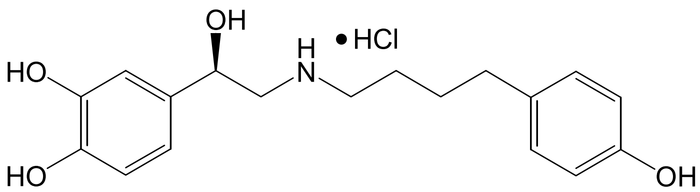
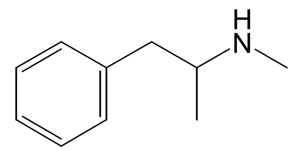
Asymmetric Henry and Aza-Henry Reactions

D.J. Osborn III

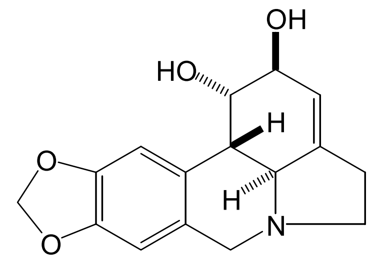
Drugs and Sugars



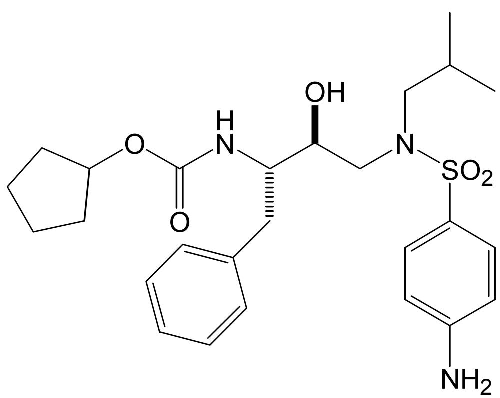
Arbutamine
Coronary Heart Disease



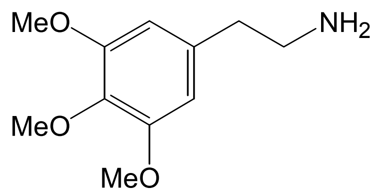
Methylamphetamine
ADHD



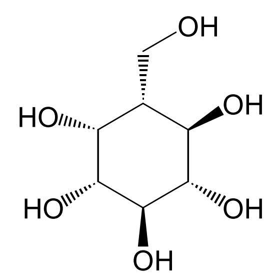
Lycorine



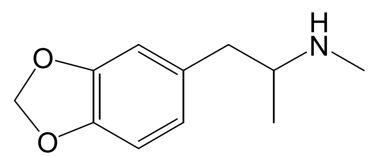
Amprenavir
HIV Protease Inhibitor



Mescaline
Seratonin Release



Substituted Inositols

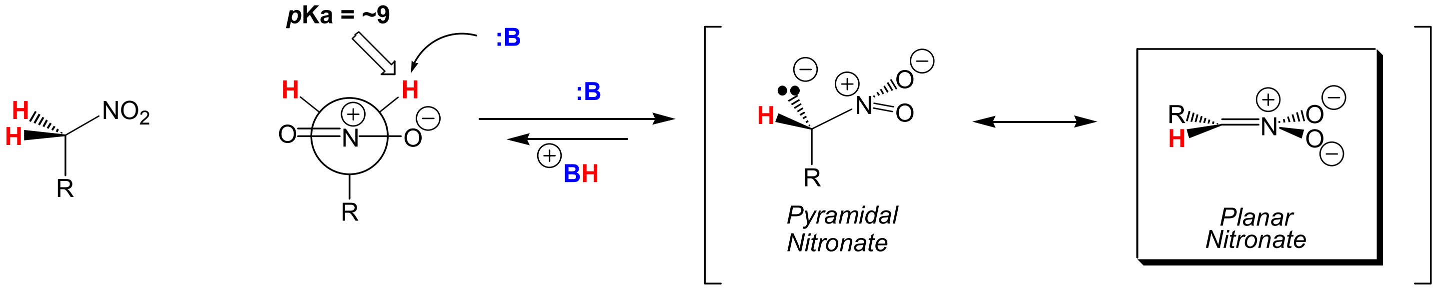


MDMA
Seratonin Release

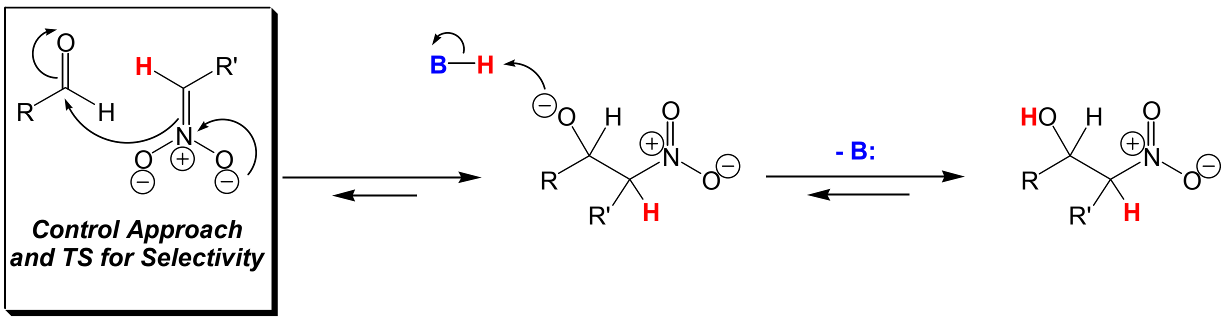
Recent Approaches to Selectivity

- Chiral Ligands
  - Shibasaki's Bimetallic Lanthanide/Lithium System
  - Trost's Zn/Chiral Phenol System
  - Lin's Zn/β-Amino Alcohol System
  - Jorgensens's Cu/BOX System
  - Evans' Cu/BOX System
- Chiral Quaternary Ammonium Salts
  - Corey
  - Maruoka
- Chiral Organic Catalysts
  - Takemoto's Chiral Thioureas
  - Johnston's Chiral Proton
- Dendrizymes
  - Smith
  - Cossio

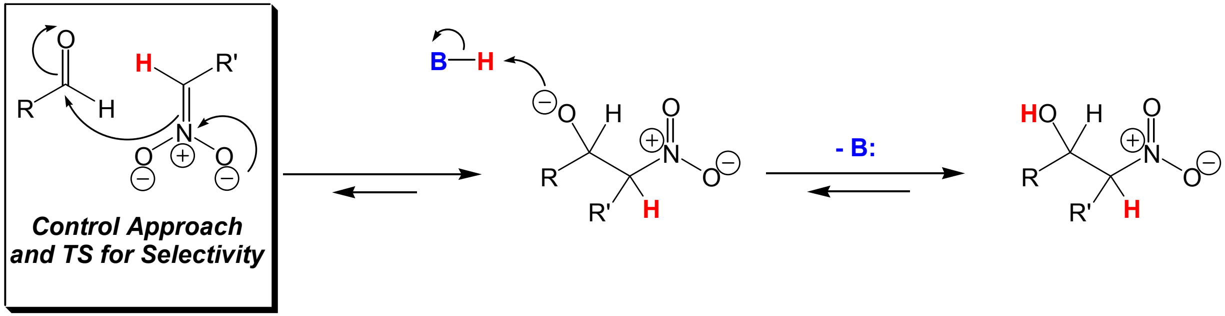
Henry Reaction – General Mechanism

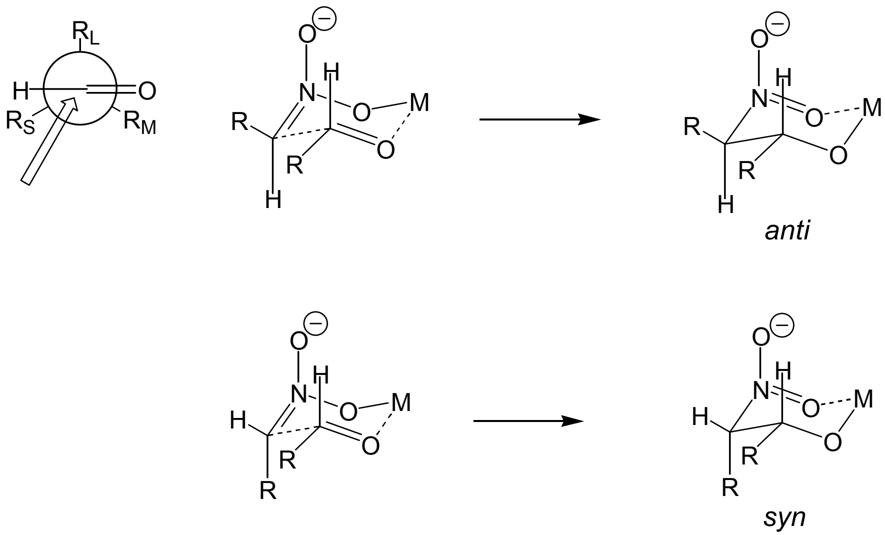


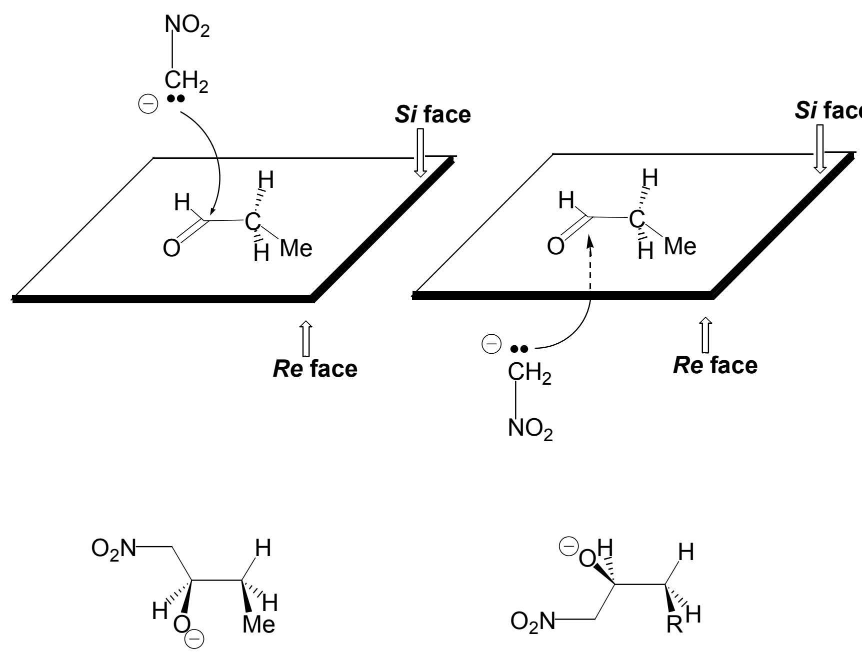
Control Nitronate Geometry and Reactivity to gain Selectivity



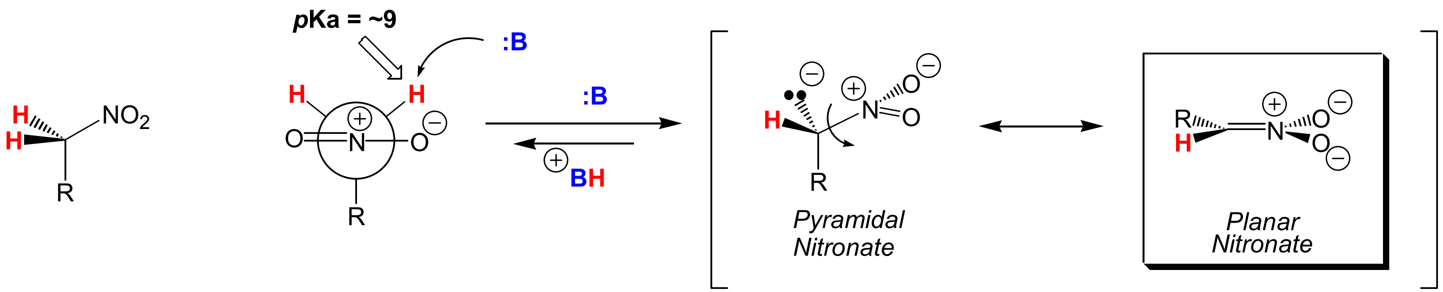
Henry Reaction – Selectivity



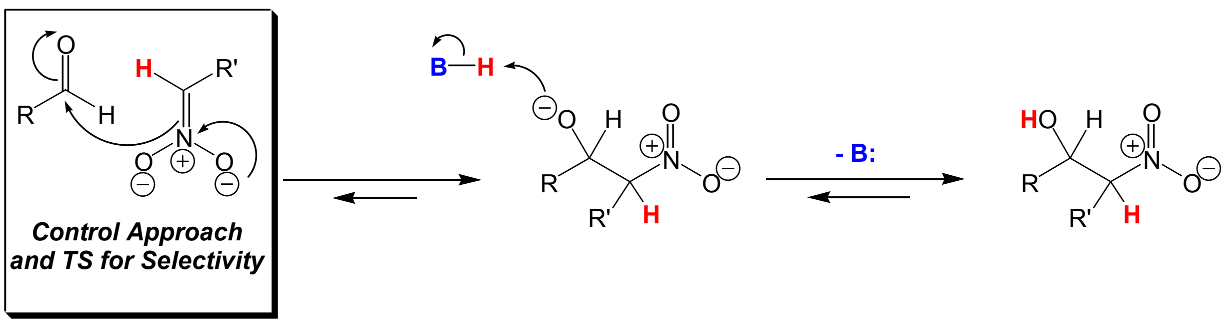


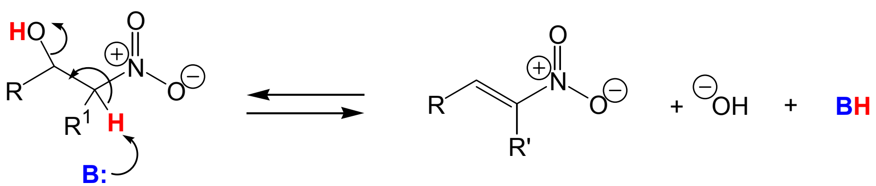


Henry Reaction – General Mechanism



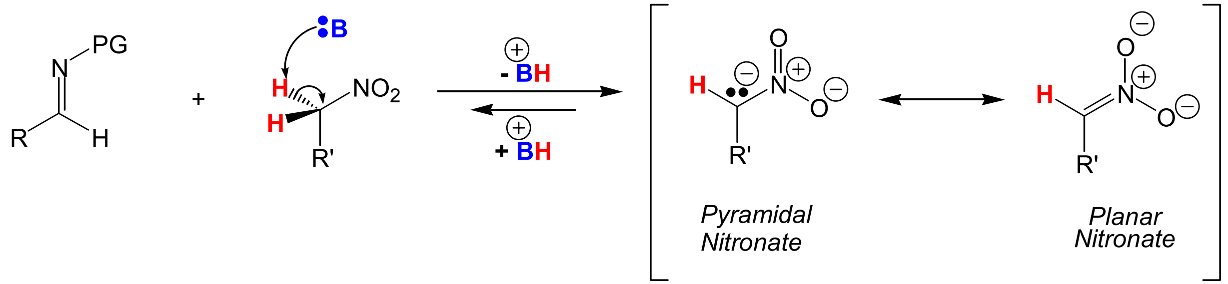
Control Nitronate Geometry and Reactivity to gain Selectivity

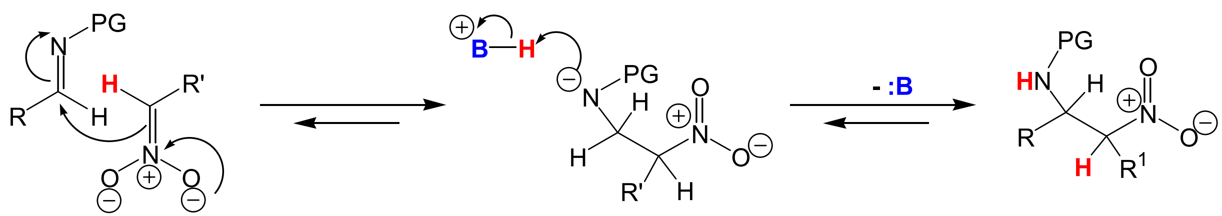




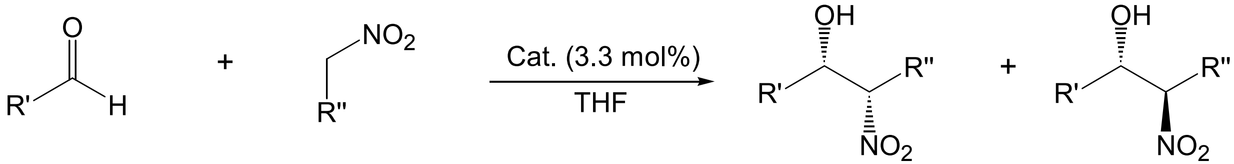
Elimination can be a problem

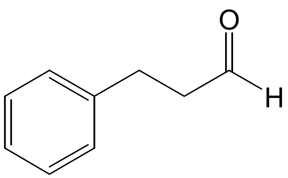
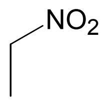
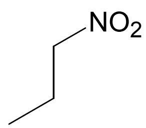
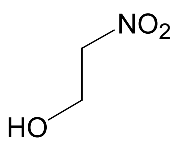
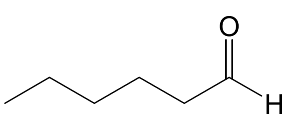
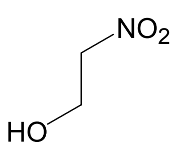
Aza-Henry Reaction – General Mechanism

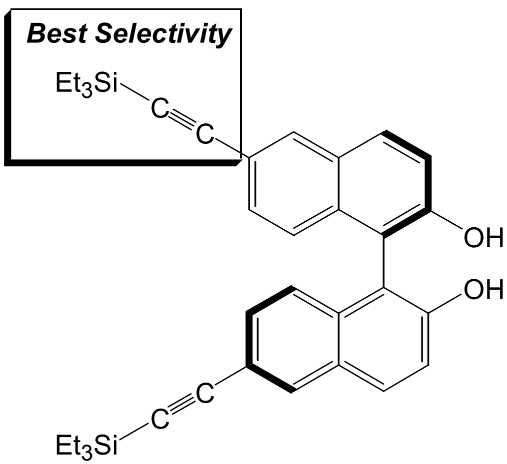




Bimetallic - Shibasaki



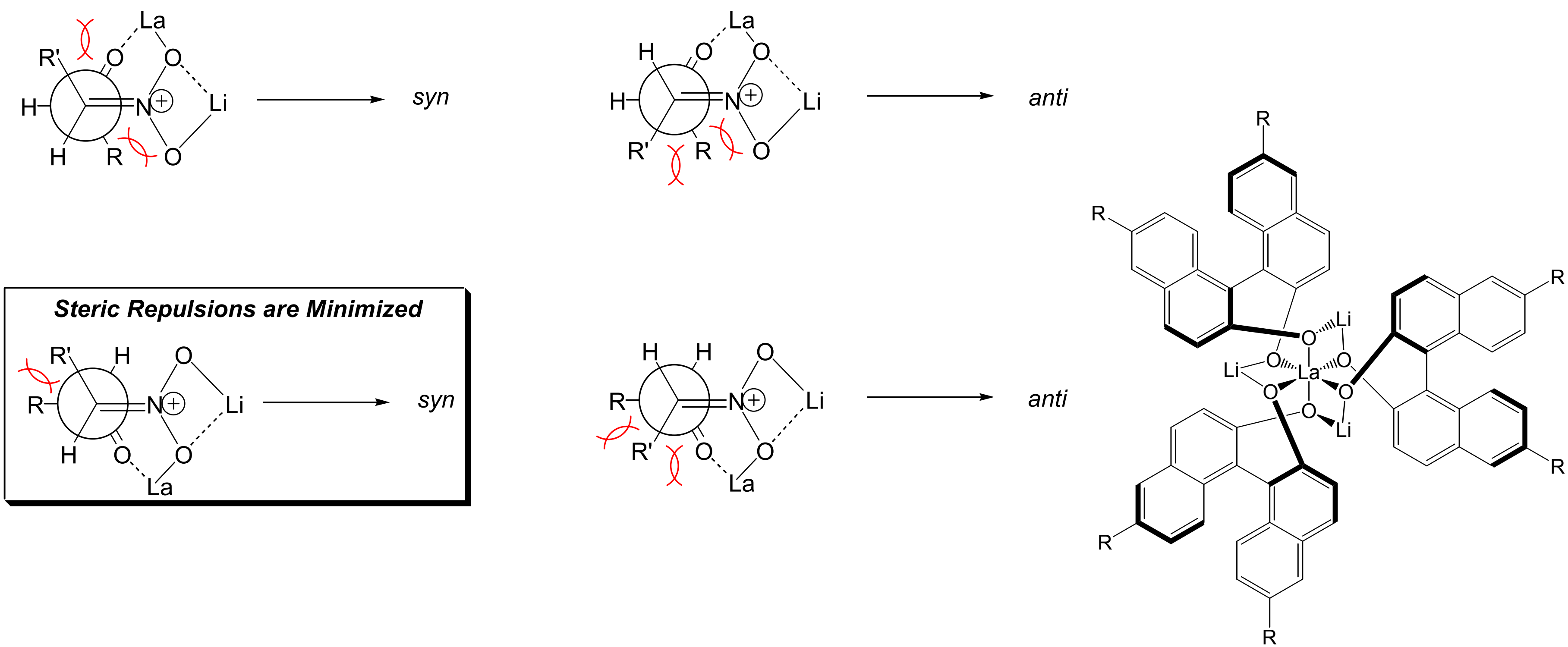
Aldehyde	Nitroalkane	Time (h)	Temp. (^oC)	Yield (%)	Syn / Anti	ee (%)
		75	-20	70	89:11	93
		138	-40	85	93:7	95
		111	-40	97	92:8	97
		93	-40	96	92:8	95



(R)-6,6'-Disubstituted BINOL

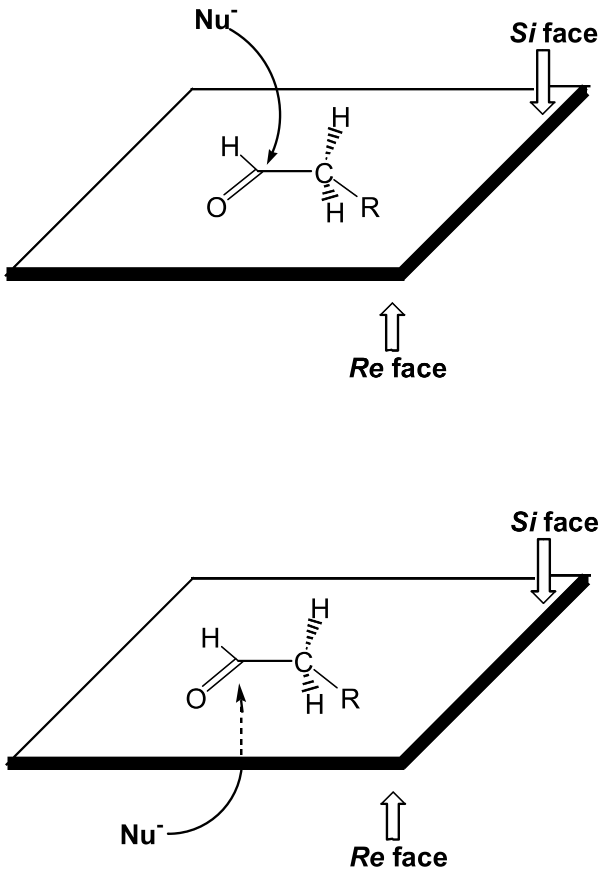
Sasai, H.; Tokunga, T.; Watanabe, S.; Suzuki, T.; Itoh, N.; Shibasaki, M. *J. Org. Chem.*, **1995**, *60*, 7388

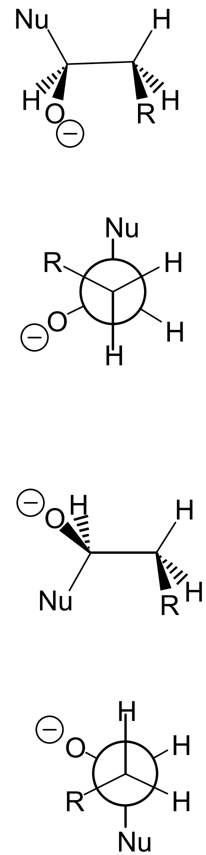
Bimetallic - Shibasaki

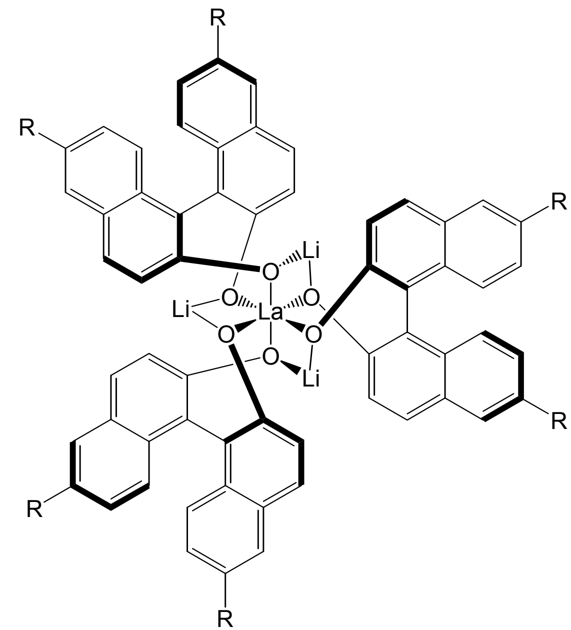


Sasai, H.; Tokunga, T.; Watanabe, S.; Suzuki, T.; Itoh, N.; Shibasaki, M. *J. Org. Chem.*, **1995**, *60*, 7388

Bimetallic - Shibasaki

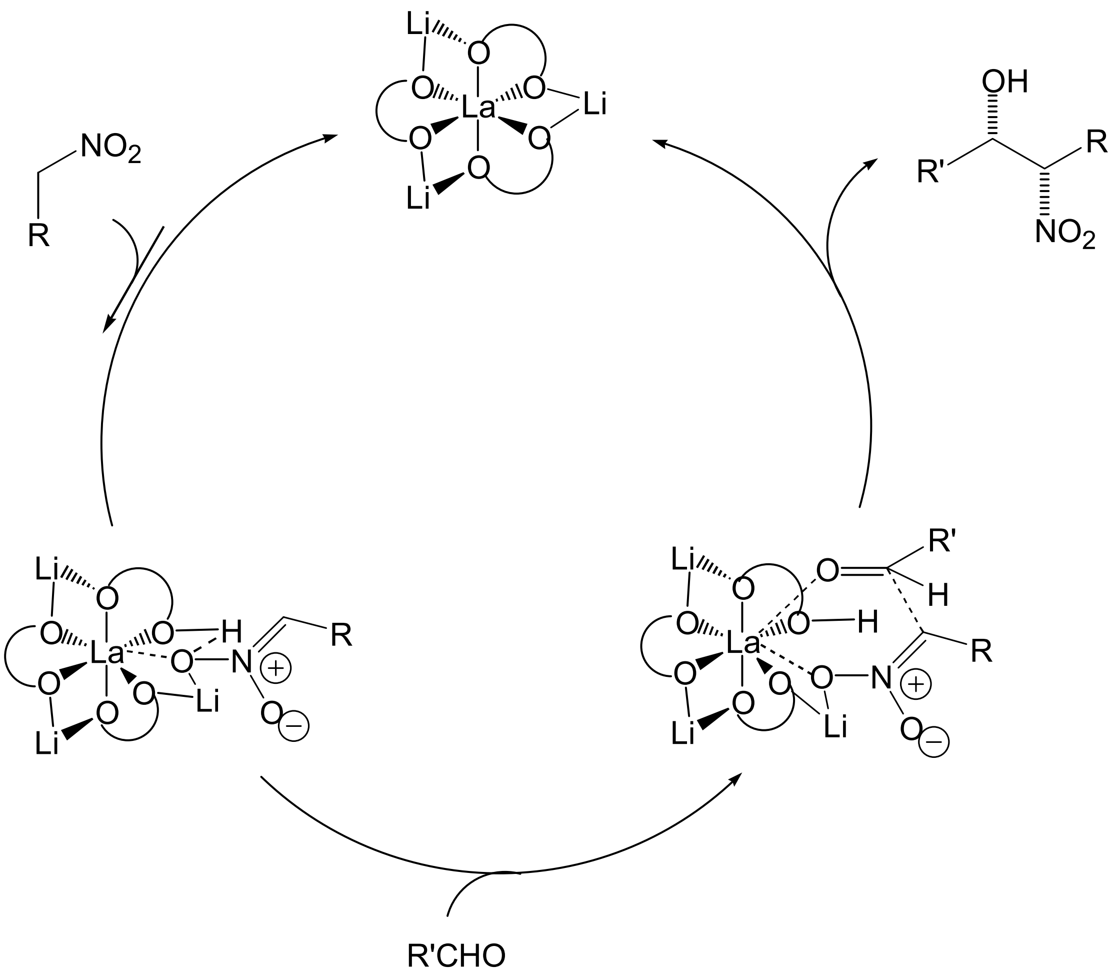


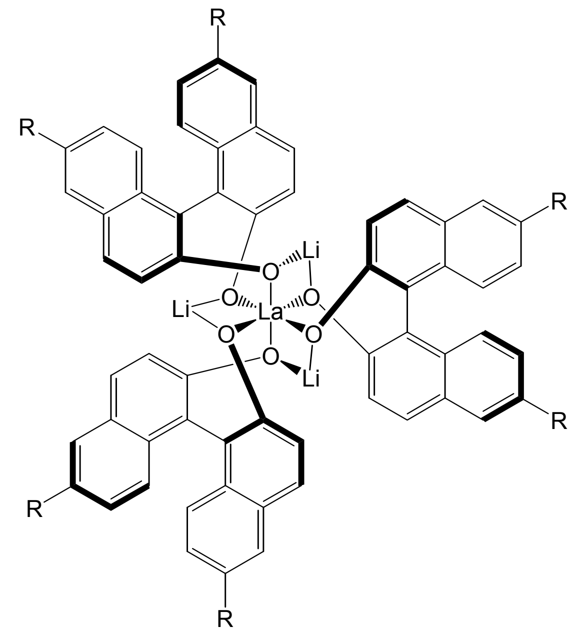




Sasai, H.; Tokunga, T.; Watanabe, S.; Suzuki, T.; Itoh, N.; Shibasaki, M. *J. Org. Chem.*, **1995**, *60*, 7388

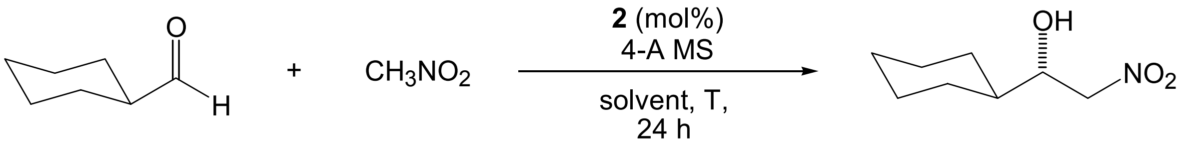
Bimetallic - Shibasaki



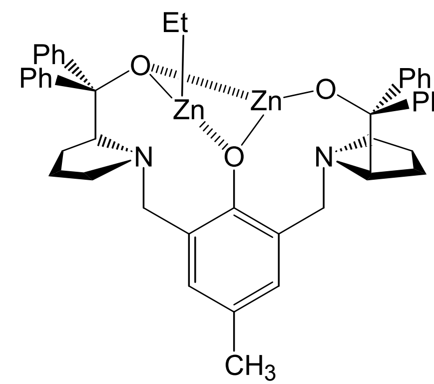


Sasai, H.; Tokunga, T.; Watanabe, S.; Suzuki, T.; Itoh, N.; Shibasaki, M. *J. Org. Chem.*, **1995**, *60*, 7388

Zinc Based - Trost



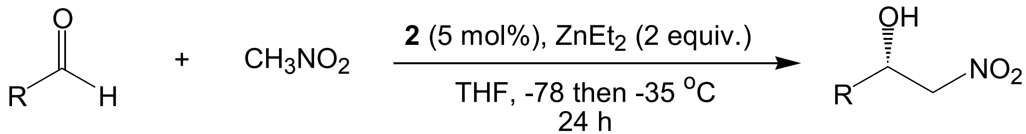
CH_3NO_2 (equiv)	Catalyst (mol%)	T (^oC)	Solvent	% Yield	% ee
10	5	5	THF	69	78
10	5	-20	THF	68	85
10	5	-20	toluene	68	57
10	5	-20	CH_2Cl_2	75	51
10	5	-20	Et_2O	20	55
2	5	-20	THF:dioxane, 4:1	17	86
2	5	-78 then -20	THF	75	85
10	2.5	-78 then -20	THF	44	85
6	5	-78 then -20	THF	70	86

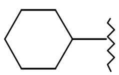
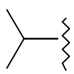
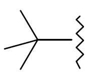
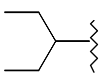
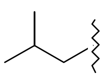
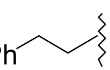
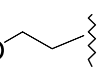


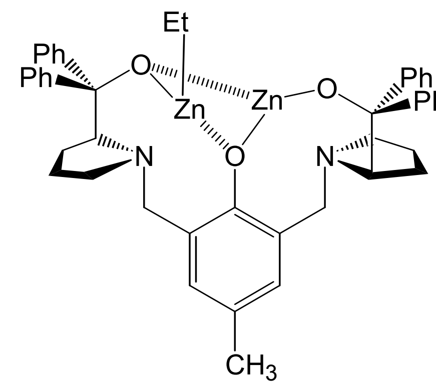
2

Trost, B. M.; Yeh, V. S. C. *Angew. Chem.-Int. Edit.* **2002**, *41*, 861

Zinc Based - Trost



R	Yield (%)	ee (%)
	75	85
	58	88
	88	93
	90	92
	84	87
	59	84
	56	86



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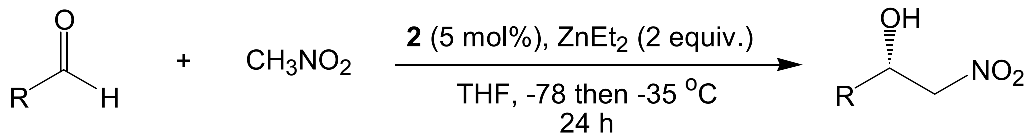
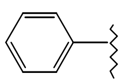
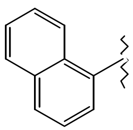
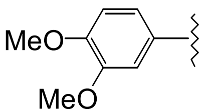
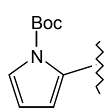
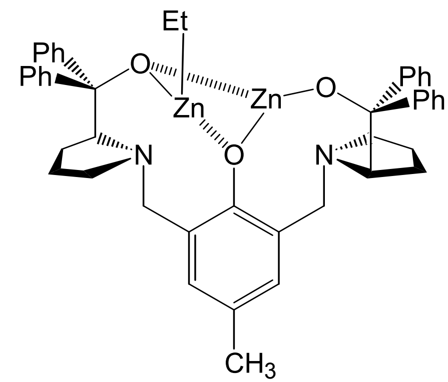
Zinc Based - Trost



R	Yield (%)	ee (%)
	75	91
	71	93
	69	78
	79	90



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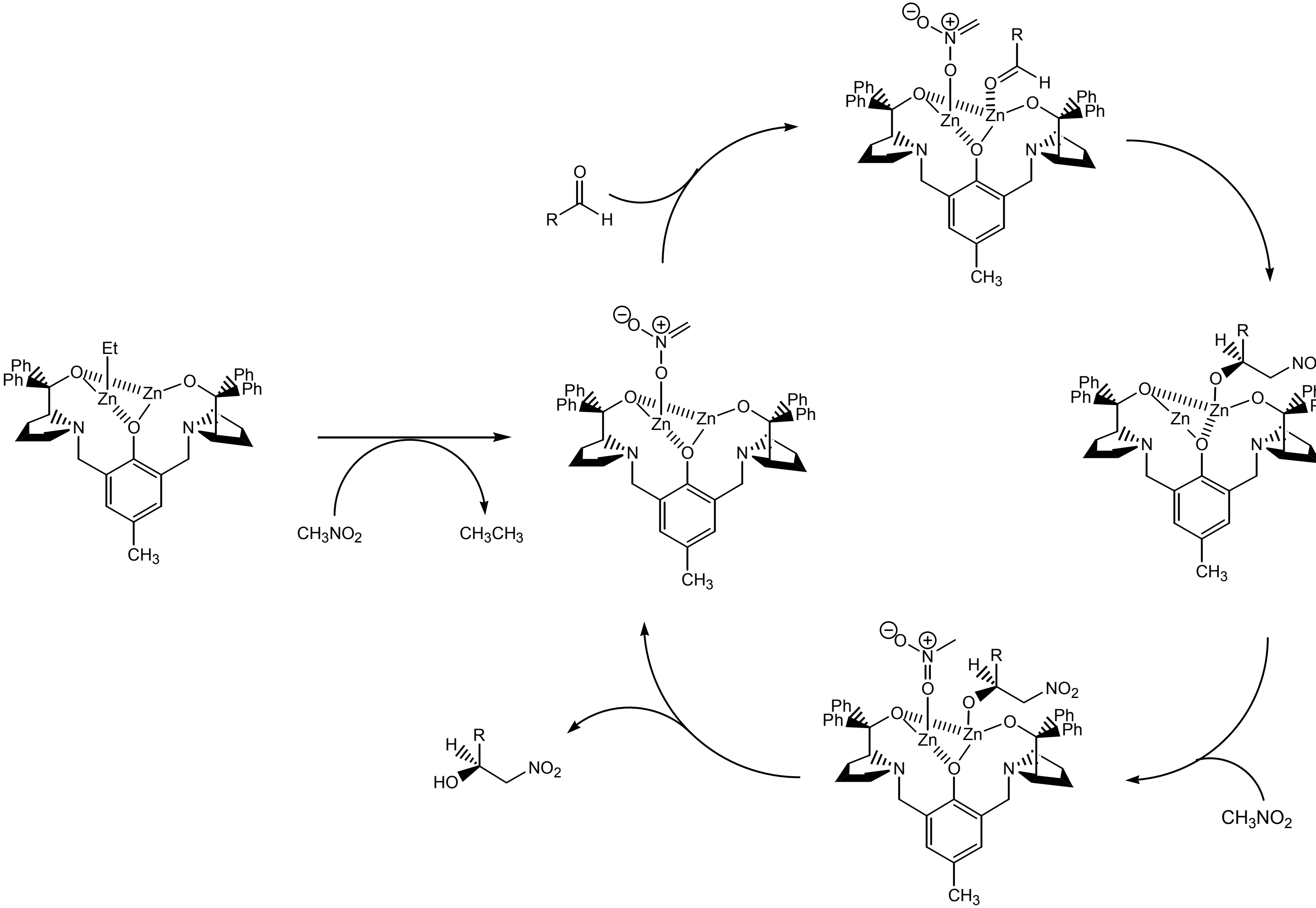
Zinc Based - Trost



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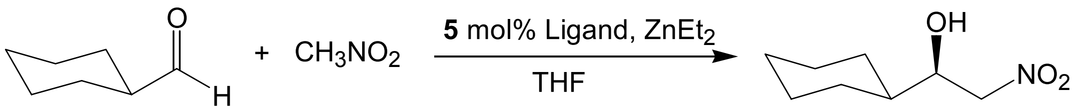
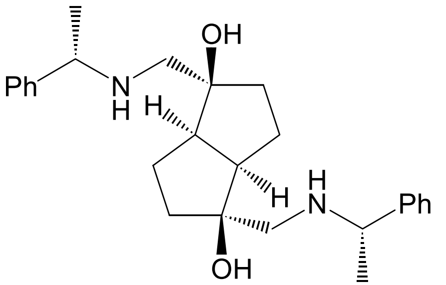
Zinc Based - Lin



Ligand	Ligand : $ZnEt_2$	Temperature	Time	Yield (%)	ee (%)
4b	1 : 3	0 °C	10	87	38
5	1 : 3	0 °C	10	81	12
4b	1 : 5	0 °C	7	93	25
4b	1 : 2	0 °C	7	77	46
4b	1 : 1	0 °C	9	59	38
4b	1 : 2	-25 °C	8	75	59
4a	1 : 2	-25 °C	8	90	52



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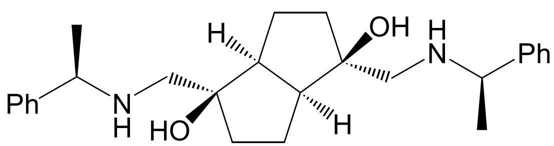
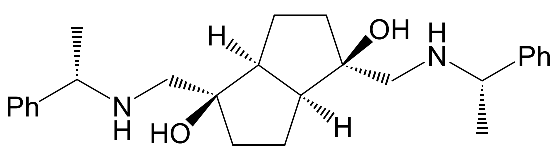


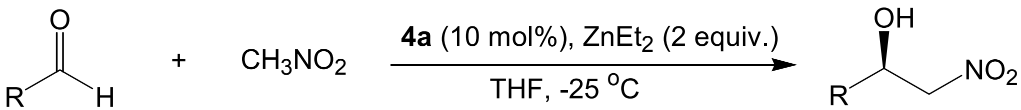
4b

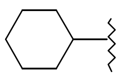
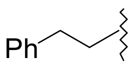
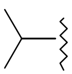
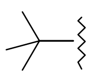
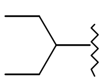
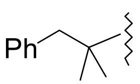


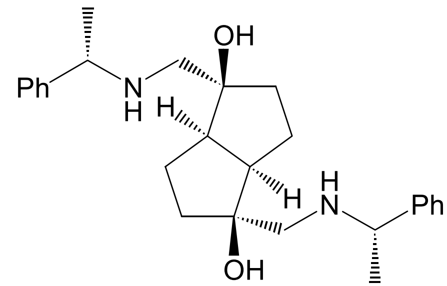
5

Zhong, Y. W.; Tian, P.; Lin, G. Q. *Tetrahedron: Asymmetry* **2004**, *15*, 771

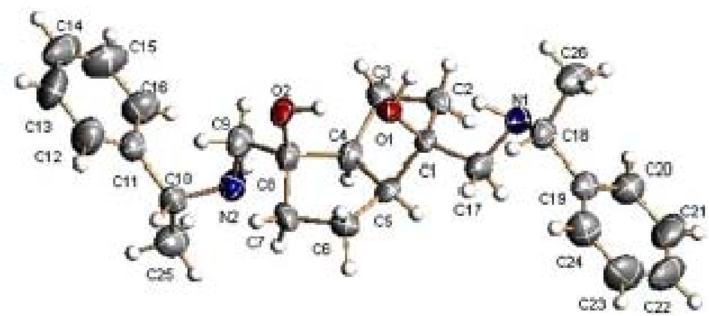
Zinc Based - Lin



R	Time	Yield (%)	ee (%)
	8	90	52
	11	74	37
	10	90	66
	12	82	67
	20	50	69
	20	40	74

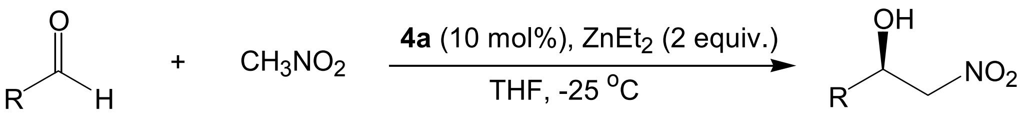


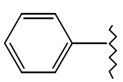
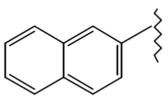
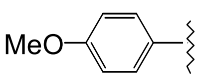
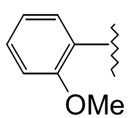
4a

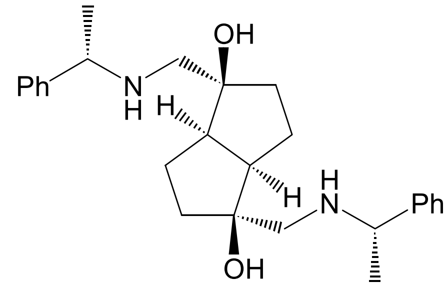


Zhong, Y. W.; Tian, P.; Lin, G. Q. *Tetrahedron: Asymmetry* **2004**, *15*, 771

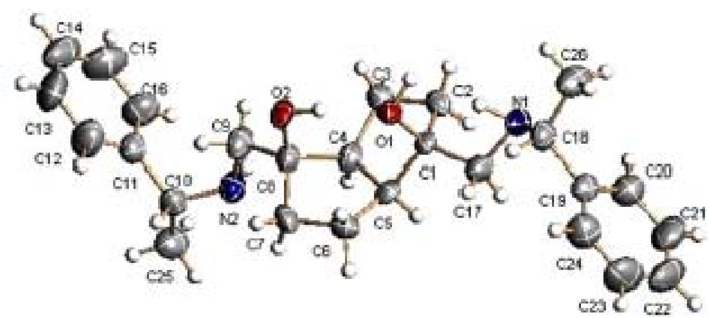
Zinc Based - Lin



R	Time	Yield (%)	ee (%)
	8	80	33
	36	81	25
	42	73	21
	23	75	49

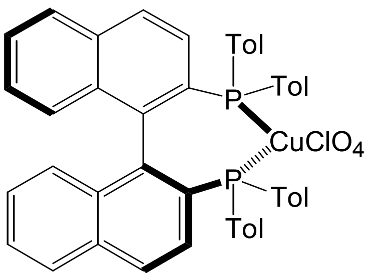


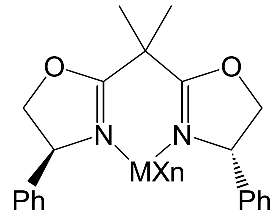
4a

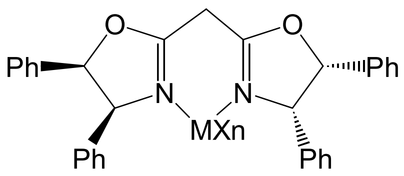


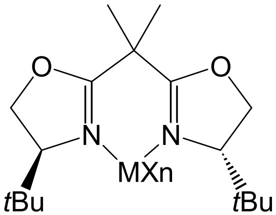
Zhong, Y. W.; Tian, P.; Lin, G. Q. *Tetrahedron: Asymmetry* **2004**, *15*, 771

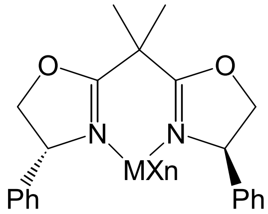
Copper Based - Jorgensen

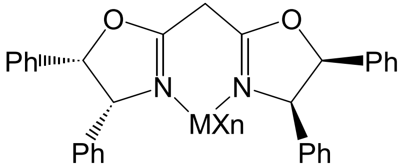




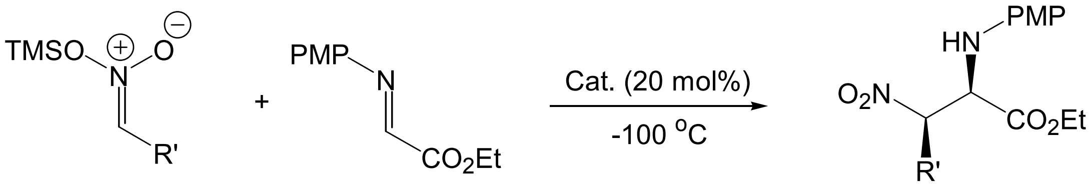




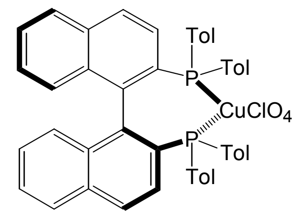




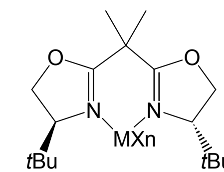
Copper Based - Jorgensen



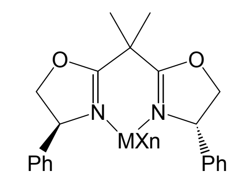
R'	Catalyst	% Yield	% ee erythro	erythro:threo	Configuration (C2,C3)
Et	(*R*)-**4**	99	16	1:3	(*R*,*R*)
Et	(*R*)-**5a**	99	12	11:1	(*S*,*S*)
Et	(*R*)-**5b**	58	56	7:1	(*R*,*R*)
Et	(*S*)-**6a**	90	90	3:1	(*S*,*S*)
Et	(*S*)-**6b**	63	56	5:1	(*S*,*S*)
Et	(*S*)-**6c**	67	89	18:1	(*S*,*S*)
Et	(*S*)-**6d**	92	70	6:1	(*S*,*S*)
Et	(4*R*,5*S*)-**7a**	52	96	6:1	(*R*,*R*)
Et	(4*R*,5*S*)-**7b**	68	97	10:1	(*R*,*R*)
Et	(4*R*,5*S*)-**7c**	54	26	9:1	(*R*,*R*)
Et	(4*R*,5*S*)-**7d**	94	95	25:1	(*R*,*R*)
Me	(*S*)-**6a**	67	>98	5:	(*S*,*S*)
Pentyl	(4*R*,5*S*)-**7d**	87	83	39:1	(*R*,*R*)
Bn	(4*R*,5*S*)-**7a**	93	88	32:	(*R*,*R*)



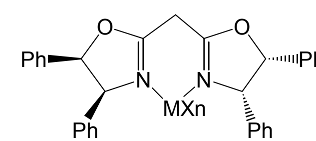
4 *(R)-Tol-BINAP*



5a: MX_n = Cu(I)ClO_4
5b: MX_n = Cu(I)$(OTf)_2$



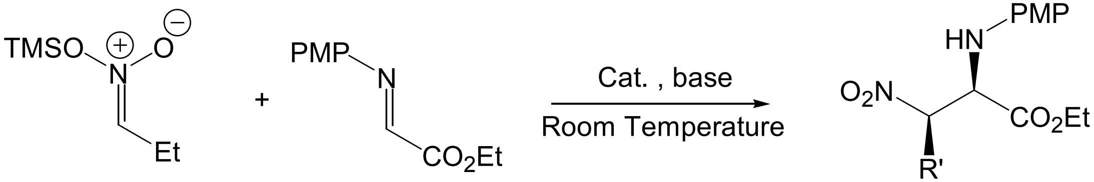
6a: MX_n = Cu(I)ClO_4
6b: MX_n = Cu(I)PF_6
6c: MX_n = Cu(I)$(OTf)_2$
6d: MX_n = Cu(I)$(SbF_6)_2$



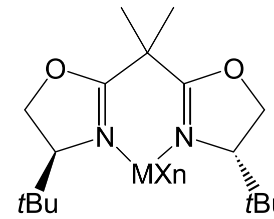
7a: MX_n = Cu(I)ClO_4
7b: MX_n = Cu(I)PF_6
7c: MX_n = Cu(I)$(OTf)_2$
7d: MX_n = Cu(I)$(SbF_6)_2$

Knudsen, K. R.; Risgaarc, T.; Nishiwaki, N.; Gothelf, K. V..; Jorgensen, K. A. *J. Am. Chem. Soc.*, **2001**, *123*, 5843

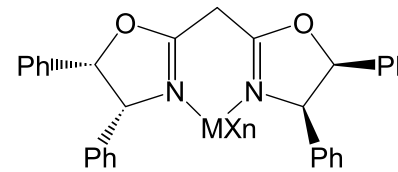
Copper Based - Jorgensen



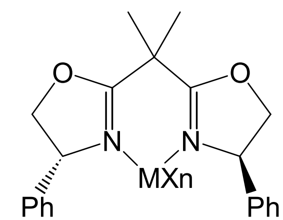
Catalyst	Mol %	Solvent	Time (days)	% Conv.	*syn* / *anti*	ee (*syn* / anti)
4a	20	CH_2Cl_2	1	8	95 / 5	87 / 70
5a	20	CH_2Cl_2	1	62	84 / 16	2 / 2
6a	20	CH_2Cl_2	1	85	92 / 8	94 / 85
6a	20	THF	1	14	96 / 4	97 / 90
6a	20	Et_2O	1	26	97 / 3	97 / 83
6b	20	CH_2Cl_2	1	85	60 / 40	26 / 21
6c	20	CH_2Cl_2	1	69	95 / 5	93 / 86
6a	20	CH_2Cl_2	1	83	82 / 18	95 / 95
6a	20	CH_2Cl_2	1	40	95 / 5	97 / 91
6a	20	CH_2Cl_2	1	80	54 / 46	72 / 76
6a	20	CH_2Cl_2	1	43	95 / 5	96 / 86
6a	10	CH_2Cl_2	7	83	92 / 8	91 / 85
6a	20	CH_2Cl_2	1	86	93 / 7	95 / 79
6a	20	CH_2Cl_2	5	87	95 / 5	97 / 87



(*S*) - **4**



(4*R*, 5*S*) - **5**

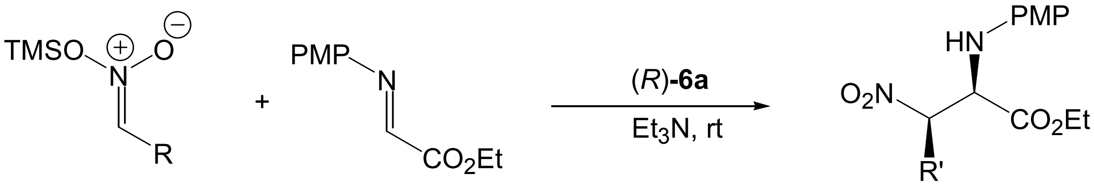


(*R*) - **6**

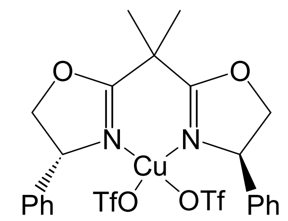
a : MX_n = Cu(I)$(OTf)_2$
b : MX_n = Cu(I)$(SbF_6)_2$
c : MX_n = Cu(I)Br_2

Nishiwaki, N.; Knudsen, K. R.; Gothelf, K. V..; Jorgensen, K. A. *Angew. Chem. Int. Ed.*, **2001**, *40*, 2992

Copper Based - Jorgensen



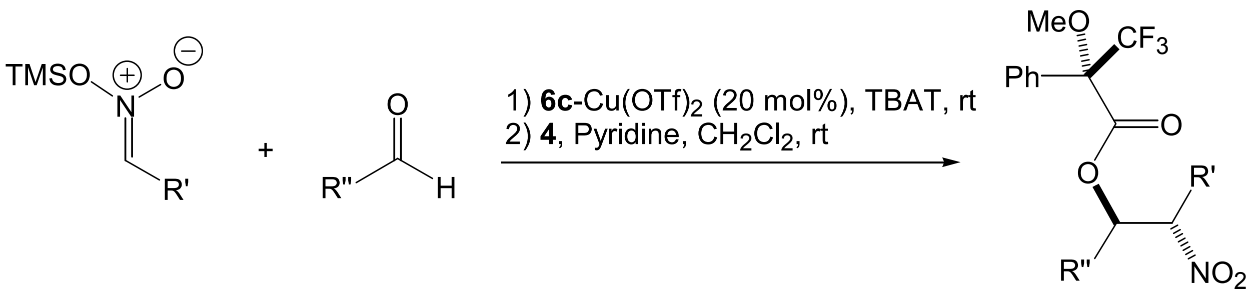
Catalyst	Temperature (^oC)	% Yield	dr *syn* / *anti*	ee (*syn* / anti)
Et	0	81	95 / 5	97 / 87
H	rt	38	——	87
Me	rt	61	70 / 30	97 / 95
Me	0	50	73 / 27	99 / 98
Pentyl	rt	52	93 / 7	97 / 89
Bn	rt	80	95 / 5	95 / 88
Ph	rt	59	55 / 45	74 / 77

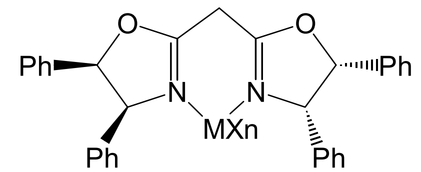


(*R*) - **6a**

Nishiwaki, N.; Knudsen, K. R.; Gothelf, K. V..; Jorgensen, K. A. *Angew. Chem. Int. Ed.*, **2001**, *40*, 2992

Copper Based - Jorgensen



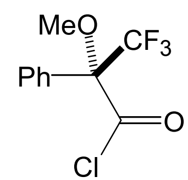


6c

R'	R''	% Yield	dr threo:erythro	%ee threo
Et	Ph	76	5 : 1	65
Et	*p*-$MeOC_6H_4$	34	3 : 1	59
Et	*p*-NCC_6H_4	47	>10 : 1	40
Et	*p*-$O_2NC_6H_4$	63	>10 : 1	50
Et	*m*-$O_2NC_6H_4$	67	>10 : 1	45
Et	2-Np	34	2.5 : 1	60
Pentyl	Ph	81	3 : 1	43
Et	(*E*)-Ph-CH=CH	44	>10 : 1	45

$(Bu)_4N^{\oplus}$ $Si(F)_2(Ph)_3^{\ominus}$

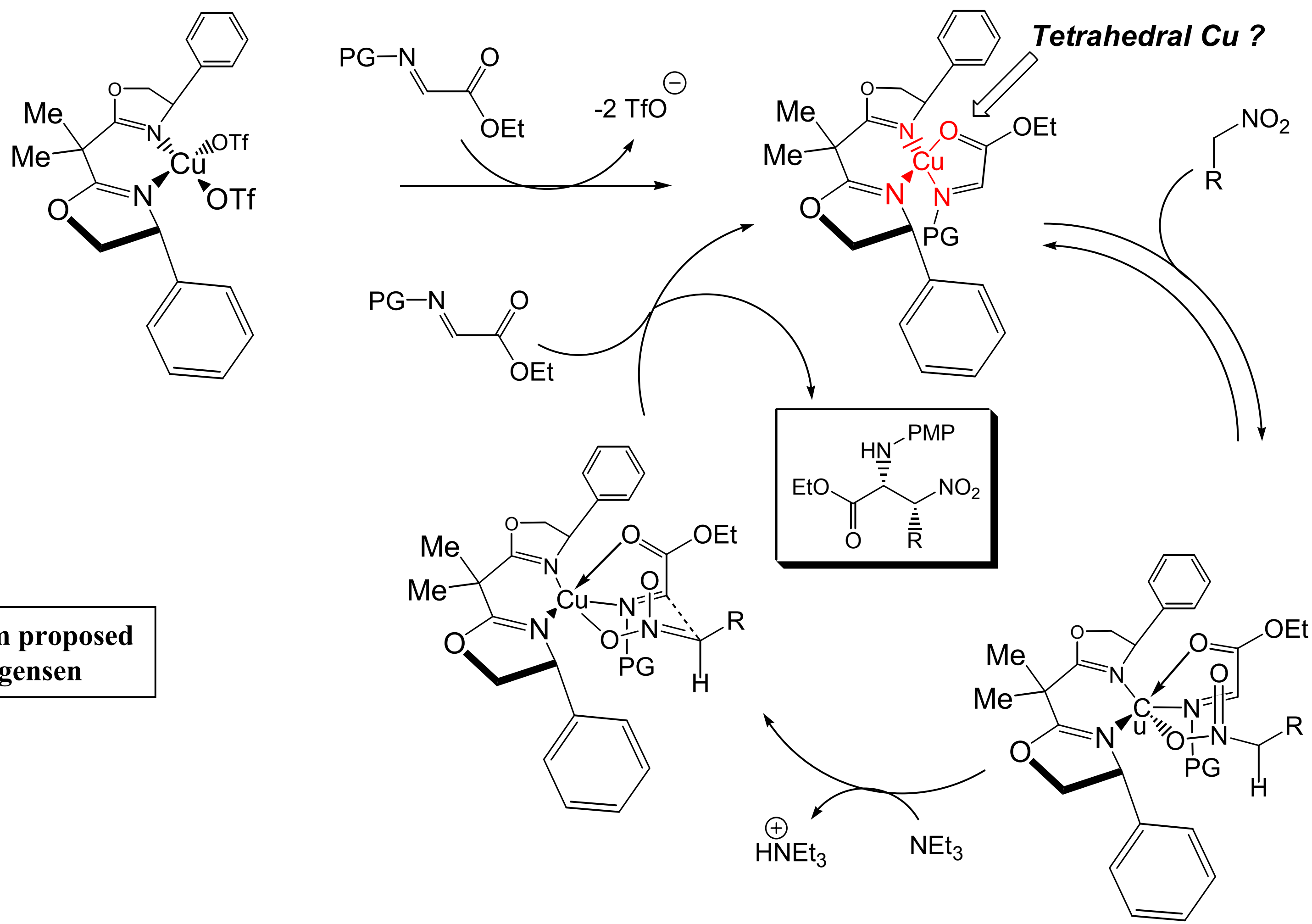
TBAT
tetrabutylammonium
triphenylsilyldifluorosilicate



4

Risgaard, T.; Gothelf, K. V.; Jorgensen, K. A. *Org. Biomol. Chem.* **2003**, *1*, 153

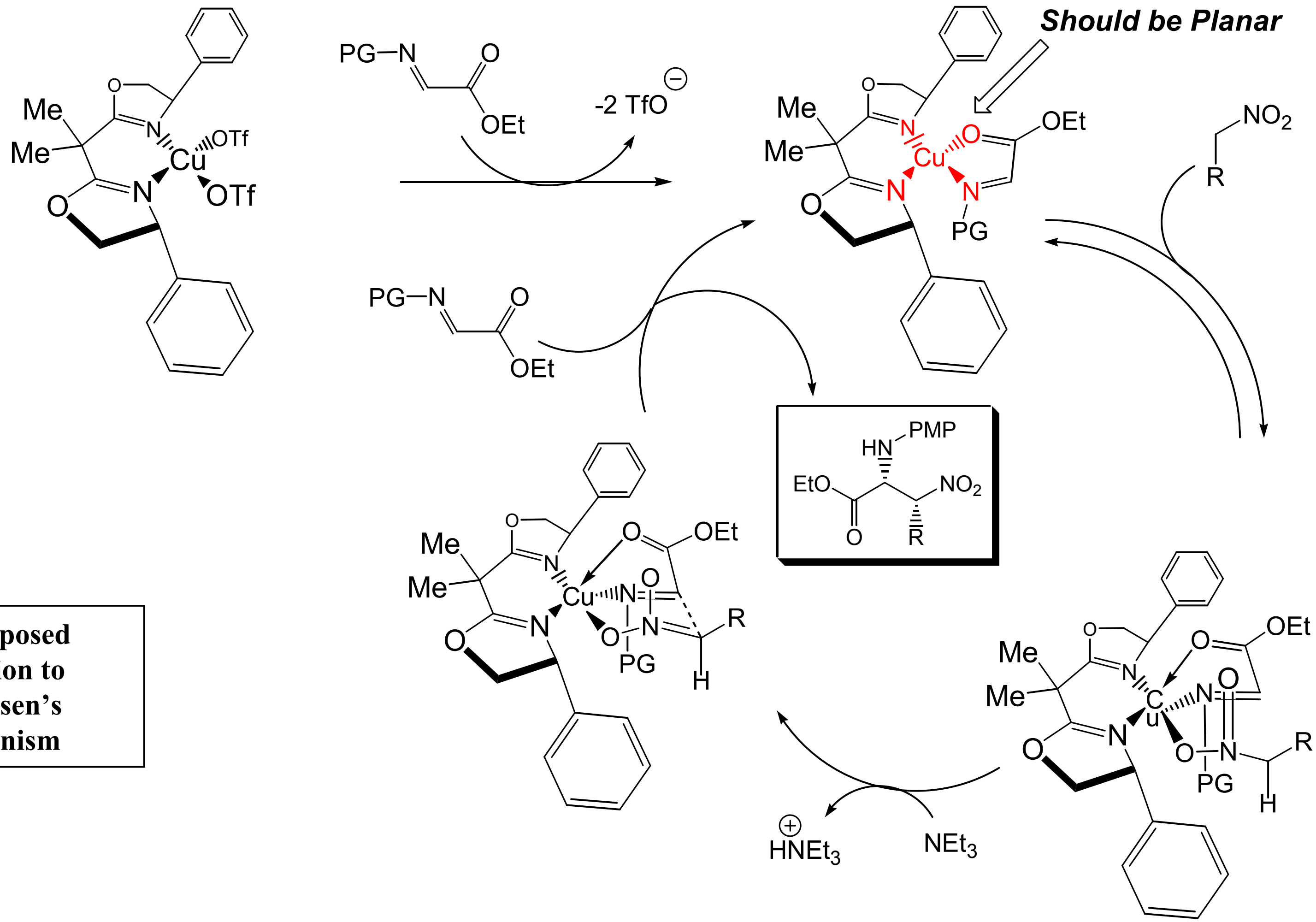
Copper Based - Jorgensen



Mechanism proposed by Jorgensen

Nishiwaki, N.; Knudsen, K. R.; Gothelf, K. V..; Jorgensen, K. A. *Angew. Chem. Int. Ed.*, **2001**, *40*, 2992

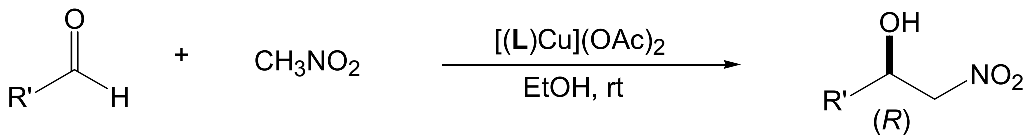
Copper Based - Jorgensen



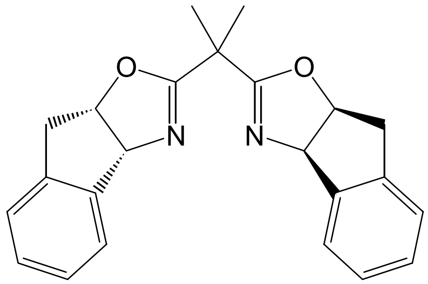
My proposed alteration to Jorgensen's Mechanism

Nishiwaki, N.; Knudsen, K. R.; Gothelf, K. V..; Jorgensen, K. A. *Angew. Chem. Int. Ed.*, **2001**, *40*, 2992

Copper Based - Evans



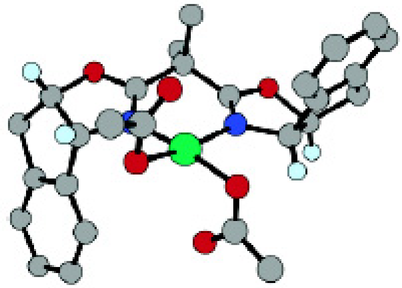
R'	Time (h)	Yield (%)	ee (%)
Ph	22	76	94
2-MeC_6H_4	42	72	93
2-$MeOC_6H_4$	27	91	93
2-NOC_6H_4	4	86	89
2-ClC_6H_4	15	88	91
1-naphthyl	15	66	87
4-FC_6H_4	45	70	92
4-ClC_6H_4	21	73	90
4-PhC_6H_4	20	70	91
$PhCH_2CH_2$	24	81	90
i-Bu	48	86	92
i-Bu	96	83	94
i-Pr	48	86	94
n-Bu	48	87	93
cyclohexyl	48	95	93

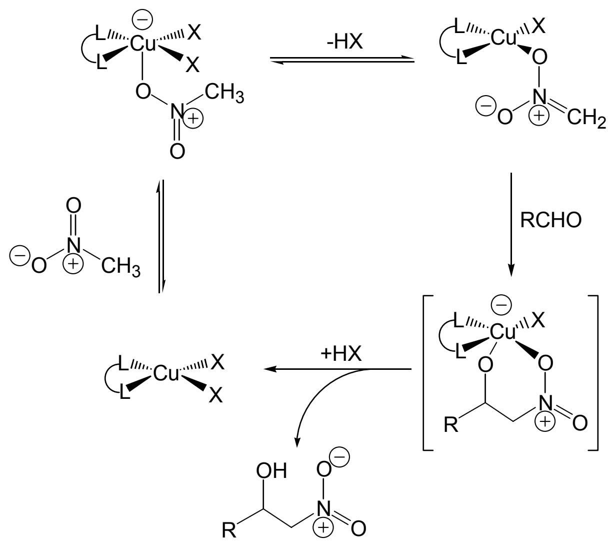


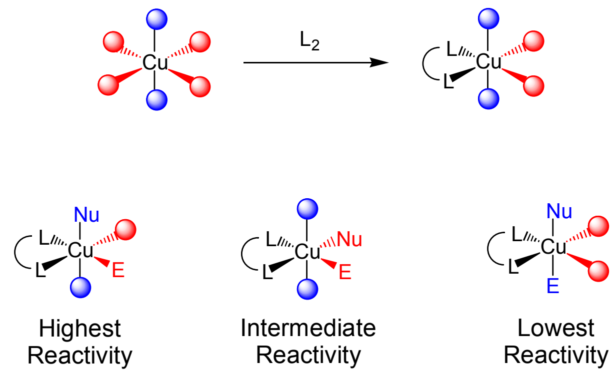
L: *bis(oxazoline) ligand*

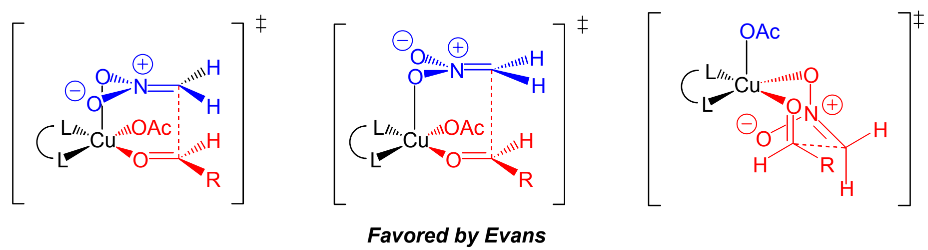
Evans, D. A.; Seidel, D.; Rueping, M.; Lam, H. W.; Shaw, J. T.; Downey, C. W. *J. Am. Chem. Soc.* **2003**, *125*, 12692

Copper Based - Evans



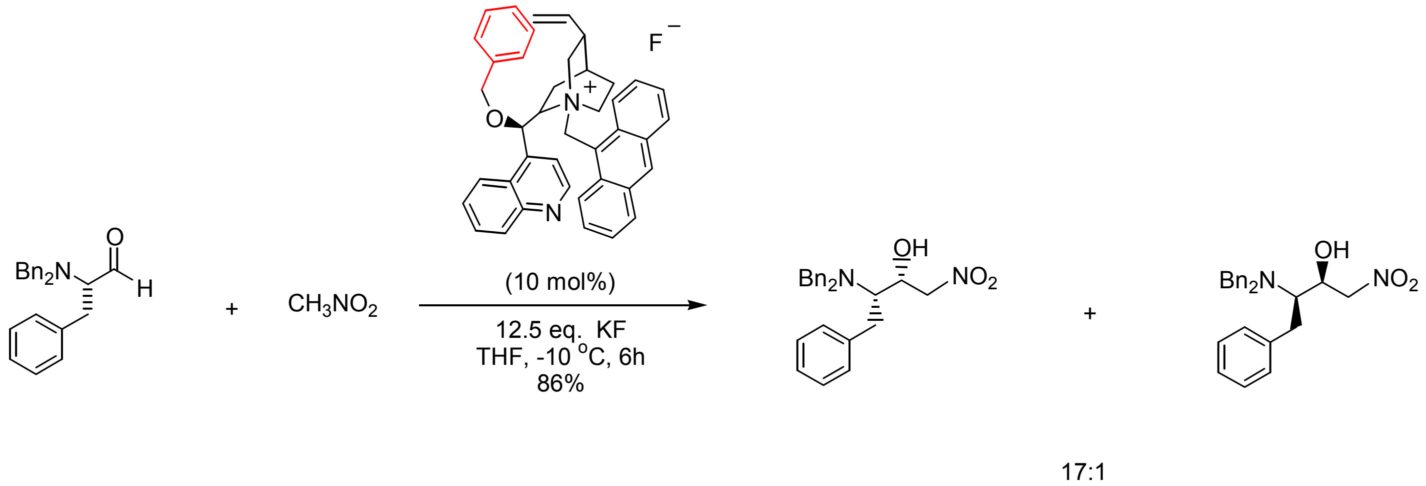


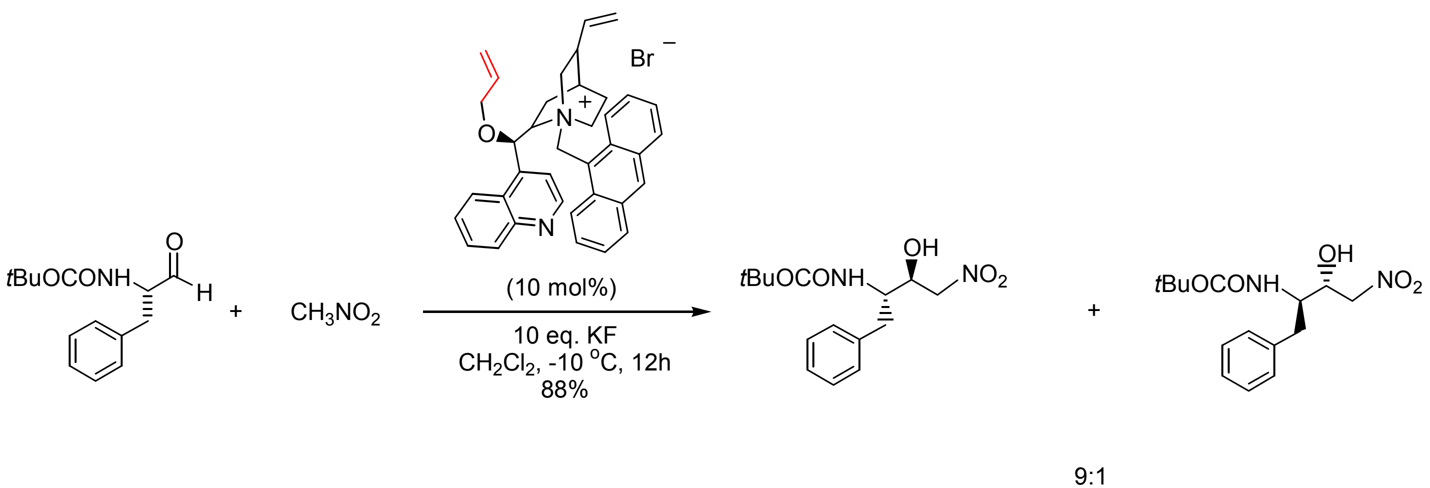




Evans, D. A.; Seidel, D.; Rueping, M.; Lam, H. W.; Shaw, J. T.; Downey, C. W. *J. Am. Chem. Soc.* **2003**, *125*, 12692

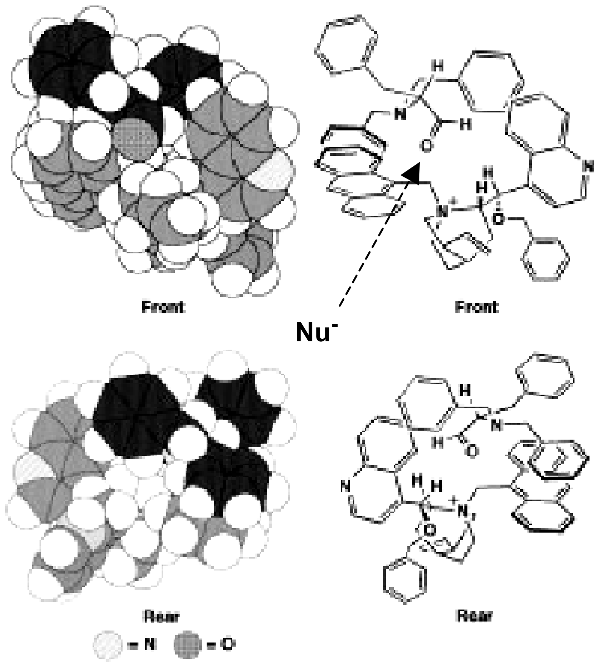
Quaternary Ammonium Salts - Corey



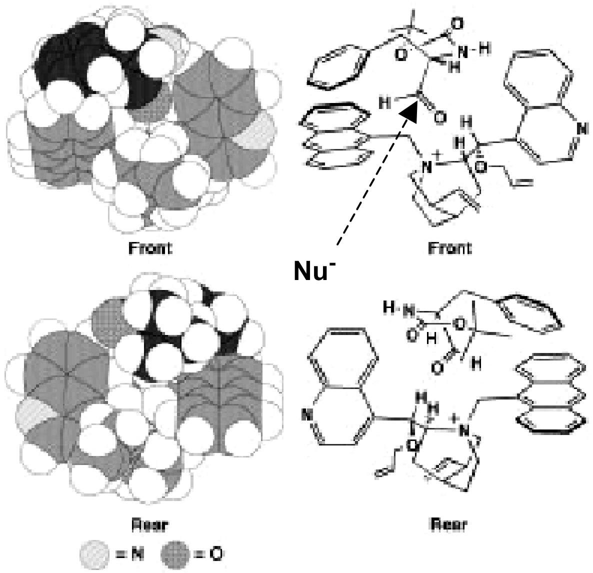


Corey, E. J. and Zhang, Fu-Yao, *Angew. Chem. Int. Ed.*, **1999**, *38*, 1931

Quaternary Ammonium Salts - Corey



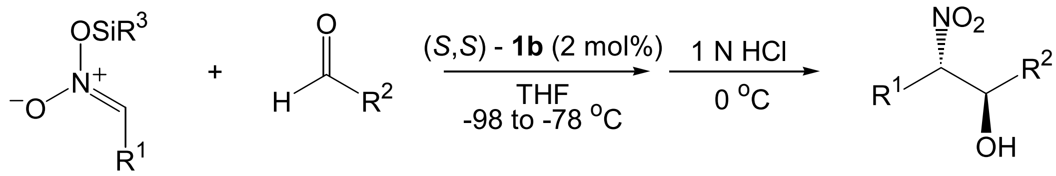
gives *syn* products



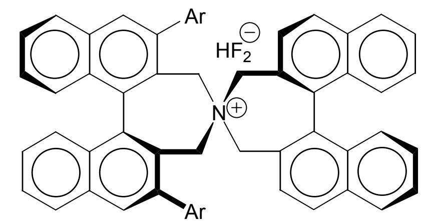
gives *anti* prodcuts

Corey, E. J. and Zhang, Fu-Yao, *Angew. Chem. Int. Ed.*, **1999**, *38*, 1931

Quaternary Ammonium Salts - Maruoka

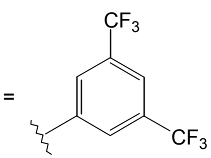


R^1	R^3	R^2	Time (h)	% Yield (anti/syn)	%ee (config.)
Me	Me_3	Ph	2	83 (74:26)	33 (1R,2S)
			3	92 (92:8)	95 (1R,2S)
			4	90 (90:10)	93 (1R,2S)
	Et_3		3	94 (85:15)	92 (1R,1S)
	$^tBuMe_2$		5	45 (57:43)	11 (1R,2S)
	Me_3	*p*-MePh	4	92 (94:6)	97
		p-FPh	4	94 (83:17)	90
		β-Np	4	88 (92:8)	93
Et		Ph	4	94 (90:10)	91
$BnO(CH_2)_2$		Ph	4	70 (87:13)	91

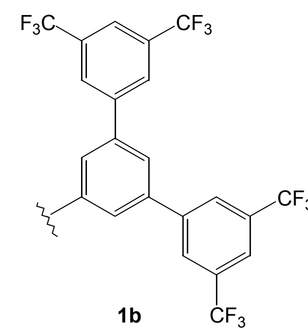


(*S*,*S*)-**1**

Ar =



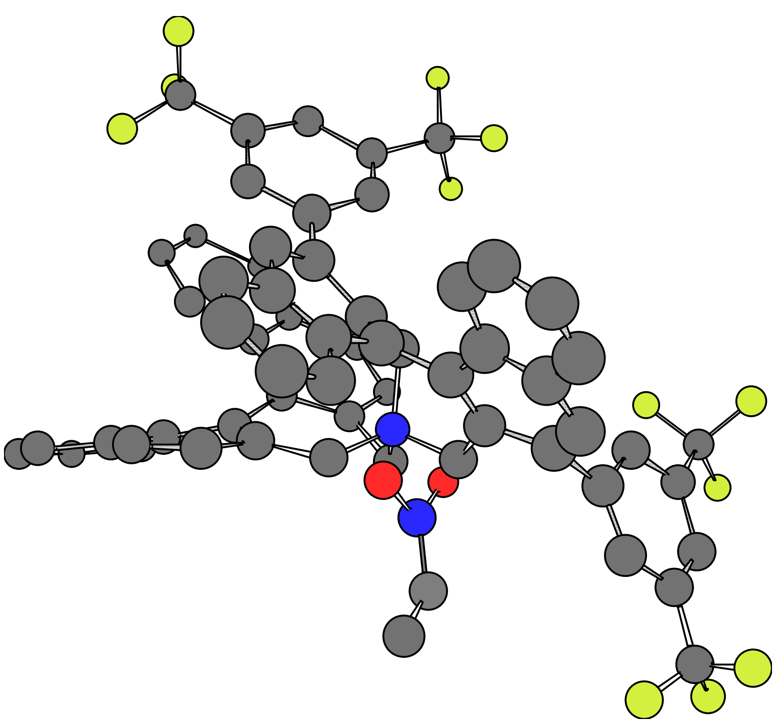
1a



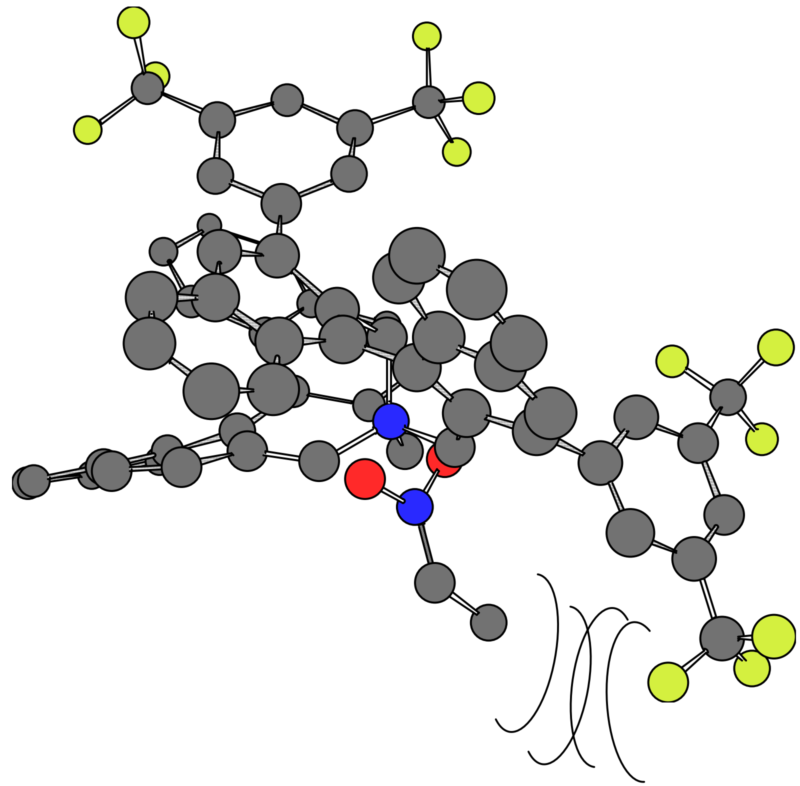
1b

Ooi, T.; Doda, K.; Maruoka, K. *J. Am. Chem. Soc.* **2003**, *125*, 2054

Quaternary Ammonium Salts - Maruoka



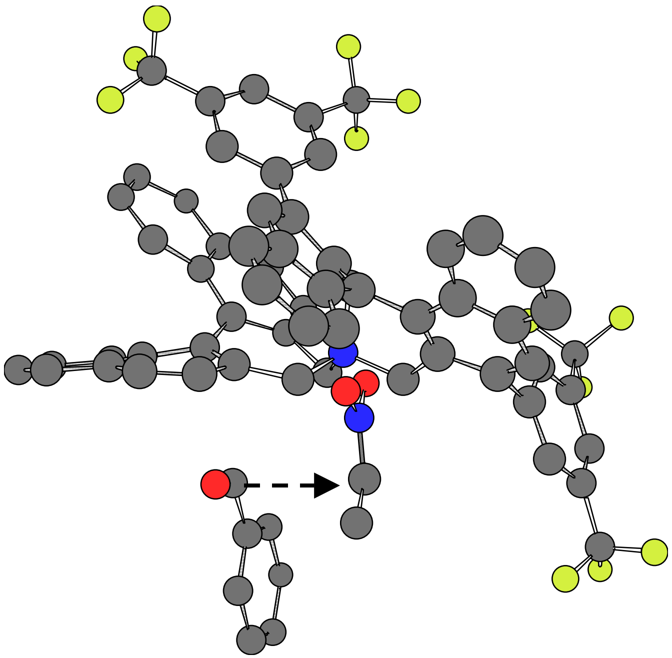
Favored

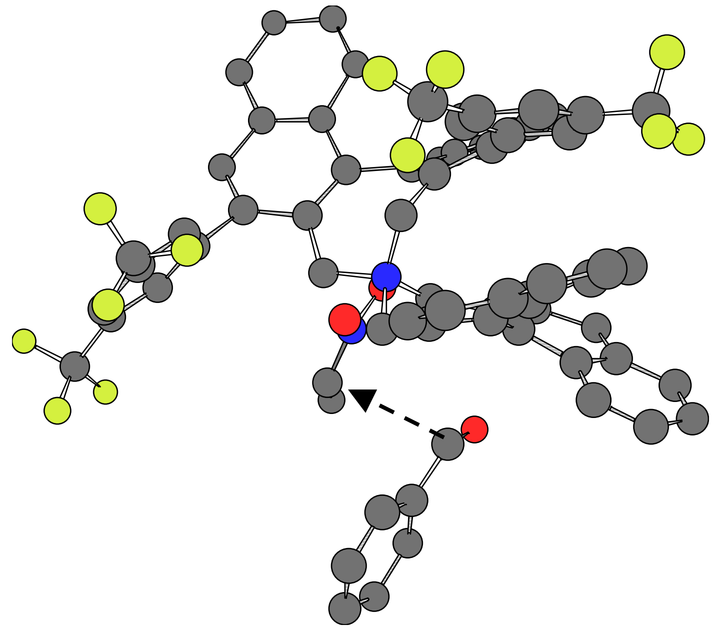


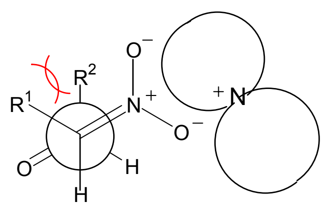
Disfavored

Ooi, T.; Doda, K.; Maruoka, K. *J. Am. Chem. Soc.* **2003**, *125*, 2054

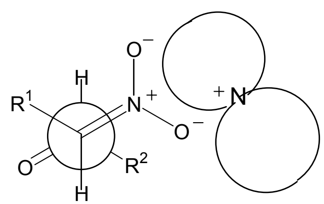
Quaternary Ammonium Salts - Maruoka







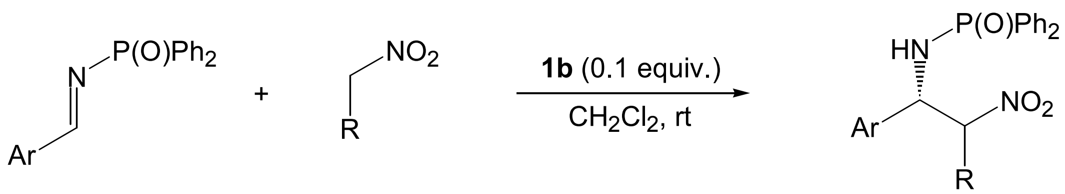
syn



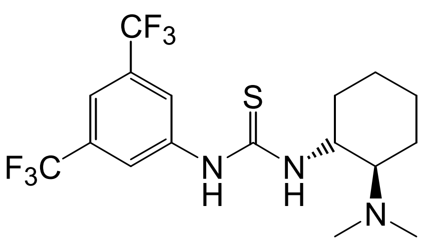
anti

Ooi, T.; Doda, K.; Maruoka, K. *J. Am. Chem. Soc.* **2003**, *125*, 2054

Substituted Thioureas - Takemoto



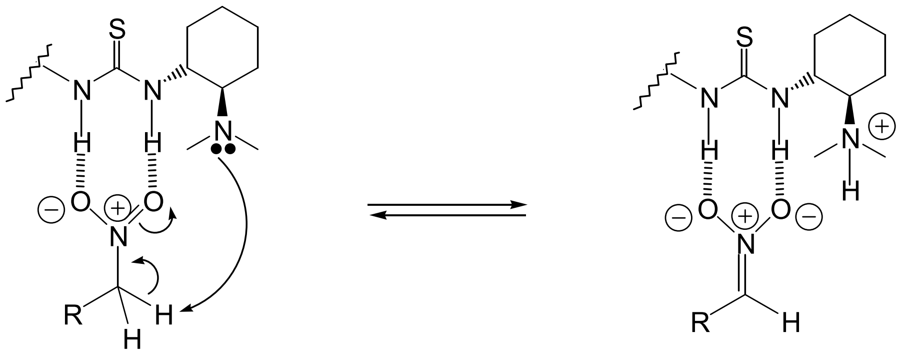
Ar	R	% Yield	%ee (dr)
Ph	H	87	67
4-MePh	H	72	63
4-ClPh	H	76	67
2-napth	H	78	70
2-furyl	H	85	76
2-pyridyl	H	91	68
2-thienyl	H	57	64
Cinnamyl	H	68	65
Ph	Me	83	67 (73:27)

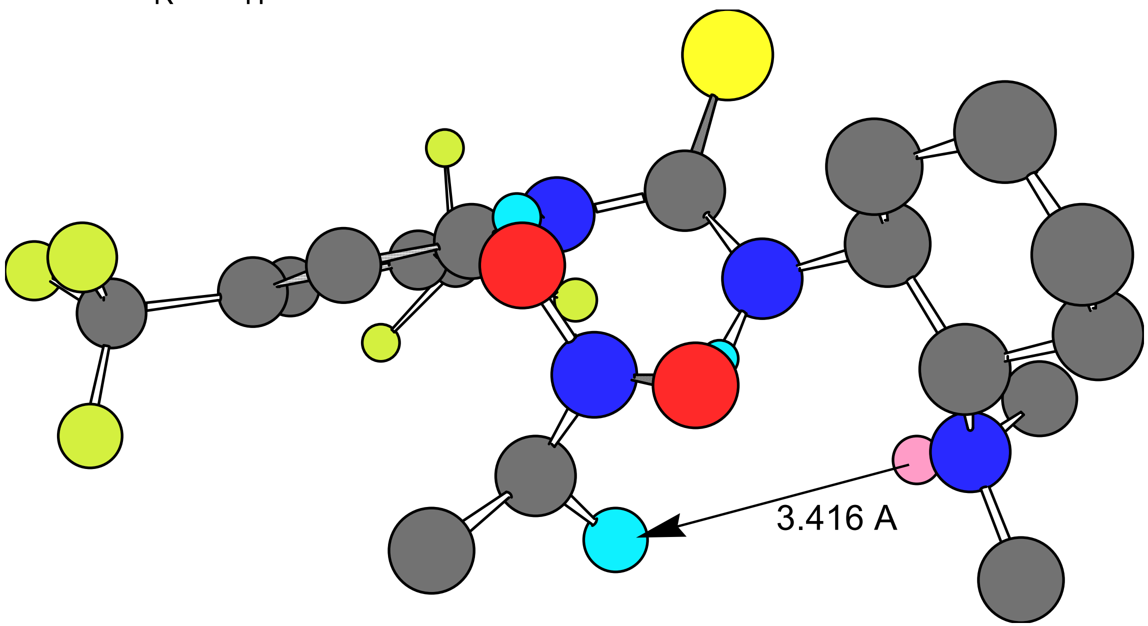


1b

Okino, T.; Nakamura, S.; Furukawa, T.; Takemoto, Y. *Org. Lett.* **2004**, *6*, 625

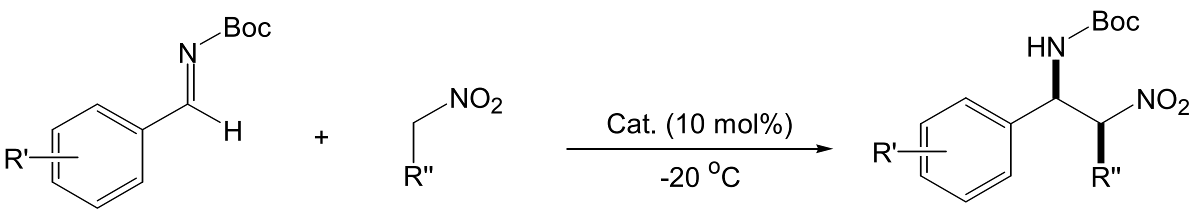
Substituted Thioureas - Takemoto

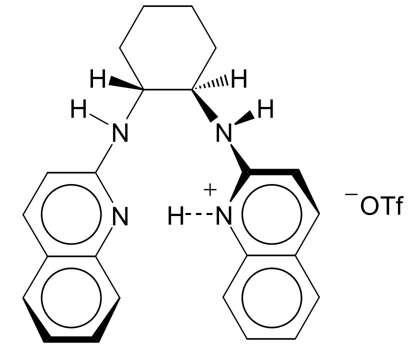




Okino, T.; Nakamura, S.; Furukawa, T.; Takemoto, Y. *Org. Lett.* **2004**, *6*, 625

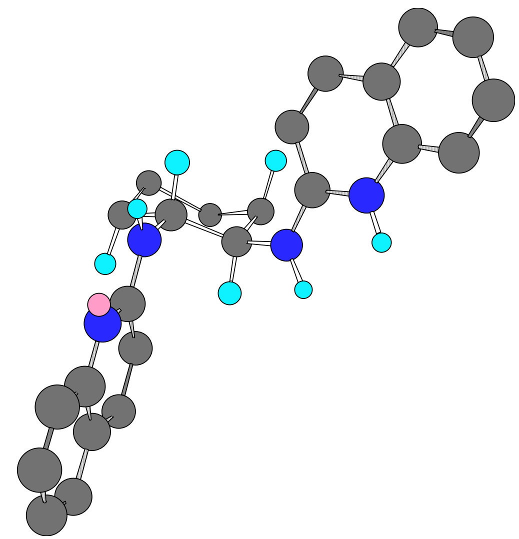
Chiral Proton Catalyst - Johnston





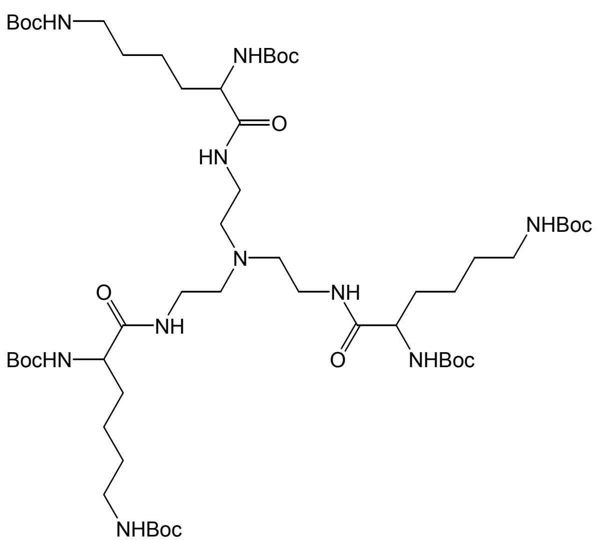
Catalyst

R'	R''	Yield (%)	dr	%ee
H	H	57	–	60
p-NO_2	H	61	–	82
m-NO_2	H	65	–	95
H	CH_3	69	14:1	59
p-CF_3O	CH_3	53	19:1	81
p-Cl	CH_3	59	17:1	82
m-NO_2	CH_3	51	11:1	89
o-NO_2	CH_3	62	7:1	82
p-CF_3	CH_3	50	19:1	84
p-NO_2	CH_3	60	7:1	90

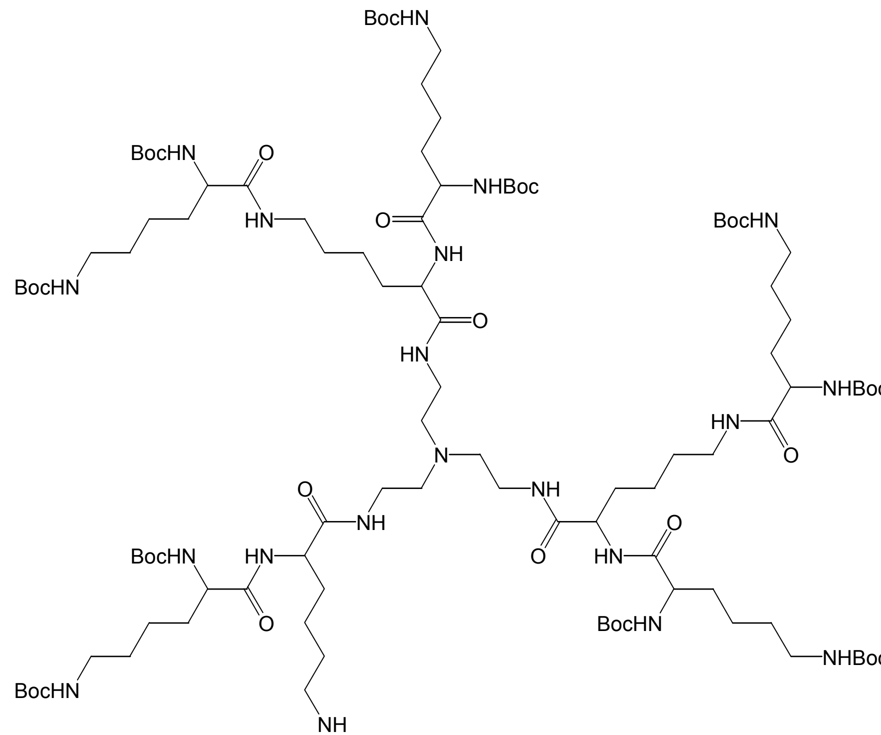


Nugent, B. M.; Yoder, R. A.; Johnston, J. N. *J. Am. Chem. Soc.* **2004**, *126*, 3418

Dendrizyme Approach - Smith



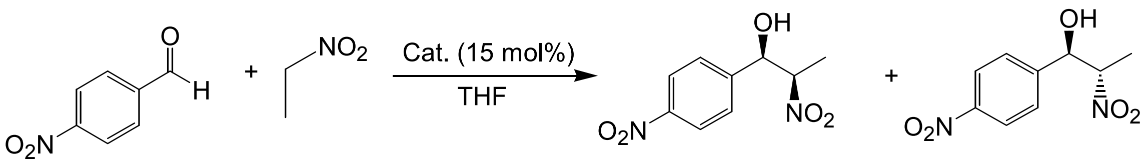
G1(N:)



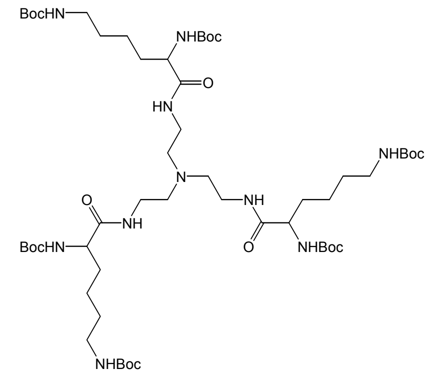
G2(N:)

Davis, A. V.; Driffield, M.; Smith, D. K. *Org. Lett.* **2001**, *3*, 3075

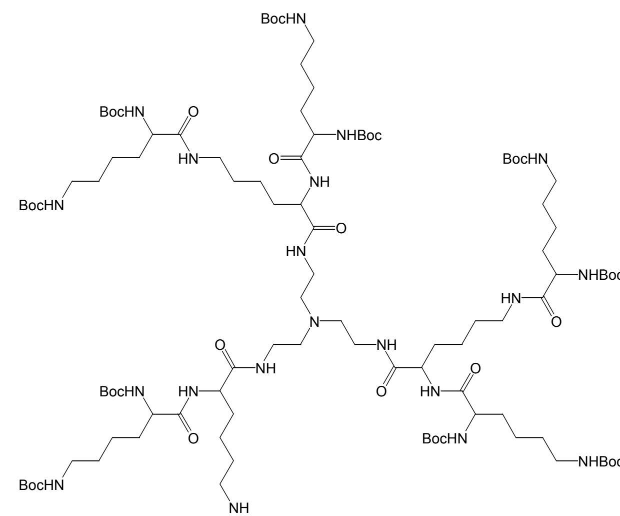
Dendrizyme Approach - Smith



Catalyst	Time	Conversion (%)	*syn* : *anti*
none	48	none	——
NEt_3	1	85	57 : 43
DIPEA	1	95	56 : 44
G1(N:)	48	92	42 : 58
G2(N:)	24	94	54 : 46
NEt_3 + acetamide (10 mol%)	0.5	91	55 : 45



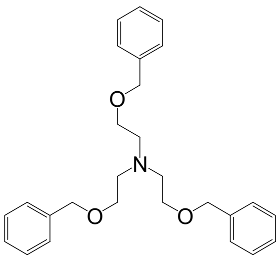
G1(N:)



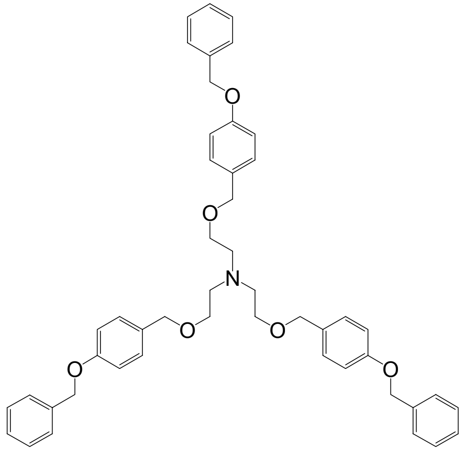
G2(N:)

Davis, A. V.; Driffield, M.; Smith, D. K. *Org. Lett.* **2001**, *3*, 3075

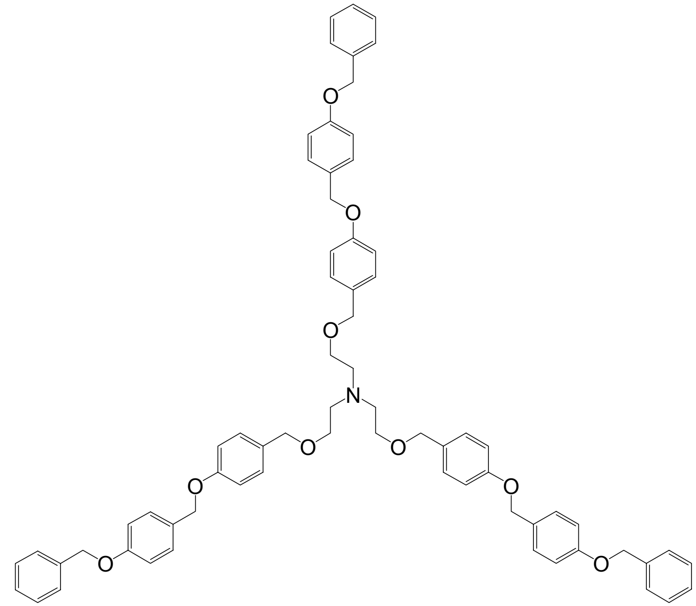
Dendrizyme Approach - Cossio



A0



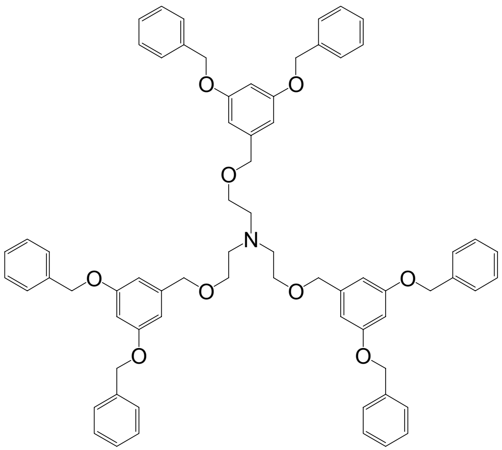
MA1



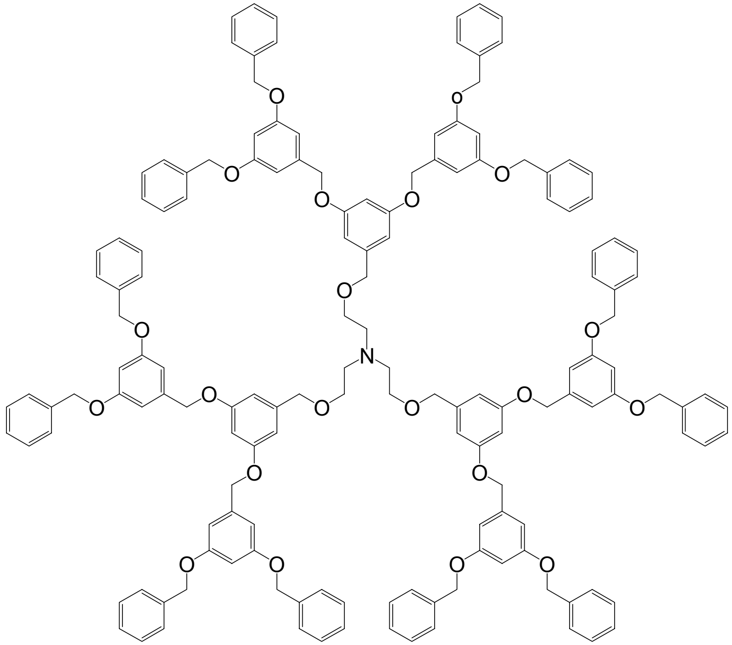
MA2

Zubia, A.; Cossio, F. P.; Morao, L. A.; Rieumont, M.; Lopez, X. *J. Am. Chem. Soc.* **2004**, *126*, 5243

Dendrizyme Approach - Cossio



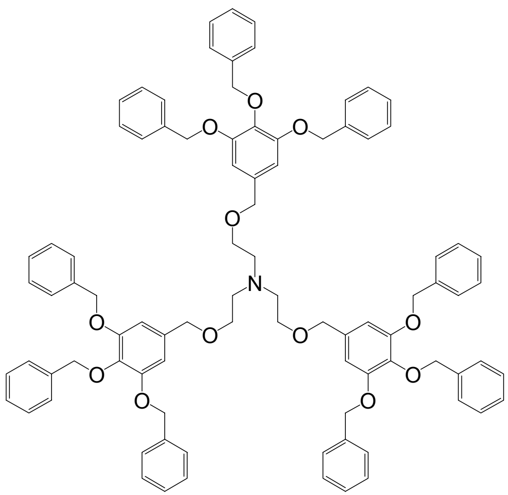
DA1



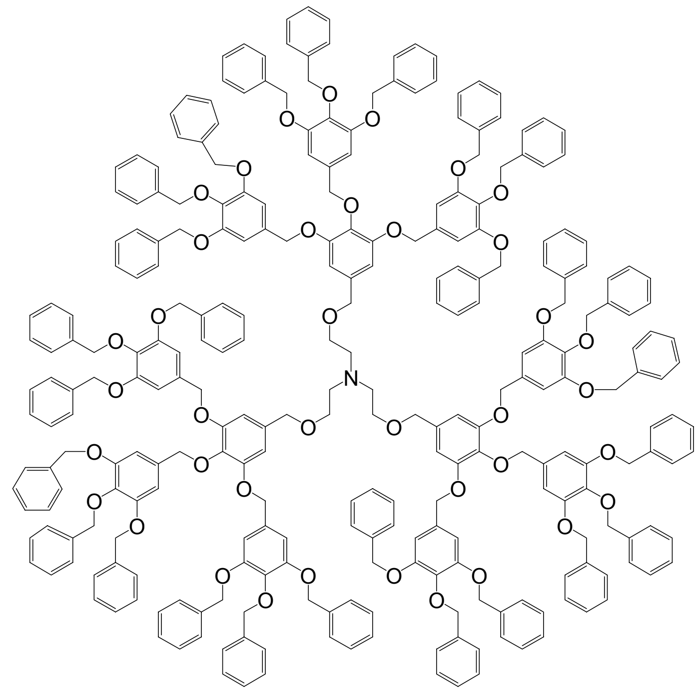
DA2

Zubia, A.; Cossio, F. P.; Morao, L. A.; Rieumont, M.; Lopez, X. *J. Am. Chem. Soc.* **2004**, *126*, 5243

Dendrizyme Approach - Cossio



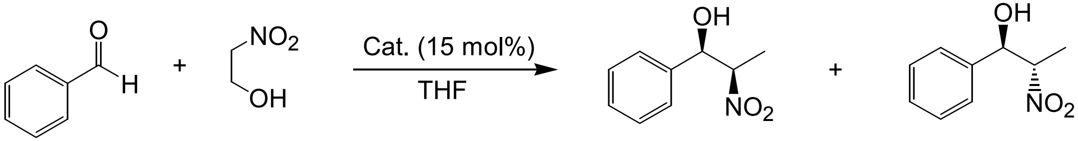
TA1

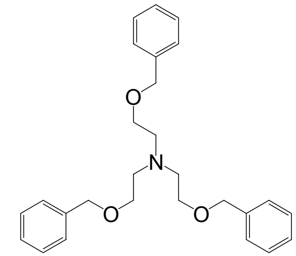


TA2

Zubia, A.; Cossio, F. P.; Morao, L. A.; Rieumont, M.; Lopez, X. *J. Am. Chem. Soc.* **2004**, *126*, 5243

Dendrizyme Approach - Cossio

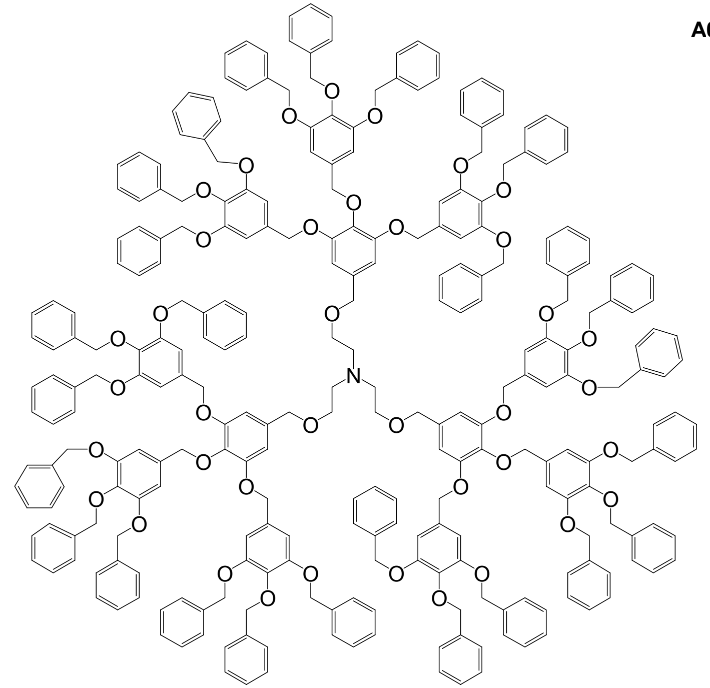




A0

Increasing Bulkiness ↓

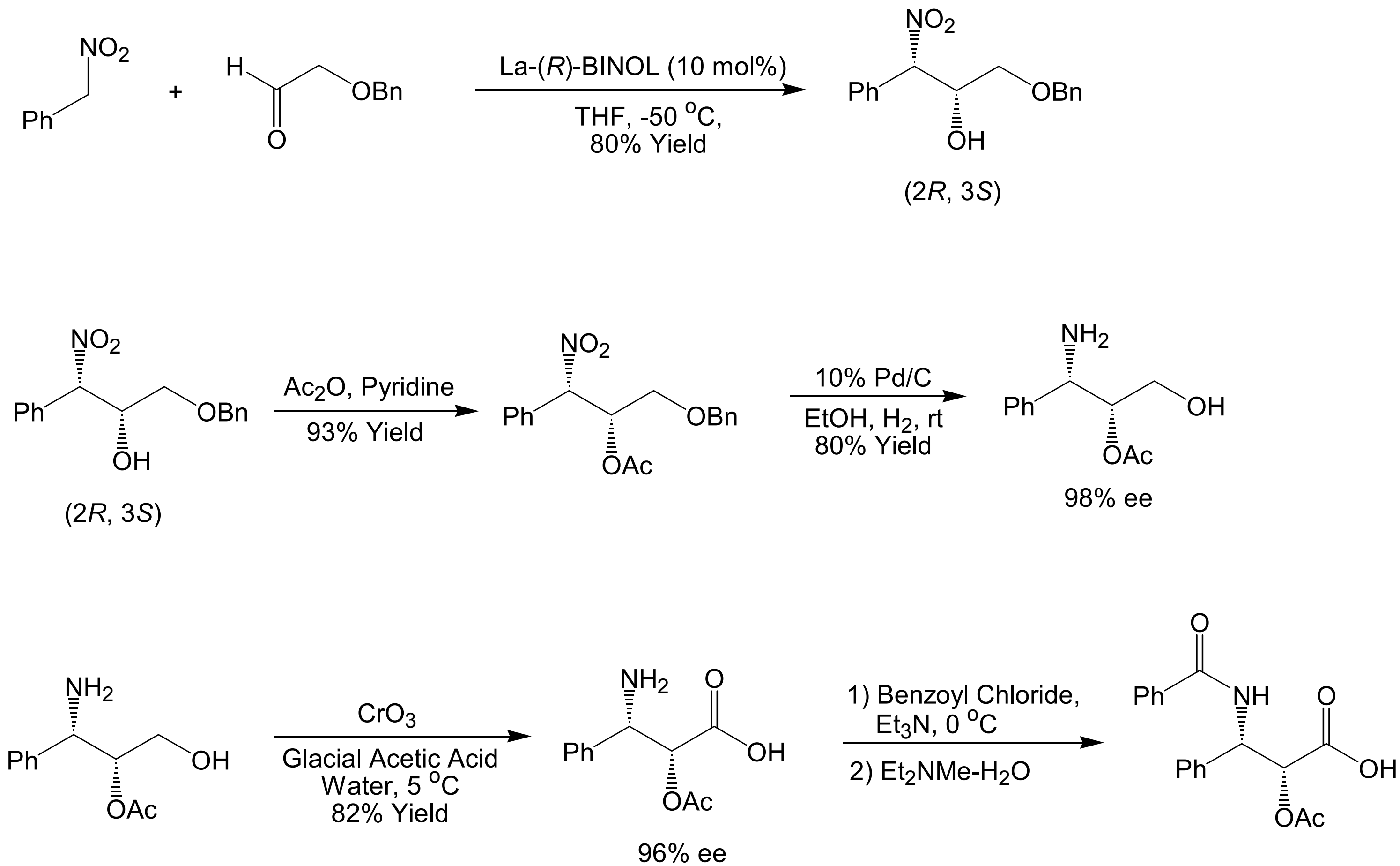
Catalyst	k_{obs} ($10^{-4}s^{-1}$)	*syn* : *anti*
A0	12.11	66 : 34
MA1	10.85	69 : 31
MA2	5.53	67 : 33
DA1	8.25	68 : 32
DA2	3.70	66 : 34
TA1	1.89	67 : 33
TA2	1.03	72 : 28



TA2

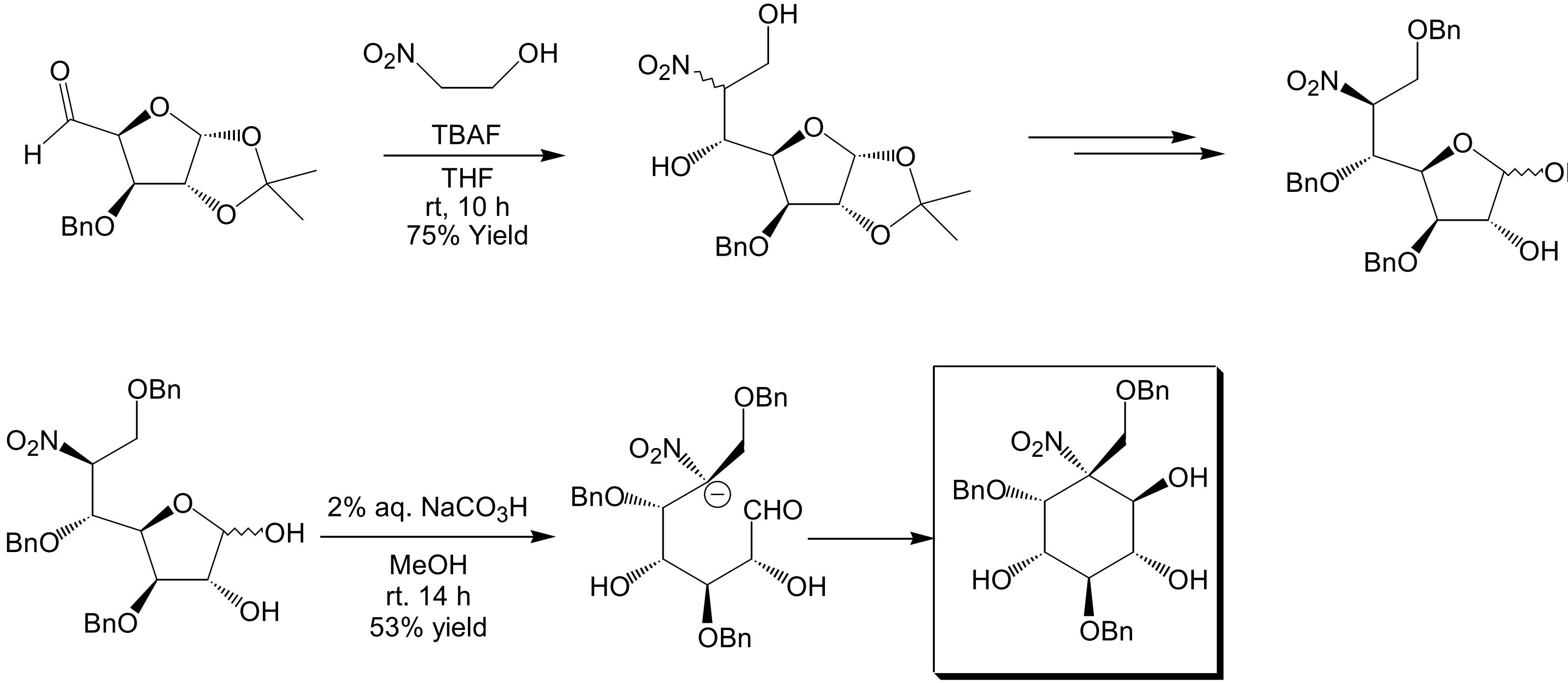
Zubia, A.; Cossio, F. P.; Morao, L. A.; Rieumont, M.; Lopez, X. *J. Am. Chem. Soc.* **2004**, *126*, 5243

C-13 Side-Chain of Taxol



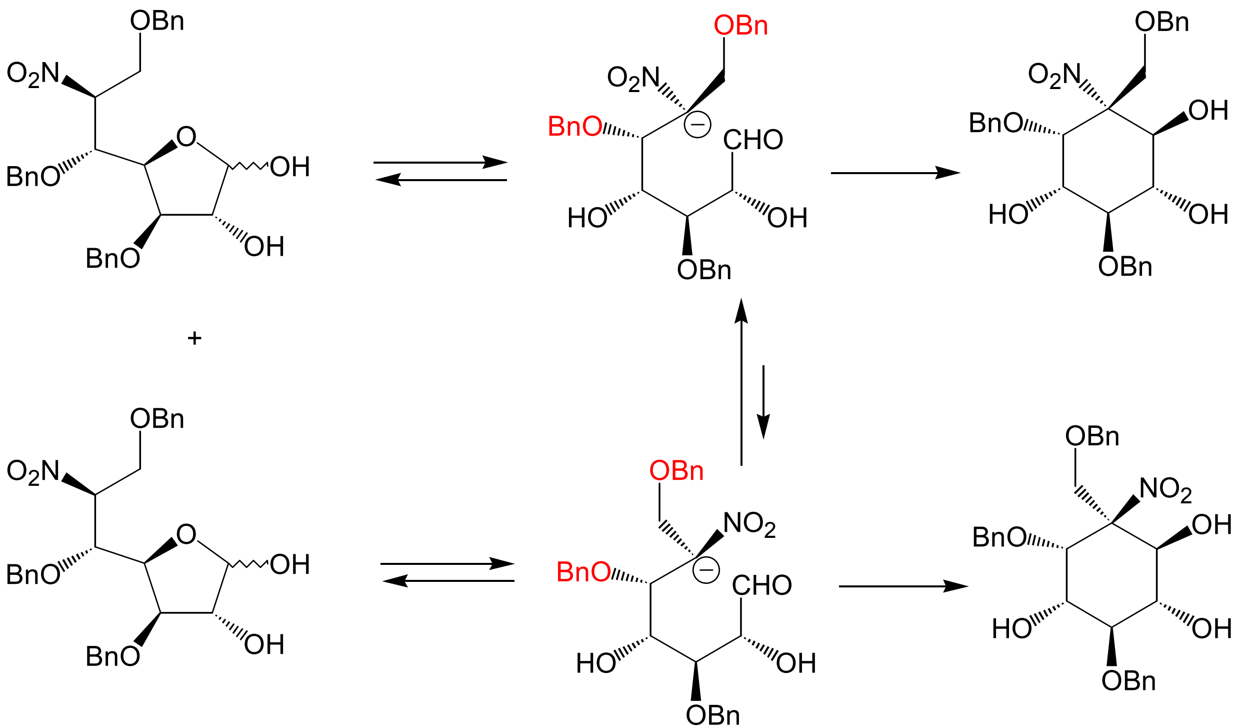
Borah, J. C.; Gogoi, S.; Boruwa, J.; Kalita, B.; Barua, N. C. *Tetrahedron Lett.* **2004**, *45*, 3689

Inositol Derivatives



Soengas, R. G.; Estevez, J. C.; Estevez, R. J. *Org. Lett.* **2003**, *5*, 4457

Inositol Derivatives



Soengas, R. G.; Estevez, J. C.; Estevez, R. J. *Org. Lett.* **2003**, *5*, 4457

Conclusions

- Chiral Ligands
  - Shibasaki's Bimetallic Lanthanide/Lithium System
  - Trost's Zn/Chiral Phenol System
  - Lin's Zn/ System
  - Jorgensens's Cu/BOX System
  - Evans' Cu/BOX System
- Chiral Quaternary Ammonium Salts
  - Corey
  - Maruoka
- Chiral Organic Catalysts
  - Takemoto's Chiral Thioureas
  - Johnston's Chiral Proton
- Dendrizymes
  - Smith
  - Cossio

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- Baker Group