].

Reversible (Shifted towards PhZnMe)

Normal time: 12 h at 60°C

Triaryl boroxine should be used

Kinetic Studies of Transmetalation of $(RBO)_3$ with Et_2Zn

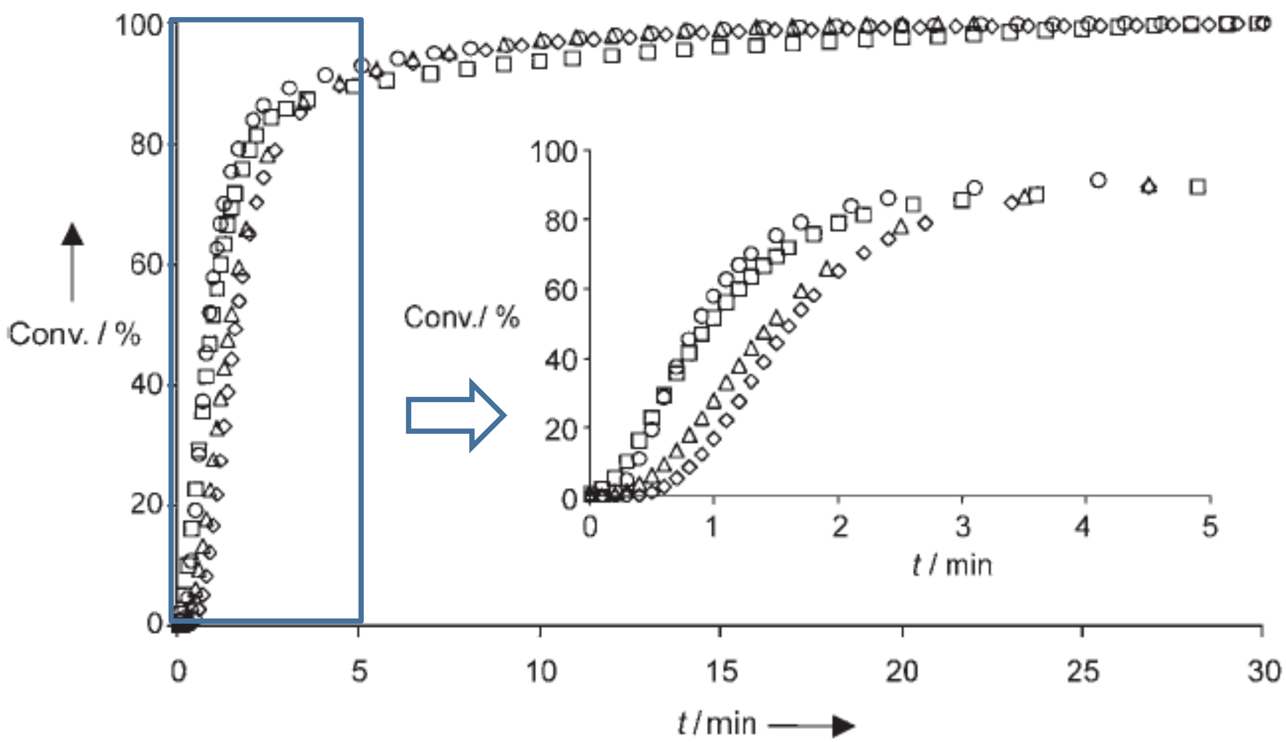


Figure 2. Kinetic profiles of the transmetalation of four different triaryl boroxines $(RBO)_3$ with Et_2Zn at 60°C. Diamonds: R = 4-ClC_6H_4; squares: R = 3,5-$Me_2C_6H_3$; triangles: R = 4-$CF_3C_6H_4$; circles: R = Ph.

* reactions reaches equilibrium in very short times (15–30 min) irrespective of the aryl substituent.

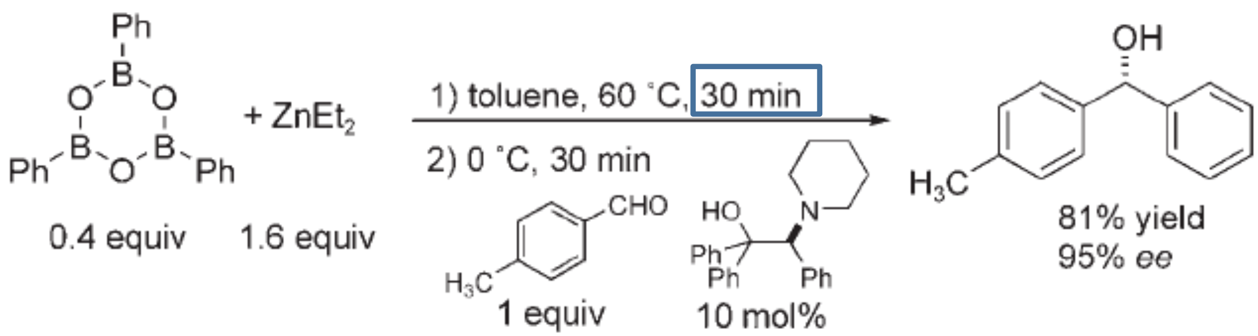
Calorimetric Studies

Table 1: Reaction heats for the transmetalation of four different boroxines.

Boroxine	Reaction heat[a]	Boroxine	Reaction heat[a]
Ph	15.2	4-ClC_6H_4	8.6
3,5-$Me_2C_6H_3$	12.7	4-$CF_3C_6H_4$	11.6

[a] At 60 °C, in kilocalories per mol of boroxine.

Reaction heat per transmetalation : 2.9 – 5.1 kcal mol^{-1} (in agreement with -1.9 kcal mol^{-1})



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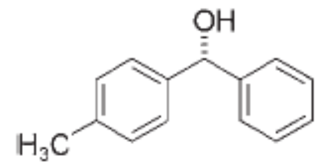
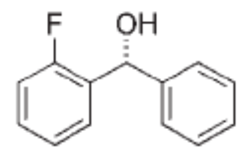
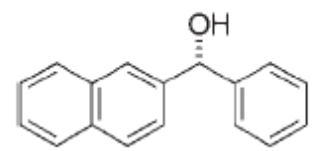
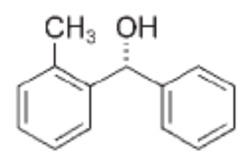
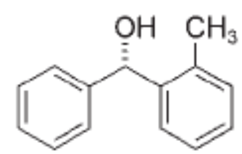
Substrate Scope

Table 2: Catalytic asymmetric addition of triaryl boroxines to aldehydes in the presence of 10 mol% (*S*)-**1**.

Entry	Boroxine	Aldehyde	Product		Yield [%][a]	*ee* [%][b]
1	phenyl[c]	4-tolyl		(*R*)-**2a**	94	95
2	phenyl[c]	2-fluorophenyl[d]		(*R*)-**2b**	98	91[e]
3	phenyl[c]	2-naphthyl[d]		(*R*)-**2c**	90	91
4	phenyl[c]	2-tolyl[f]		(*R*)-**2d**	98	94
5	2-tolyl[c]	phenyl		(*S*)-**2d**	84	65

Pericas, M. A.; Jimeno, C.; Sayalero, S.; Fjermestad, T.; Colet, G.; Maseras, F.
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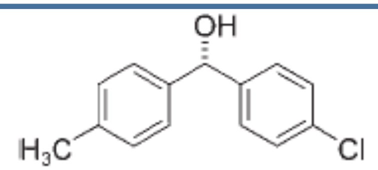
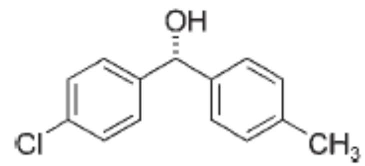
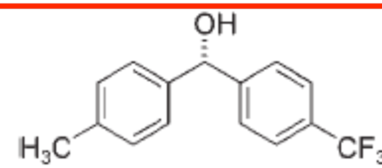
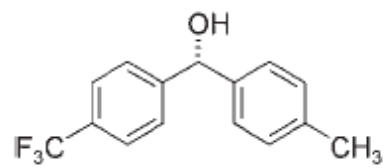
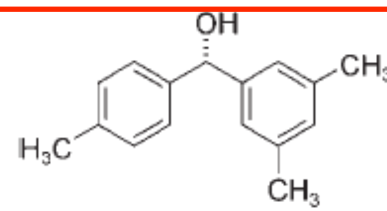
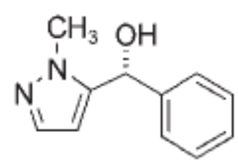
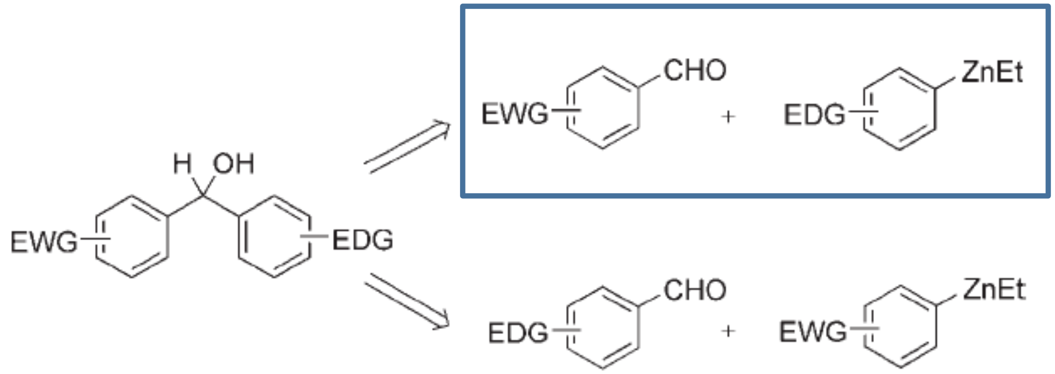
Entry	Boroxine	Aldehyde	Product	Yield [%][a]	*ee* [%][b]
6	4-chlorophenyl[c]	4-tolyl	 (*S*)-**2e**	96	73
7	4-tolyl[g]	4-chlorophenyl	 (*R*)-**2e**	93	94
8	4-(trifluoro-methyl)phenyl[c]	4-tolyl	 (*S*)-**2f**	18	2
9	4-tolyl[g]	4-(trifluoro-methyl)phenyl	 (*R*)-**2f**	72	88
10	3,5-dimethylphenyl[c]	4-tolyl	 (*S*)-**2g**	96	86
11	phenyl[c]	*N*-methylpyrazol-5-yl	 (*R*)-**2h**	81[h]	87[h]

Pericas, M. A.; Jimeno, C.; Sayalero, S.; Fjermestad, T.; Colet, G.; Maseras, F.
Angew. Chem. Int. Ed. **2008**, *47,* 1098-1101

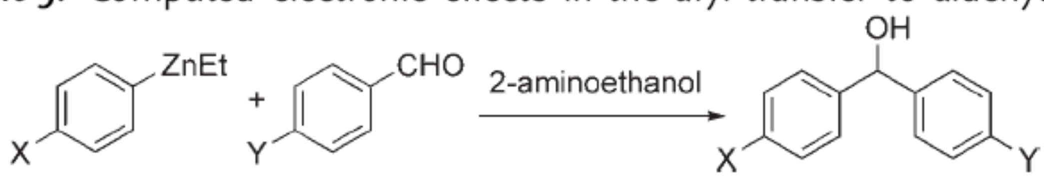
Calculations to Study the Effect of Substituents on Arylation Step

Non-catalytic reaction takes place at an appreciable rate at 0 °C



Scheme 3. Alternative ways to arylate aryl aldehydes.

Table 3: Computed electronic effects in the aryl transfer to aldehydes.



B3LYP/LANL2DZ

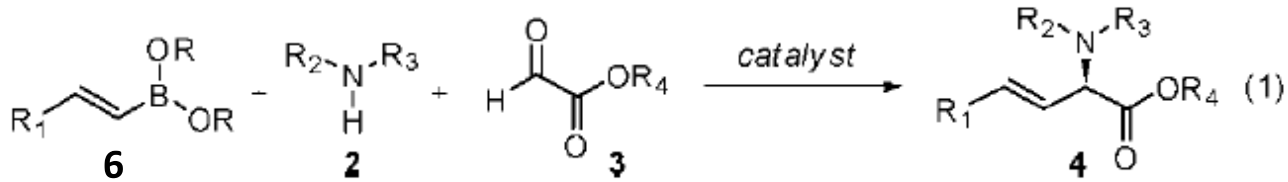
Entry	X	Y	$E_{rel}^{\neq}$ [kcal mol^{-1}]
1	H	H	0
2	MeO	H	−0.54
3	H	MeO	+1.64
4	NO_2	H	+2.69
5	H	NO_2	−3.33

Relative Activation enery

Pericas, M. A.; Jimeno, C.; Sayalero, S.; Fjermestad, T.; Colet, G.; Maseras, F. *Angew. Chem. Int. Ed.* **2008**, *47,* 1098-1101

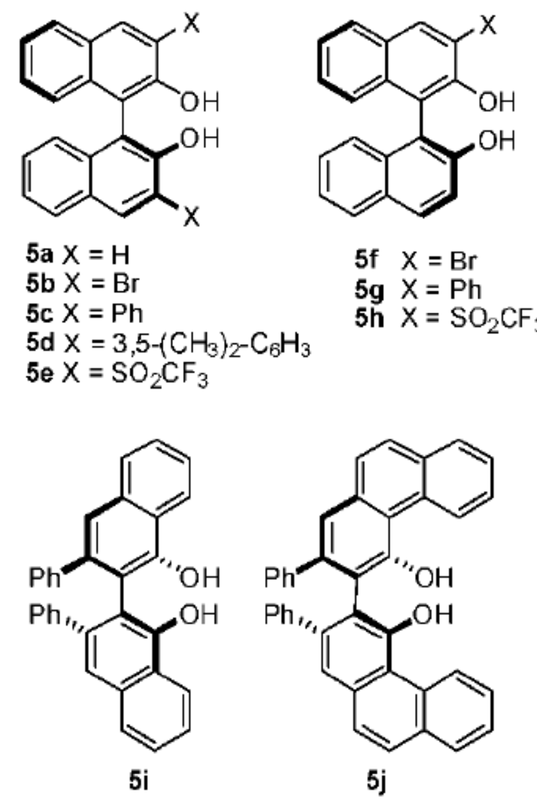
Catalytic Asymmetric Vinylation of Iminium cations

R_1 = Ph
R_2 = R_3 = Bn
R_4 = Et



Alkenyl boronate glyoxylate Chiral α amino ester

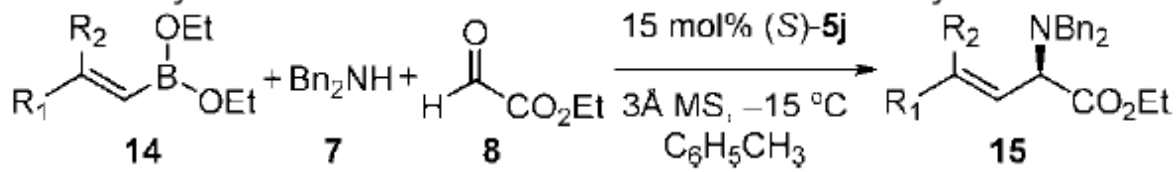
entry	boronate	R	catalyst	% yield[b]	er[c]
1	**6a**	H		80	
2	**6b**	*i*-Pr		<5	
3	**6b**	*i*-Pr	**5a**	45	60:40
4	**6b**	*i*-Pr	**5b**	65	75:25
5	**6b**	*i*-Pr	**5c**	51	70:30
6	**6b**	*i*-Pr	**5d**	25	59:41
7	**6b**	*i*-Pr	**5e**	70	55:45
8	**6b**	*i*-Pr	**5f**	60	70:30
9	**6b**	*i*-Pr	**5g**	43	64:36
10	**6b**	*i*-Pr	**5h**	67	72:28
11	**6b**	*i*-Pr	**5i**	77	85:15
12	**6b**	*i*-Pr	**5j**	80	87:13
13	**6c**	CH_3	**5j**	90	90:10
14	**6d**	Et	**5j**	81	95.5:4.5
15	**6e**	*n*-Bu	**5j**	77	93:7
16	**6a**	H	**5j**	90	57:43



Schaus, S. E.; Lou, S. *J. Am. Chem. Soc.* **2008**, *130*, 6922-6923

Catalytic Asymmetric Vinylation of Iminium cations with Dibenzylamine

Table 2. Asymmetric Petasis Reaction with Dibenzylamine **7**[a]



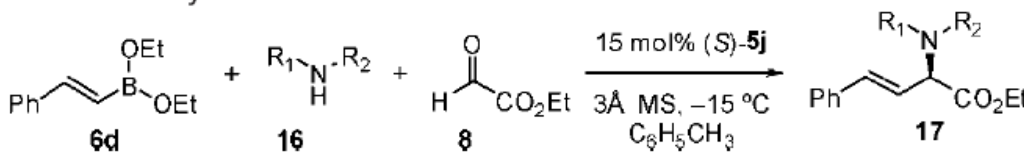
entry	R_1	R_2	product	% yield[b]	er[c]
1	Ph	H	**15a**	81	95.5:4.5
2	*p*-$CH_3O-C_6H_4$	H	**15b**	84	96:4
3	*p*−Br-C_6H_4	H	**15c**	82	95:5
4	*m*−F-C_6H_4	H	**15d**	80	95:5
5	*m*-$CF_3-C_6H_4$	H	**15e**	82	95:5
6	3-C_4H_3S	H	**15f**	87	95:5
7[d]	C_6H_{11}	H	**15g**	76	97:3
8[d]	*n*-Bu	H	**15h**	73	95:5
9[d]	$BnOCH_2$	H	**15i**	74	95.5:4.5
10	Ph	CH_3	**15j**	78	95:5
11[d]	*n*-Bu	CH_3	**15k**	71	93:7

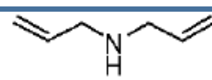
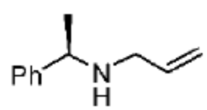
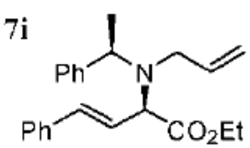
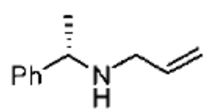
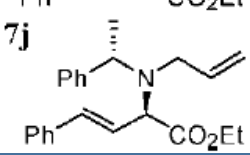
[a] Reactions were run with 0.25 mmol **14**, 0.25 mmol amine, 0.25 mmol glyoxylate, 0.0375 mmol (*S*)-**5j**, and 3 Å molecular sieves in toluene for 36 h under Ar, followed by flash chromatography on silica gel. [b] Isolated yield. [c] Determined by chiral HPLC analysis. [d] Reactions were run at 0 °C.

Schaus, S. E.; Lou, S. *J. Am. Chem. Soc.* **2008**, *130*, 6922-6923

Catalytic Asymmetric Vinylation of Iminium cations with boronate (Ph)

Table 3. Asymmetric Petasis Reaction with Boronate **6d**[a]

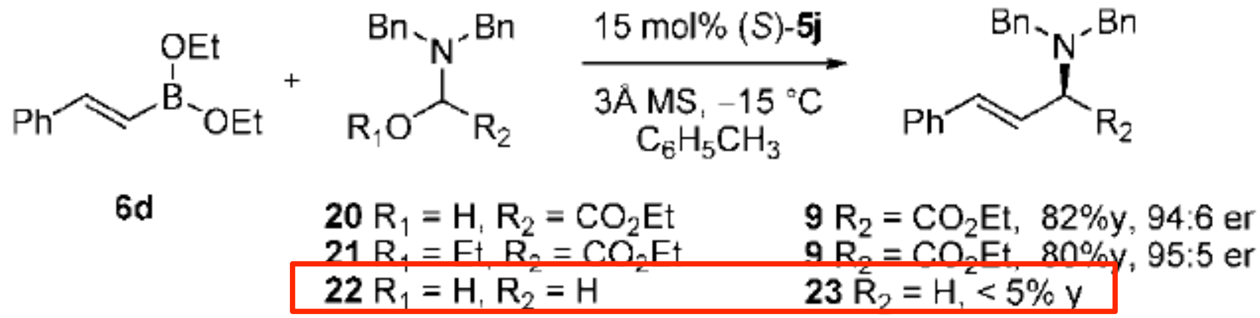


entry	amine	product	% yield[b]	er[c]
1	Bn-NH-CH_3	**17a**	81	95:5
2	Bn-NH-*t*-Bu	**17b**	73	93:7
3	Bn-NH-CH_2CH_2Ph	**17c**	82	97:3
4	Bn-NH-CH_2CH_2CN	**17d**	80	98.5:1.5
5	Bn-NH-CH_2CO_2Et	**17e**	94	95:5
6	Bn-NH-CH_2TMS	**17f**	84	95.5:4.5
7	Ph-NH-Et	**17g**	74	89:11
8		**17h**	87	97:3
9		**17i** 	81	dr 90:10 (*R,R*:*R,S*)
10		**17j** 	89	dr 84:16 (*S,R*:*S,S*)

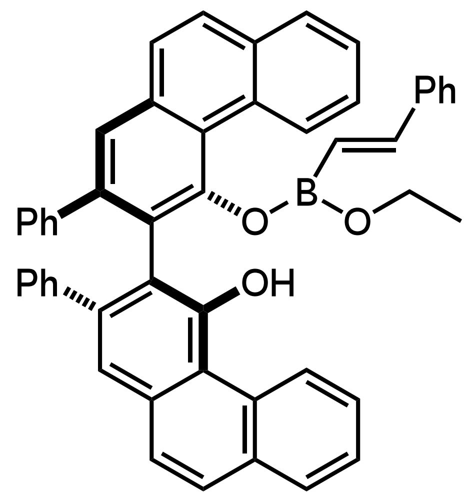
Schaus, S. E.; Lou, S. *J. Am. Chem. Soc.* **2008**, *130*, 6922-6923

Mechanistic Studies

Scheme 2

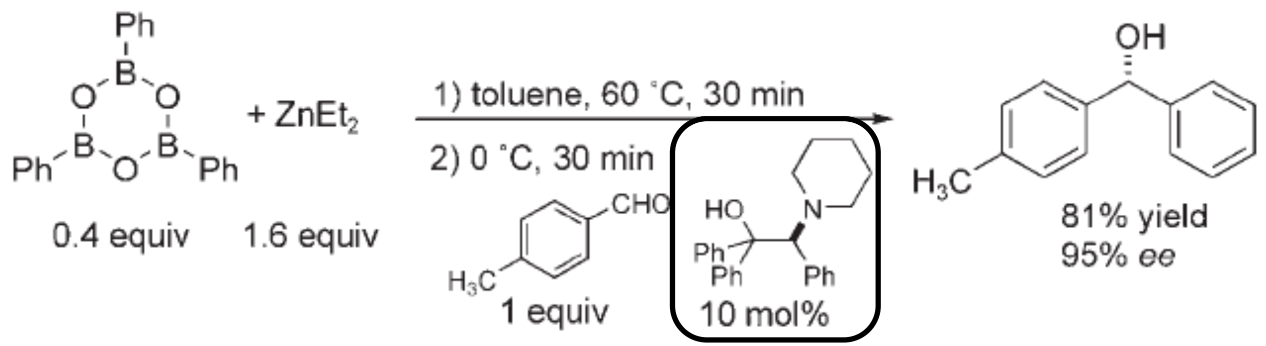


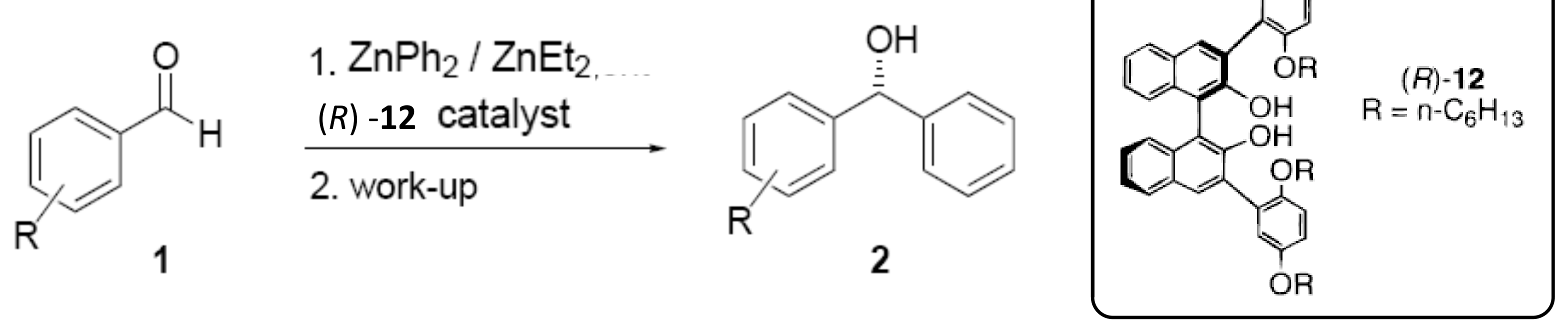
Importance of Ester

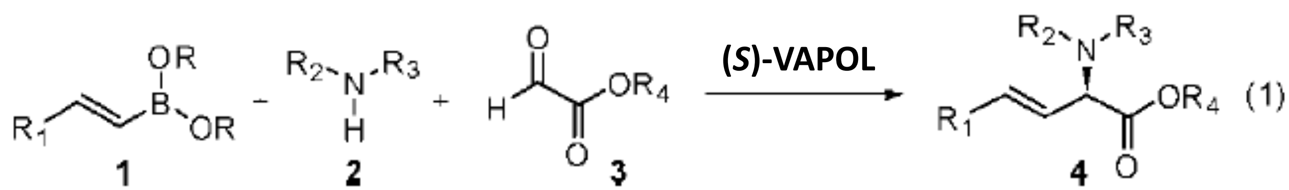


Single Ligand Exchange
(based on NMR and ESI-MS Studies)

Careful Observation of all the reactions



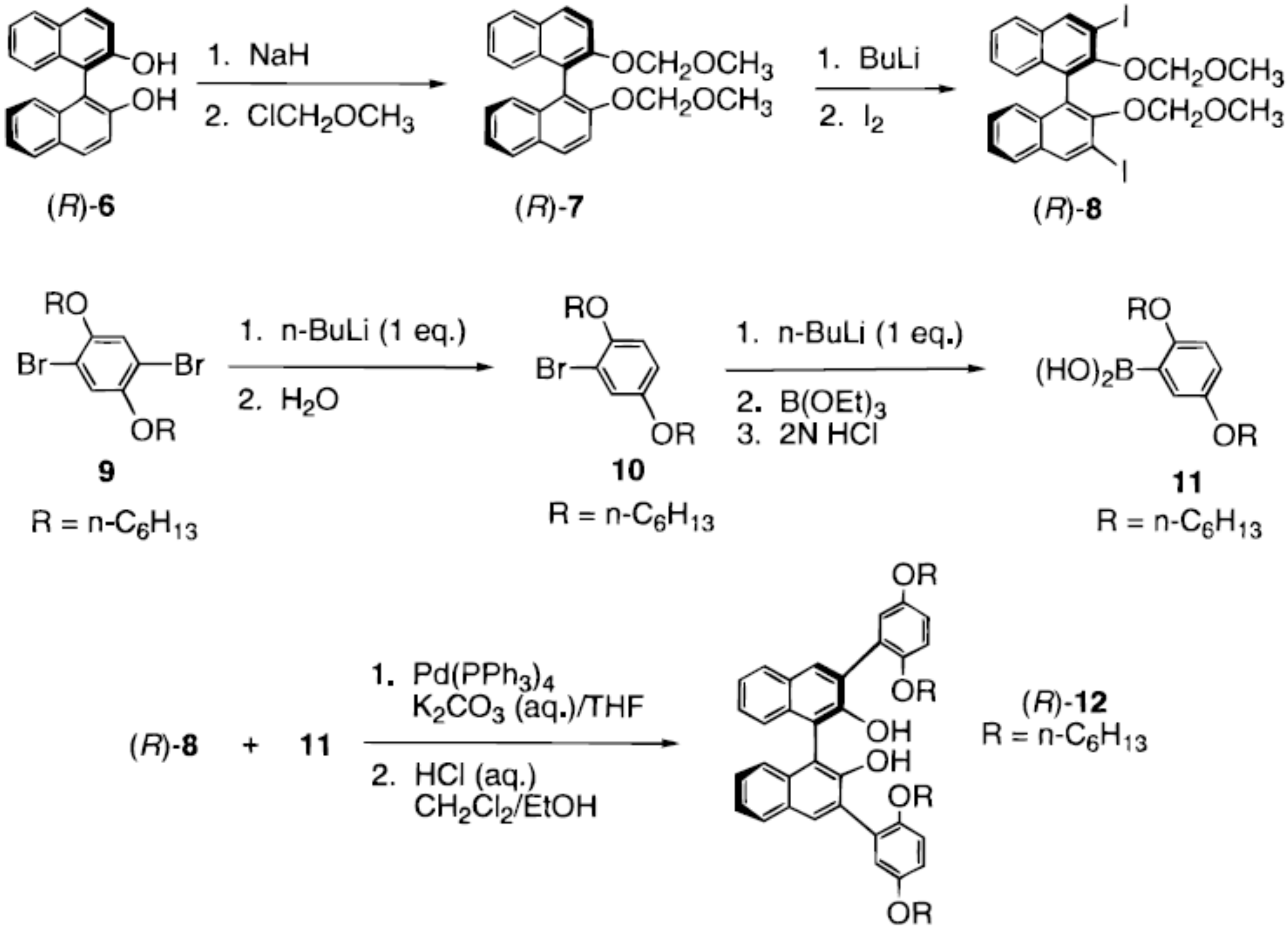




Alkenyl boronate glyoxylate Chiral α amino ester

Huang, W.-S.; Hu, Q.-S.; Pu, L. *J. Org. Chem.* **1999**, *64,* 7940-7956

Scheme 1. Synthesis of a Monobinaphthyl Model Compound (*R*)-12



Huang, W.-S.; Hu, Q.-S.; Pu, L. *J. Org. Chem.* **1999**, *64,* 7940-7956

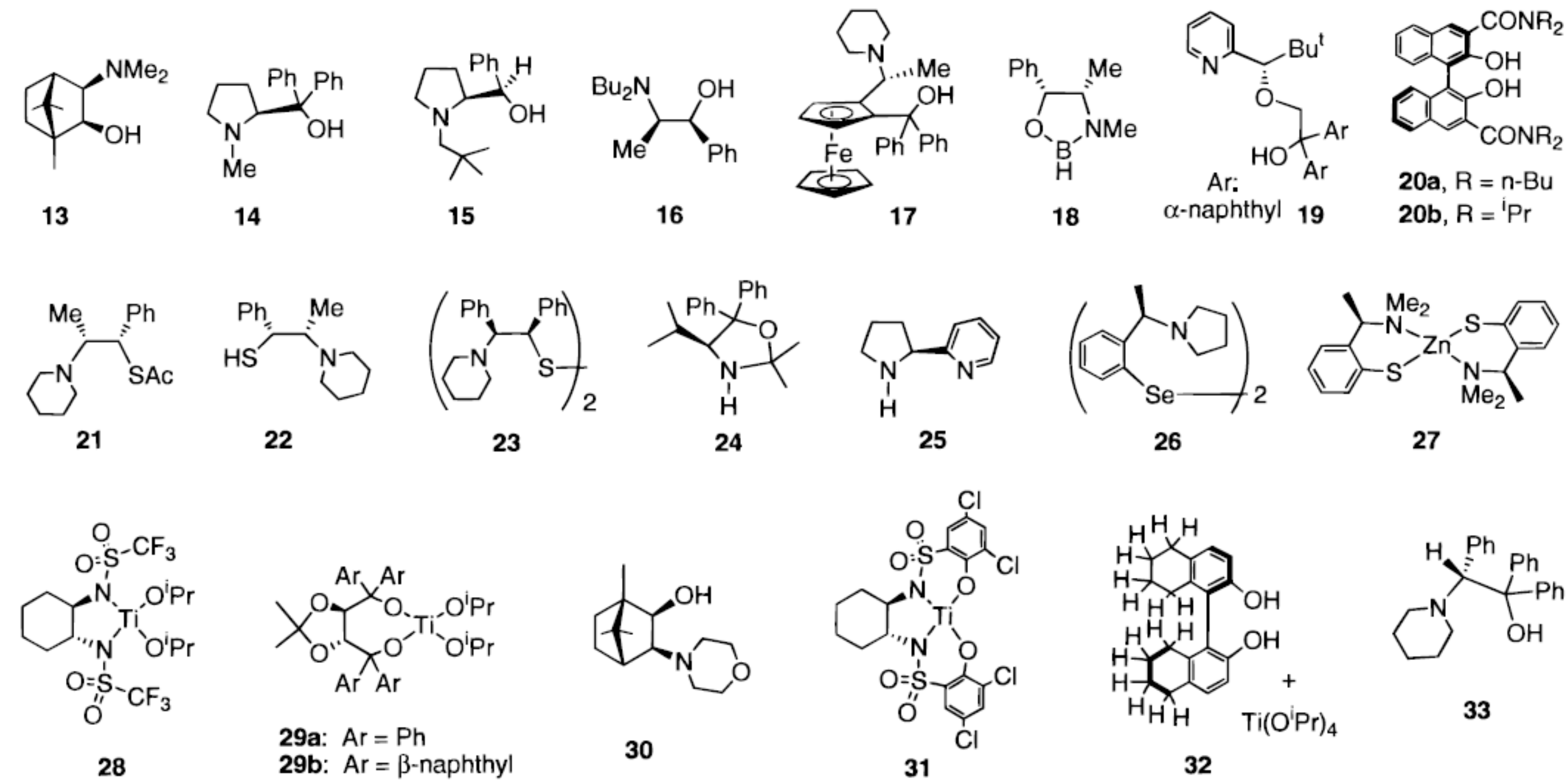


Figure 2. Currently known good catalysts for the enantioselective diethylzinc addition to aldehydes.

Huang, W.-S.; Hu, Q.-S.; Pu, L. *J. Org. Chem.* **1999**, *64,* 7940-7956