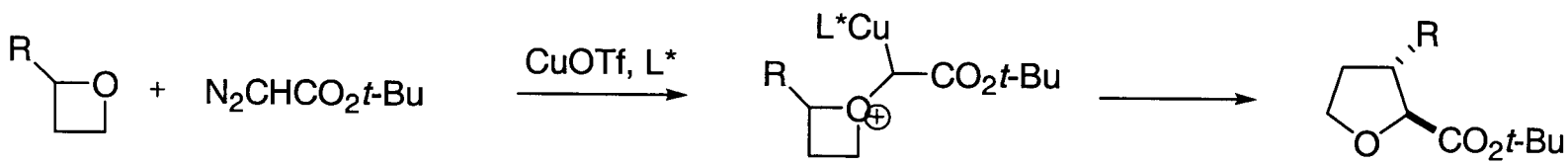
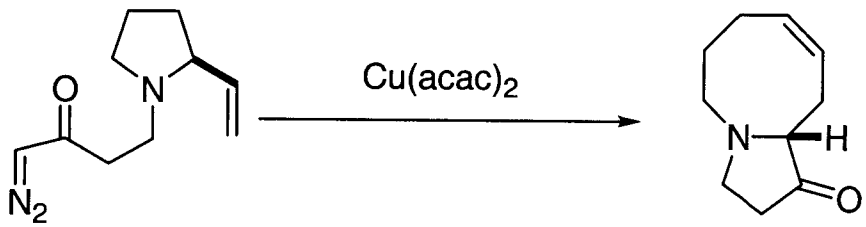
Rearrangement of Oxonium and Ammonium Ylides



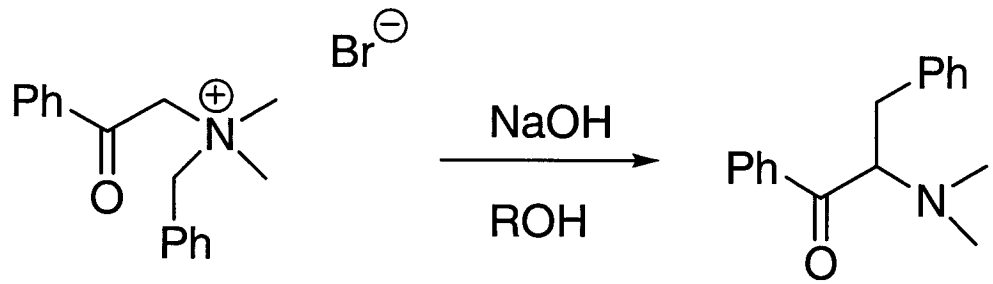


Steve Tymonko

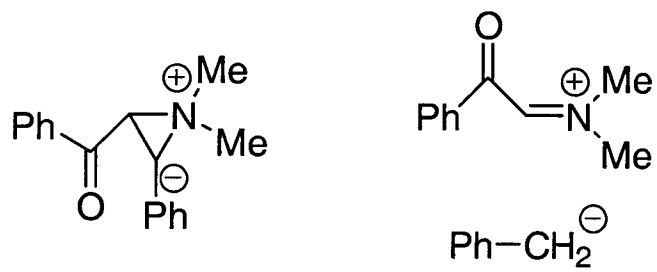
SED Group Meeting

6/28/05

Original Observation

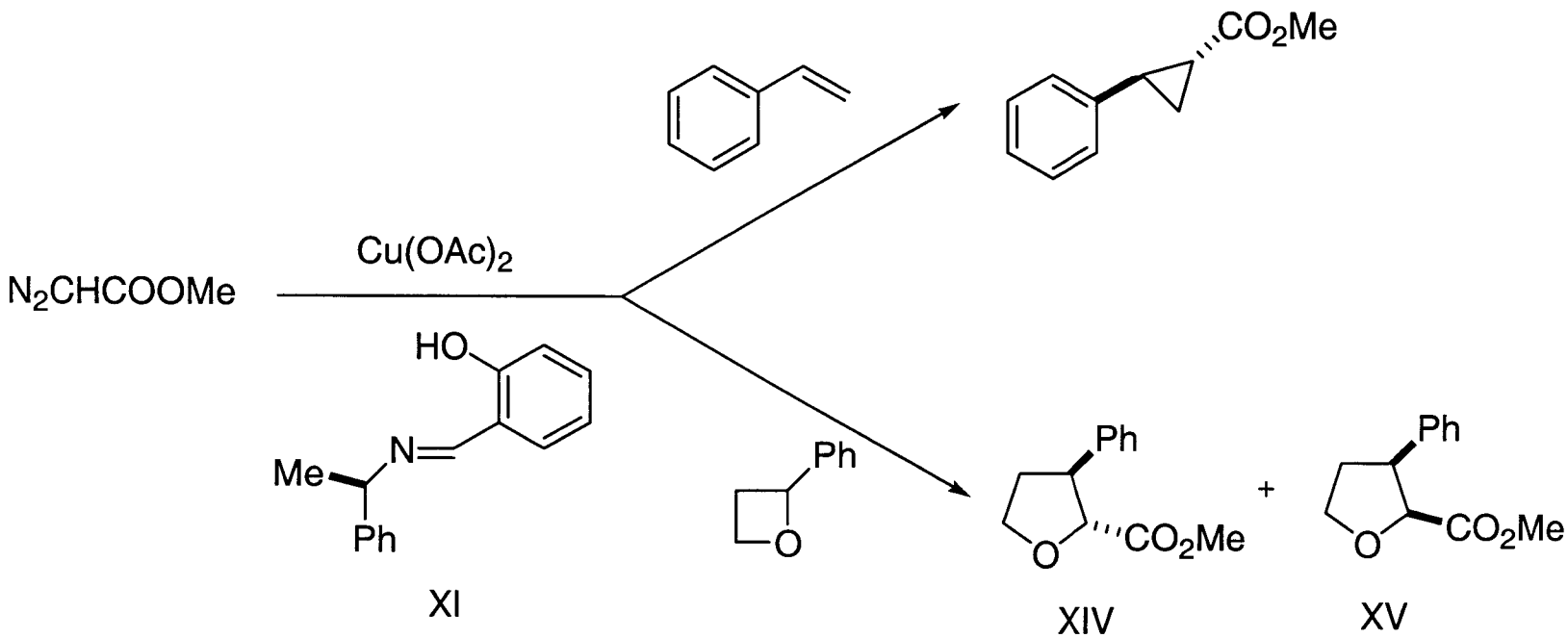


Proposed:



Stevens, T.; et Al. *J. Chem. Soc.* **1928**, 3193

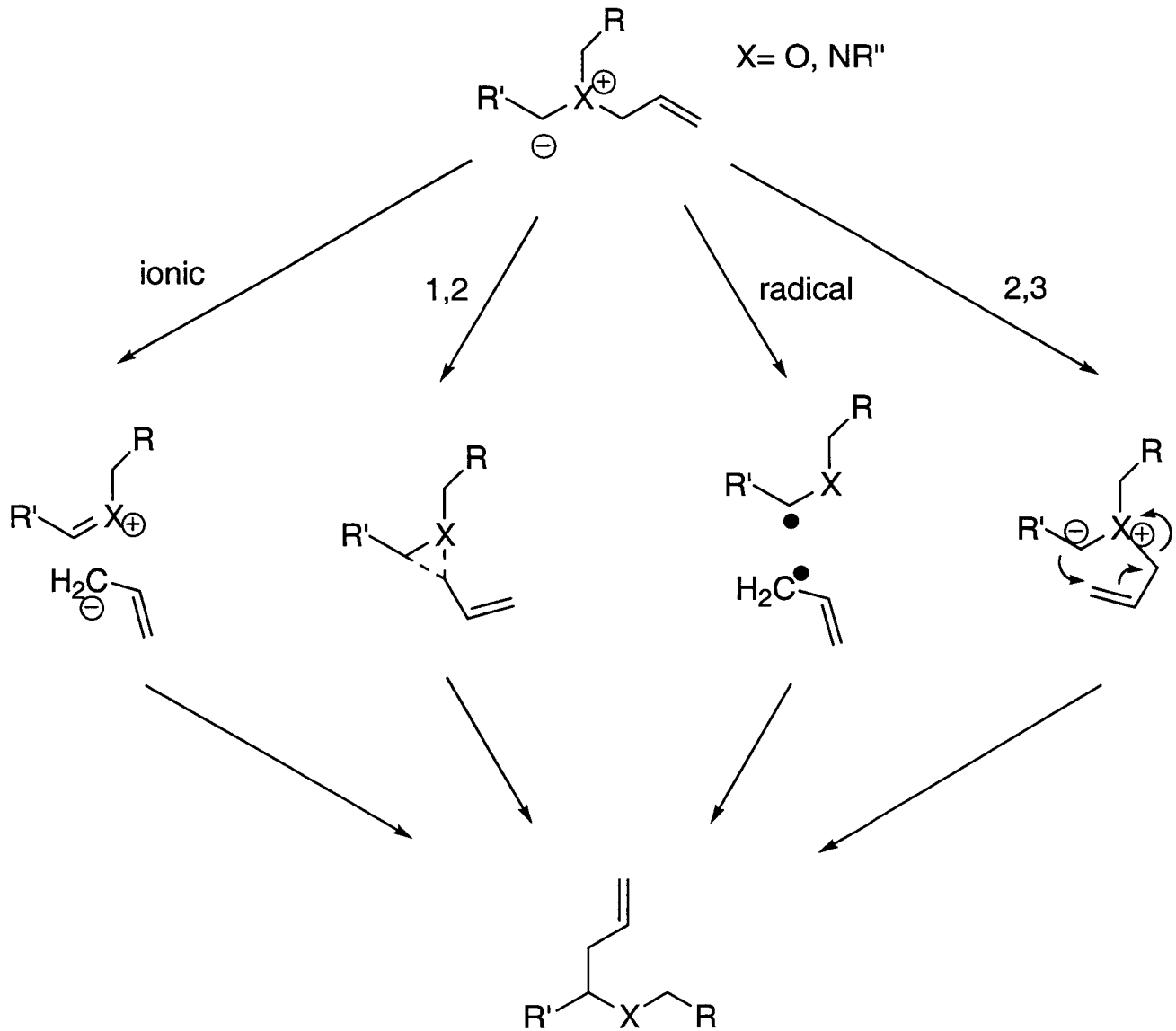
Enantioselective Oxonium Rearrangements?



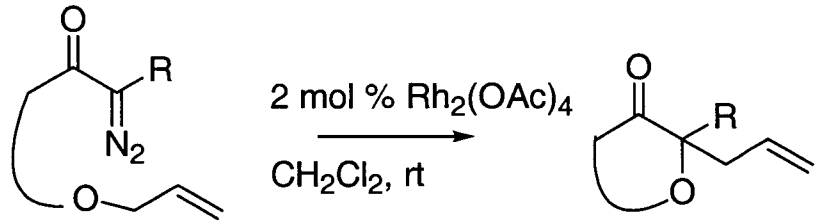
"It has been discovered that catalytic decomposition of methyl diazoacetate in the presence of the chelate XI modifies the reaction so as to yield an optically active mixture of XIV and XV."

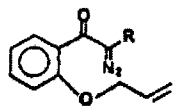
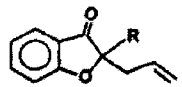
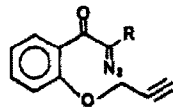
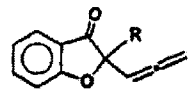
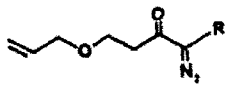
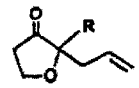
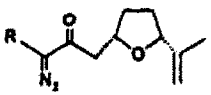
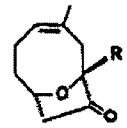
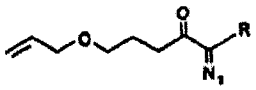
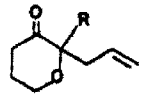
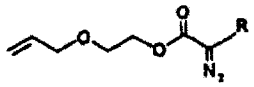
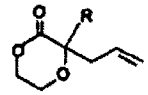
Nozaki, H.; Takaya, H., Moriuti, S.; Noyori, R. *Tetrahedron*, **1968**, 3655

Possible Mechanistic Pathways



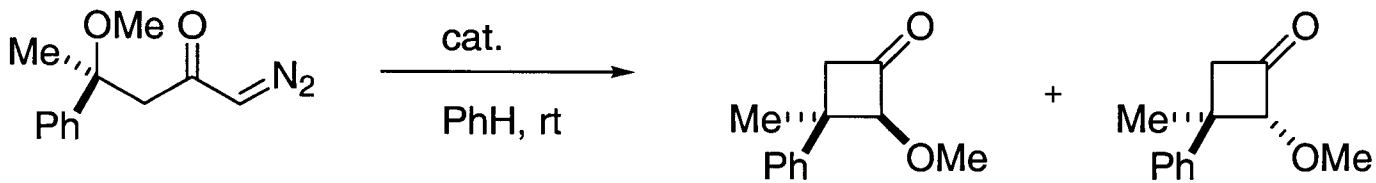
2,3 – Oxonium Ylide Rearrangements



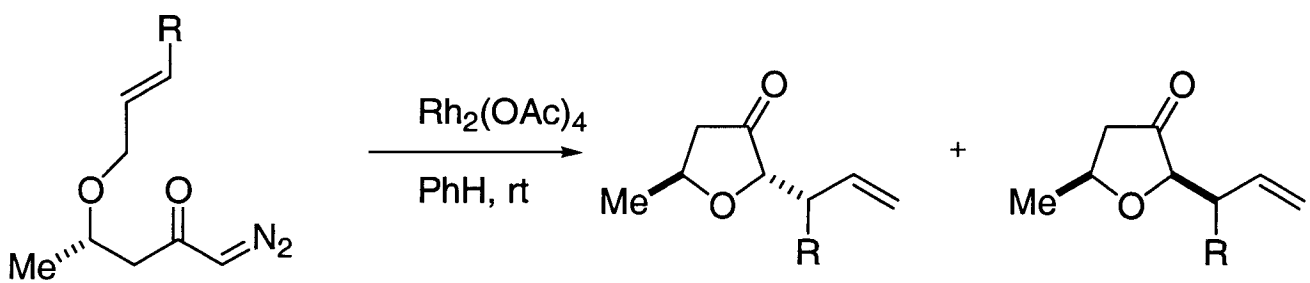
entry	diazo compounds[18]	heterocyclic products	R = H		R = CO_2R'		
			yield[b]	time[c]	yield[b]	time[c]	R′
1			71	0.2	95	8.0	Et
2			0[d]	1.0	92	8.0	Me
3			70[e]	2.0	91	2.0	Me
4			81	0.2	67	1.5	Me
5			33[f]	3.0	53[g]	1.0	Me
6			0[h]	0.5	51	4.0	Et

Pirrung, M.; Werner, J. *JACS*, **1986**, 6060

Catalyst Association



cat = $Rh_2(OAc)_4$	3	:	1
$Cu(acac)_2$	1	:	6
$RhCl(PPh_3)_3$	1	:	10

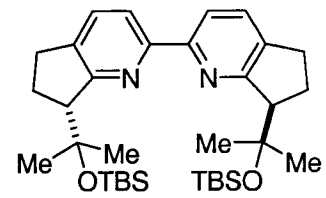


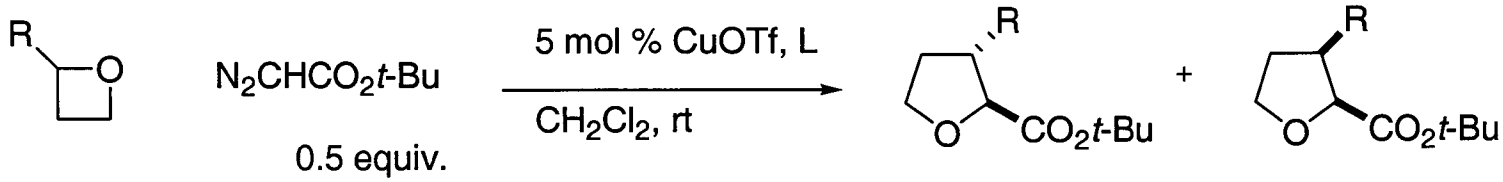
R = H,	12	:	1
R = Me	1	:	0

Catalyst associated during rearrangement

Roskamp, E.; Johnson, C. *JACS*, **1986**, 6062

Enantioselectivity in 1,2 – Oxonium Ylide RAR





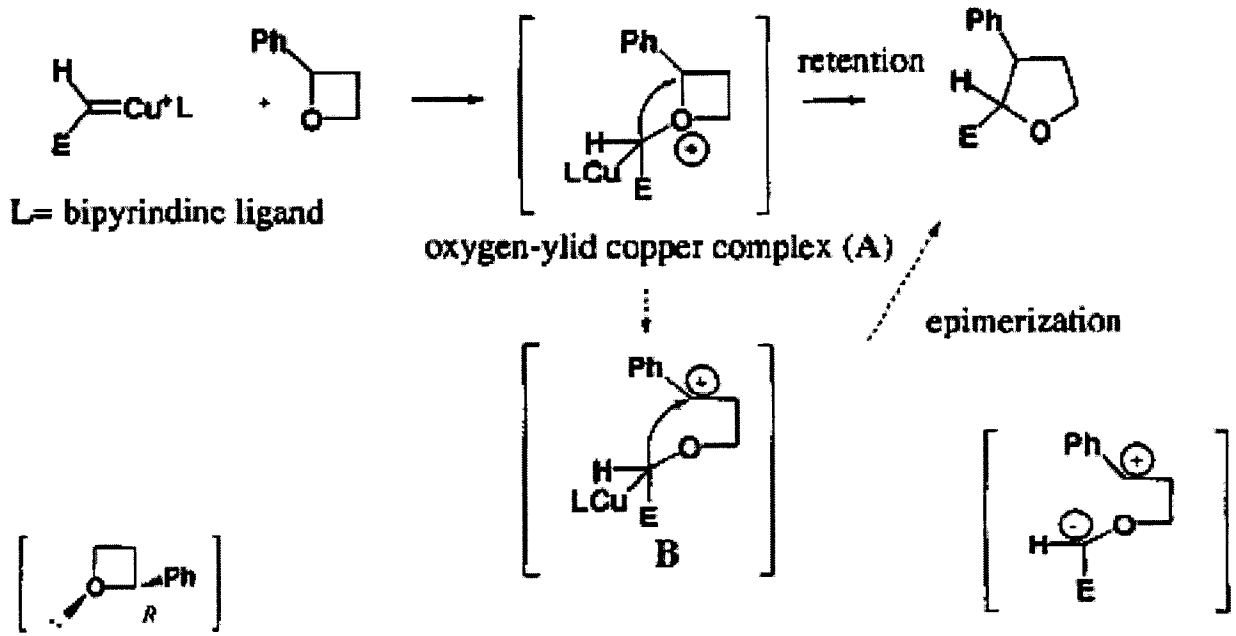
Initial ee = 89 %

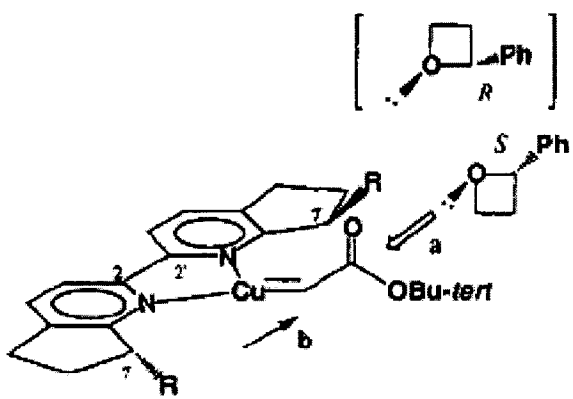
R	trans : cis	ee recovered oxetane	ee trans	ee cis
Ph	59 : 41	5	75	81
(R)-Ph	89 : 11	87	92	16
(S)-Ph	25 : 75	87	11	93
4-ClC_6H_4	54 : 46	1	75	80

Provide a mechanistic rational for these results

Ito, K.; Yoshitake, M.; Katsui, T. *Heterocycles* **1996**, 305

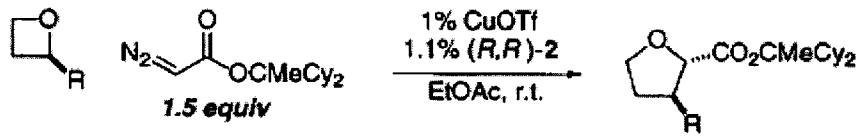
Enantioselectivity in 1,2 – Oxonium Ylide RAR



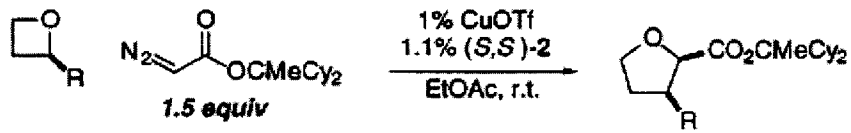


Ito, K.; Yoshitake, M.; Katsui, T. *Heterocycles* **1996**, 305

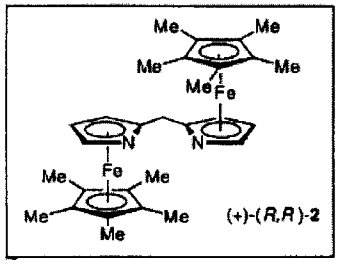
More Ring Expansions



Entry	*R*	Oxetane ee (%)	*trans*/*cis*	*trans* ee (%)	Yield (%)
1	Ph	99	95:5	98	74
2	4-$(F_3C)C_6H_4$	97	94:6	98	81
3	4-$(MeO)C_6H_4$	98	75:25	69	29
4	1-Naphthyl	99	86:14	91	75
5	n-$C_7H_{15}C{\equiv}C$	99	89:11	97	64



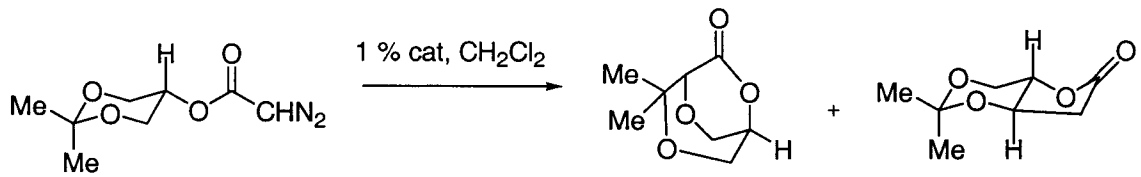
Entry	*R*	Oxetane ee (%)	*cis*/*trans*	*cis* ee (%)	Yield (%)
1	Ph	99	84:16	95	74
2	4-$(F_3C)C_6H_4$	97	86:14	95	52
3	4-$(MeO)C_6H_4$	98	58:42	82	20
4	1-Naphthyl	99	85:15	95	72
5	n-$C_7H_{15}C{\equiv}C$	99	84:16	94	60



Electron rich substituents lead to significant erosion of selectivity

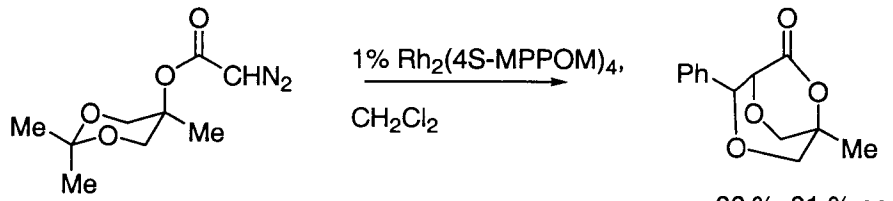
Lo, M.; Fu, G. *Tetrahedron*, **2001**, 2621

Desymmetrisation

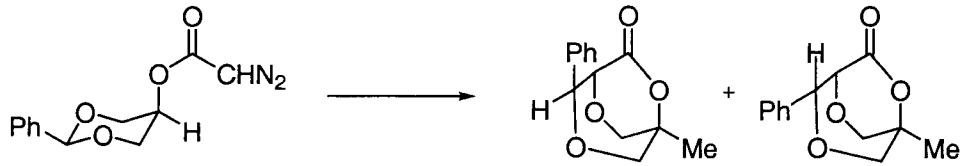


1 : 3.5 to 1 : 0.5

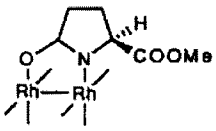
55 - 65 % ee 85 - 99 % ee



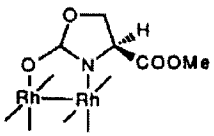
86 %, 81 % ee



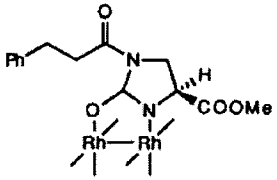
	yield		
Rh_2(4S-MEOX)$_4$	69	67 (39% ee)	33 (33% ee)
Rh_2(5S-MEPY)$_4$	88	60 (42 % ee)	40 (52% ee)
Rh_2(4S-MPPIM)$_4$	88	56 (40 % ee)	44 (88% ee)



Rh_2(5*S*-MEPY)$_4$[11]



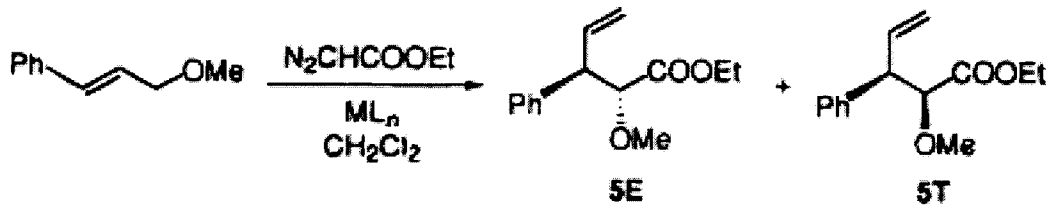
Rh_2(4*S*-MEOX)$_4$[12]



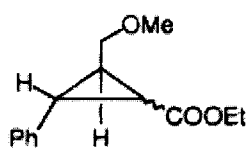
Rh_2(4*S*-MPPIM)$_4$[13]

Doyle, M. et Al. *Tetrahedron Lett.* **1997**, 4367

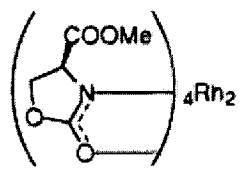
Acyclic 2,3 – Oxonium RAR



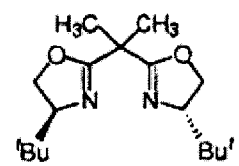
entry	stoich. (equiv) ether:EDA	catalyst (1.0 mol%)	5:6	selectivity (%ee)[b] 5E:5T
1	2:1	$Rh_2(4R\text{-MEOX})_4$	91:9	17(94):83(99)
2	2:1	$Rh_2(4S\text{-MEOX})_4$	89:11	15(94):85(99)
3	2:1	$Rh_2(^t\text{Bu-}S\text{-Pro})_4$[c]	66:34	81(-):19(11)[d]
4	2:1	$Rh_2(4S\text{-MPPIM})_4$	52:48	53(-):47(75)[d]
5	2:1	$CuPF_6$/8	86:14	82(27):18(5)



6



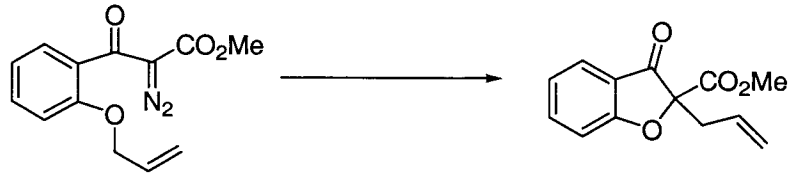
7

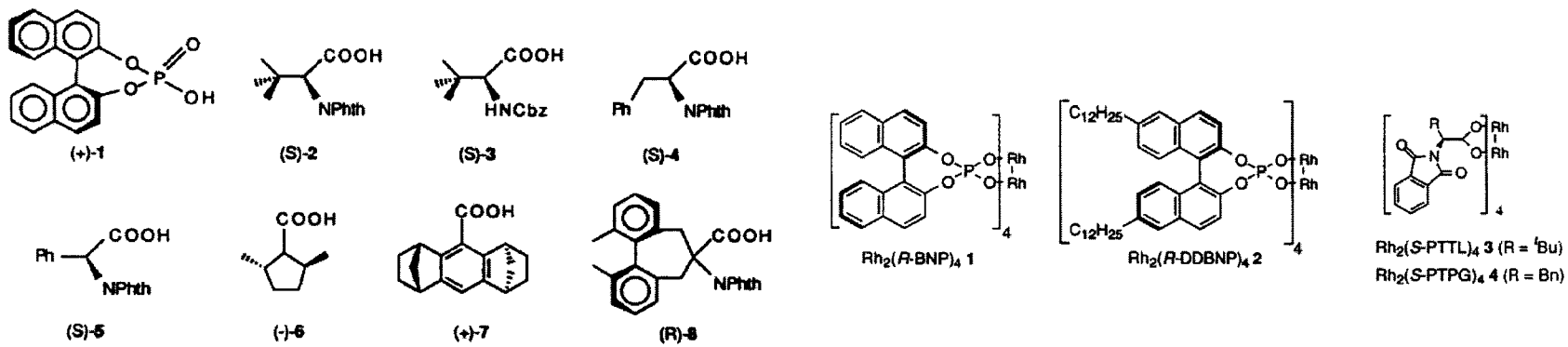


8

Doyle, M el Al. *JACS*, **1998**, 7653

Cyclic 2,3 – Oxonium RAR



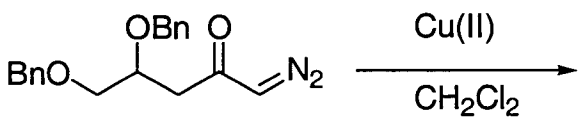


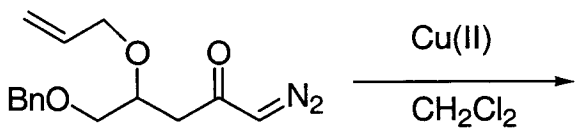
Of all above ligands, best case was (S)-2 at rt in hexane
96 % yield, 60 % ee

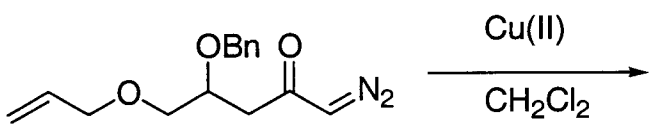
Hodgson, D.; Petroliagi, M. *Tetrahedon Asymmetry* **2001**, 877
McKervey, A. et. Al. *Tetrahedron Lett.* **1997**, 4705

Ring Size and 1,2 - vs. 2,3 - Shifts

Predict (and explain) the products of the following ylide rearrangements.

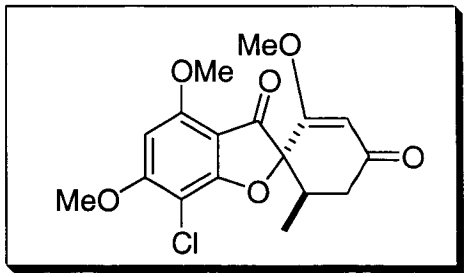




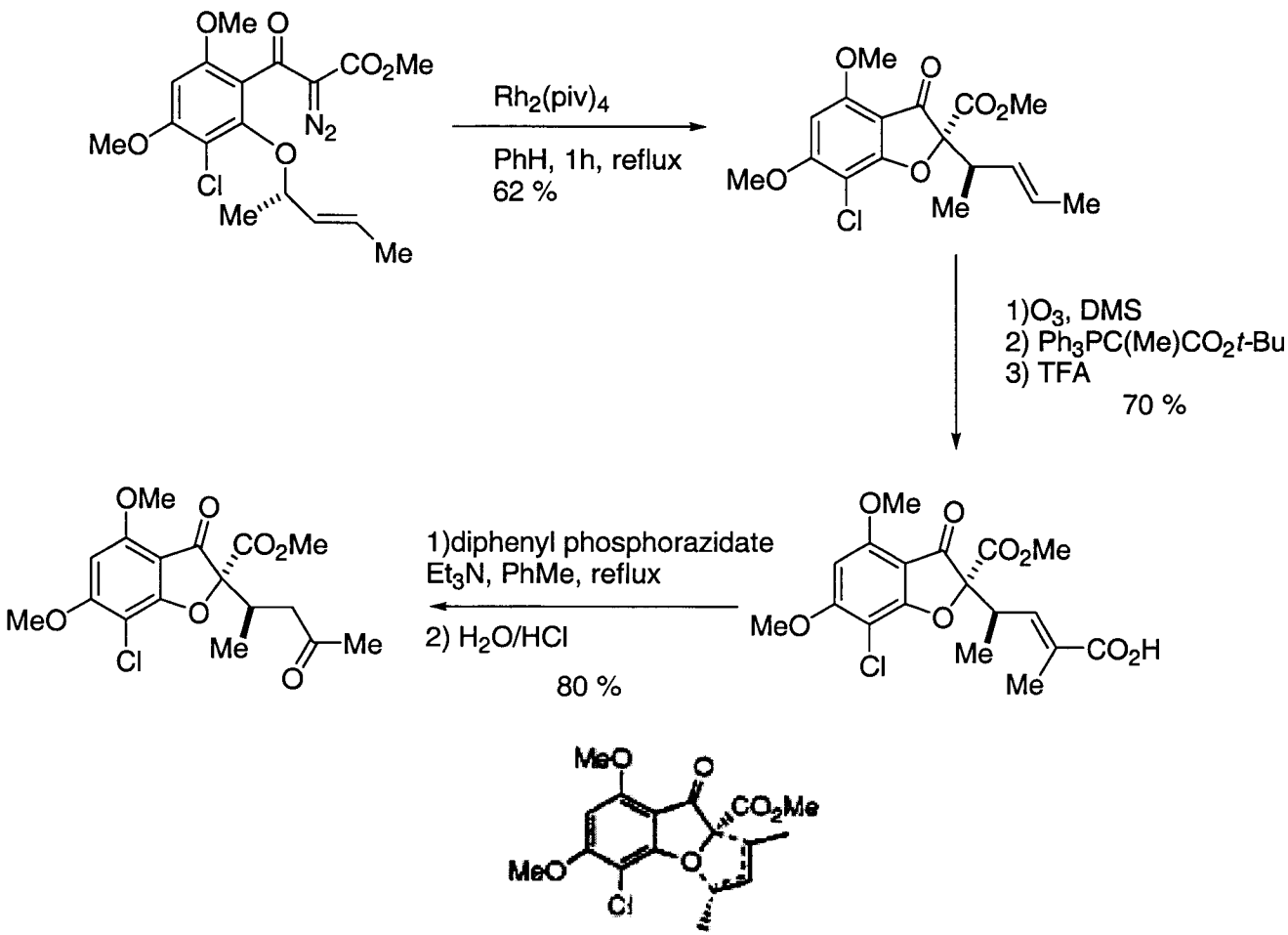


Marmsater, F.; Vanecko, J.; West, F. *Org. Lett.* **2004**, 1657

Synthesis of (+)- Griseofulvin

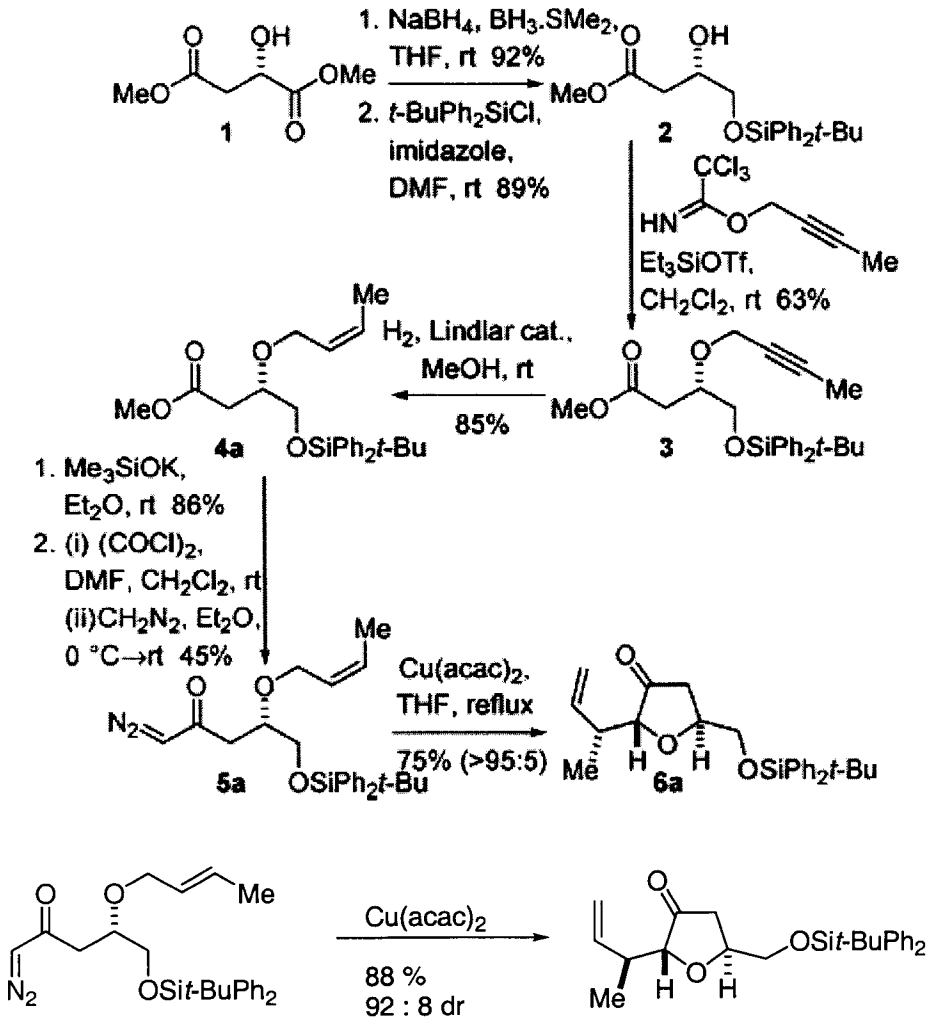


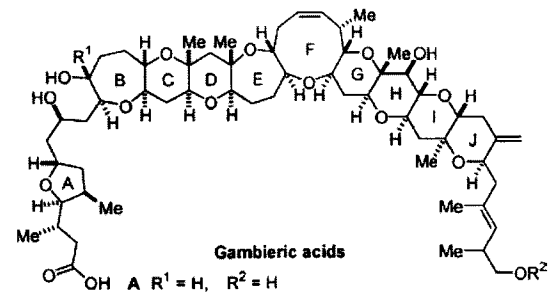
Griseifulvin

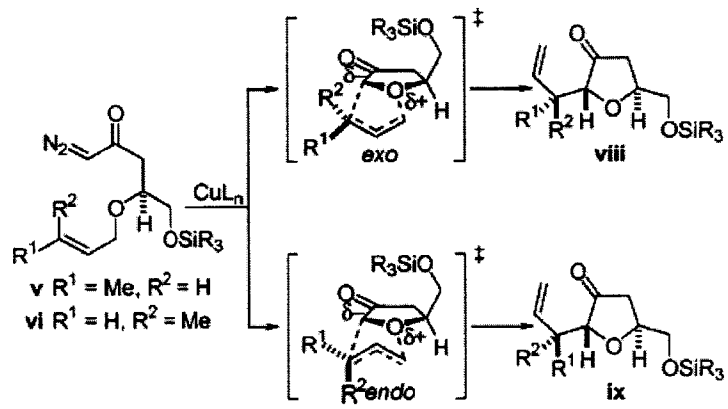


Pirrung, M. el At. *JACS*, **1991**, 8561

Gambieric Acid A Ring







Clark, J.; Fessard, T.; Wilson, C. *Org. Lett.* **2004**, 1773

Ammonium Ylide Computations

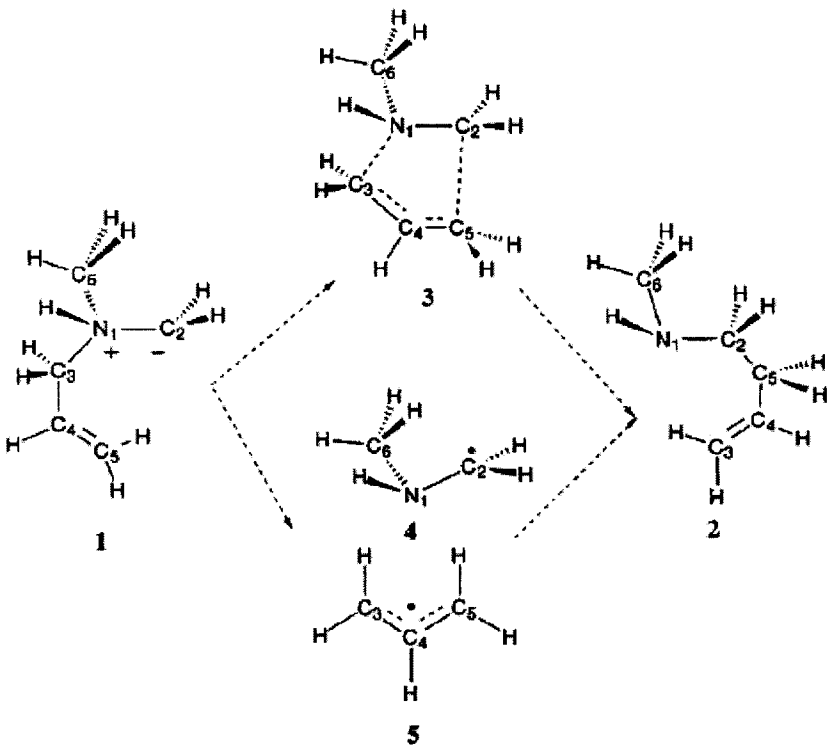


Table 9. Relative SCRF Energies (in kJ mol^{-1} from Amine 2) for Rearrangement of 1 at MP2/6-31G(d)

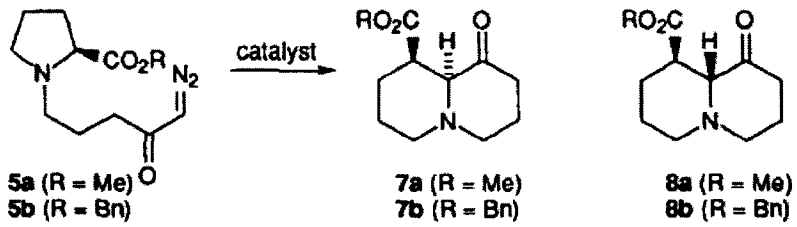
solvent	ϵ	ylide (1)	Sommelet–Hauser (3)	Stevens (4 + 5)
none	1.0	306	338	350
THF	2.95	290	327	348
HMPA	30.0	284	324	348
CH_3CN	35.9	283	324	348
DMF	36.7	283	324	348
H_2O	78.5	283	324	348
CH_3CN^a	35.9	258	303	345

N-sub	C_4-sub	ΔE- (Stevens)	ΔE- (S-H)	ΔE- (S-H−Stevens)
H	H	4	51	47
CN	H	−19	60	79
NH_2	H	1	60	59
CHO	H	−48	51	99
$CH{=}CH_2$	H	−36	33	69
CH_3	H	−26	37	63
CH_2CH_3	H	−30	37	67
$CH(CH_3)_2$	H	−31	37	68
H	CN	1	25	24
H	NH_2	9	54	45
H	CHO	4	22	18
H	$CH{=}CH_2$	2	36	34
H	CH_3	7	52	45
H	CH_2CH_3	4	44	40
H	$CH(CH_3)_2$	4	46	42

Closely matched activation energies should make predicting reaction pathway difficult

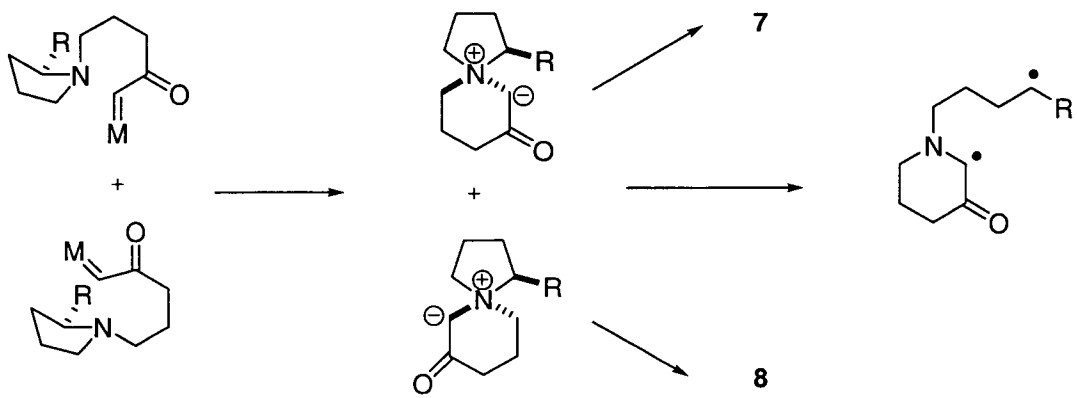
Heard, G.; Yates, B. *JOC*, **1996**, 7276

Proline Derived Ylides



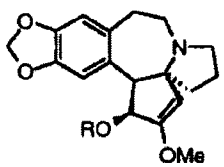
Entry	Substrate	Catalyst (mol%)/solvent/Temp	Chemical Yield (%)	Diastereoselectivity (7:8)
1	**5a**	$Rh_2(OAc)_4$ (3)/CH_2Cl_2/rt	76	11:89
2	**5a**	$Cu(acac)_2$ (5)/$PhCH_3$/reflux	82	16:84
3	**5a**	Cu powder (50) /$PhCH_3$/reflux	83	18:82
4	**5b**	$Rh_2(OAc)_4$ (3)/CH_2Cl_2/rt	74	25:75
5	**5b**	$Cu(acac)_2$ (5)/$PhCH_3$/reflux	84	5:95
6	**5b**	Cu powder (50) /$PhCH_3$/reflux	87	6:94
7	**5b**	Cu powder (15) /$PhCH_3$/reflux	87	7:93

Product from entry 4 – 55 % ee
Product from entry 5 – 75 % ee

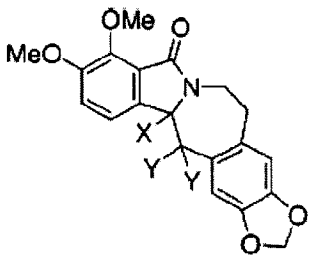


Naidu, B.; West, F. *Tetrahedron*, **1997**, 16565

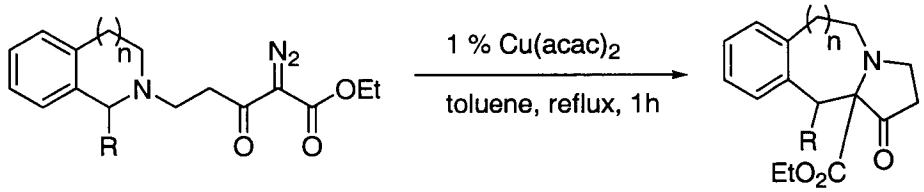
Alkaloid Skeletons



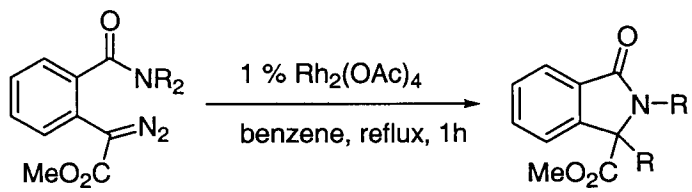
(-)-Cephalotaxine, R = H (6)



3; X = Y = H; lennoxamine

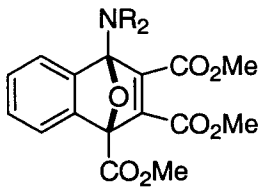


n = 0	R = H,	68 %
n = 1	R = H	96 %
n = 1	R = Me	77 %
n = 1	R =	77 %

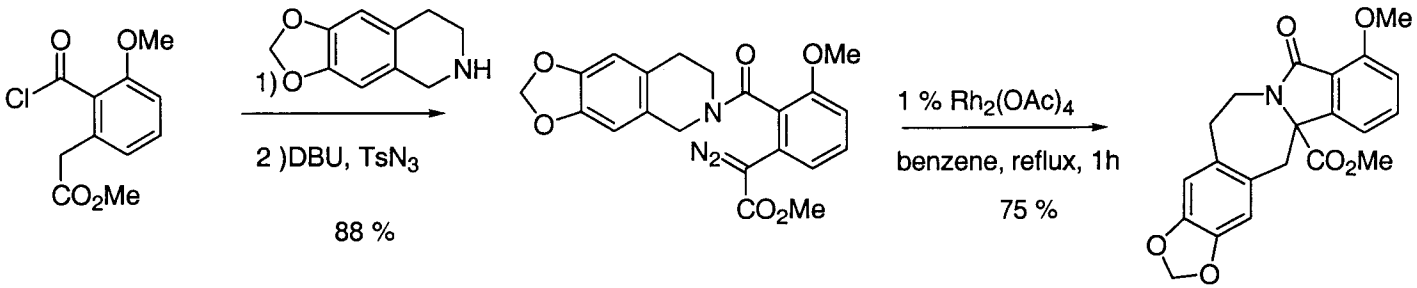


R= Bn, Et, Ph

not observed

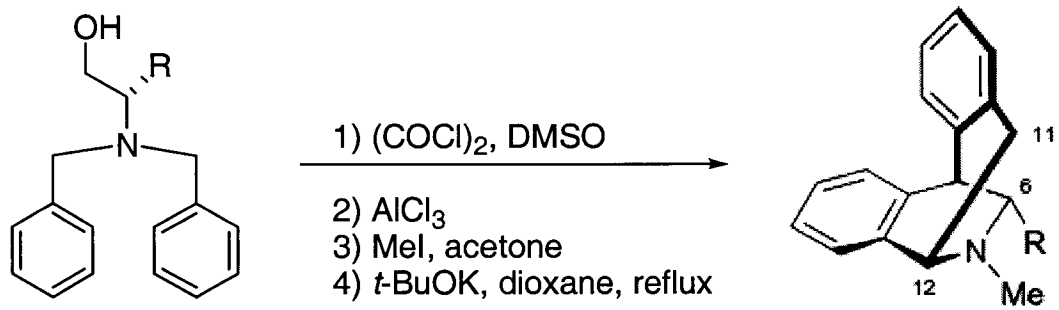


trapped in 85 - 97 % yield



Beall, L.; Padwa, A. *Tetrahedron Lett.* **1997**, 4159
Padwa, A. et Al. *JOC*, **2001**, 2414

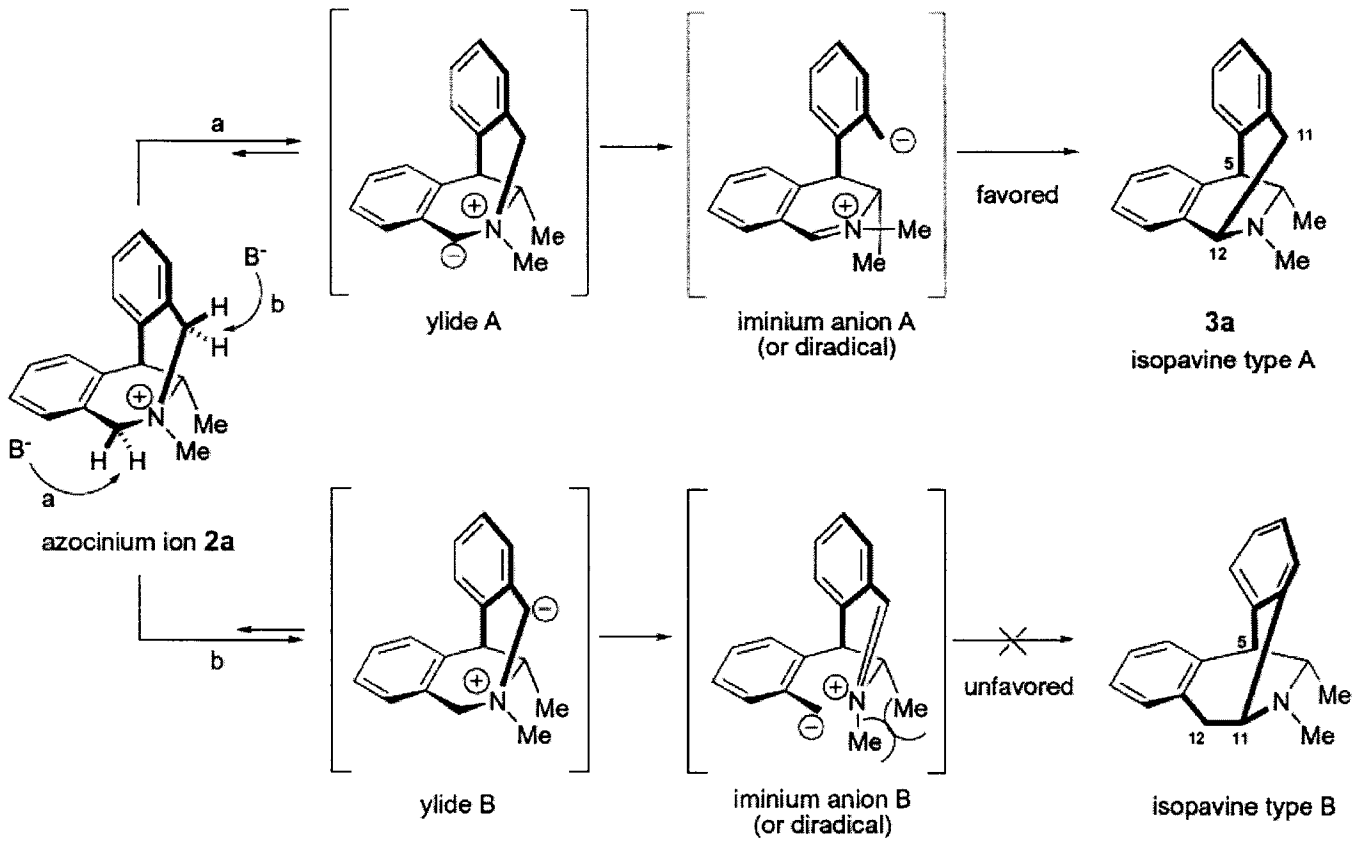
Isopavine



Provide intermediates and explain selectivity in the above transformation.

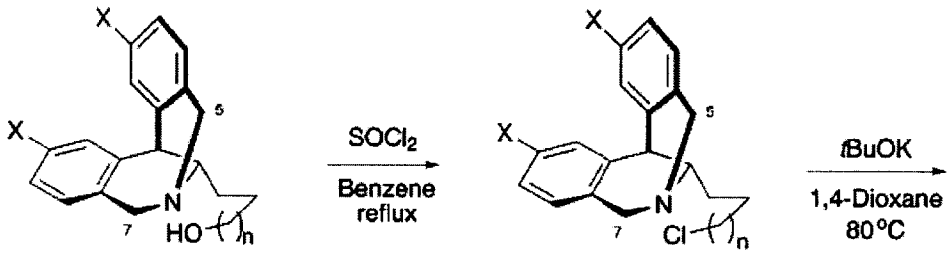
Hanessian, S.; Mauduit, M. *ACIE,* **2001**, 3810

Isopavine



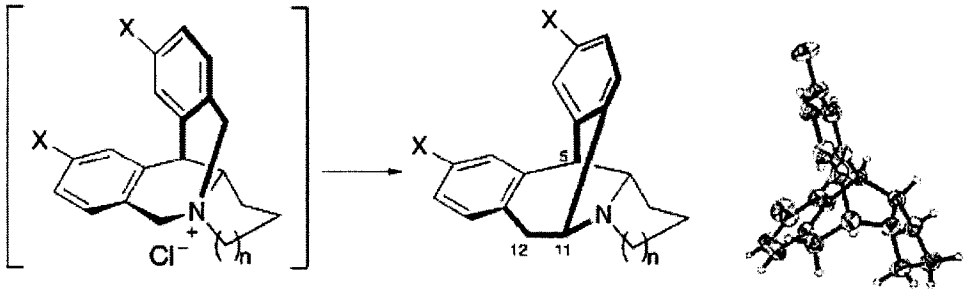
Hanessian, S.; Mauduit, M. *ACIE,* **2001**, 3810

Isopavine



1g : n = 1, X = H; **1i** : n = 2, X = H
1j : n = 1, X = F; **1k** : n = 2, X = F

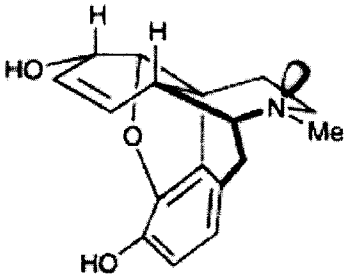
7g, 7i, 7j, 7k



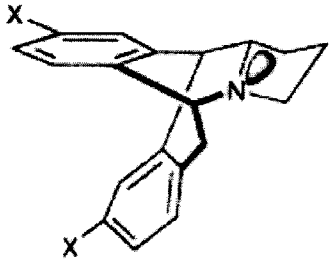
8g, 8i, 8j, 8k

9g : 77%; **9i** : 80%
9j : 72%; **9k** : 50%

X-ray crystal structure of **9j**



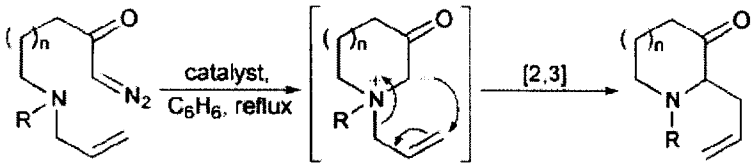
morphine IC_{50} = 0.6 nM



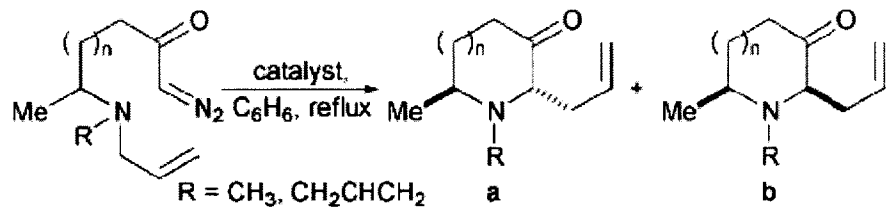
isopavine **9g** : X = H IC_{50} = 66 nM
9j : X = F IC_{50} = 106 nM

Hanessian, S.; Mauduit, M. *ACIE,* **2001**, 3810

Scope of 2,3 Rearrangements



Substrate	R	n	Catalyst	Product	Yield (%)
2a	CH_3	0	$Cu(acac)_2$	**20**	73
2a	CH_3	0	$Rh_2(OAc)_4$	**20**	58
2b	CH_2CHCH_2	0	$Cu(acac)_2$	**21**	76
2b	CH_2CHCH_2	0	$Rh_2(OAc)_4$	**21**	70
9	CH_2CHCH_2	1	$Cu(acac)_2$	**22**	79
9	CH_2CHCH_2	1	$Rh_2(OAc)_4$	**22**	74
11	CH_3	2	$Cu(acac)_2$	**23**	84
11	CH_3	2	$Rh_2(OAc)_4$	**23**	56
12	CH_2CHCH_2	3	$Cu(acac)_2$	**24**	39
12	CH_2CHCH_2	3	$Rh_2(OAc)_4$	**24**	5

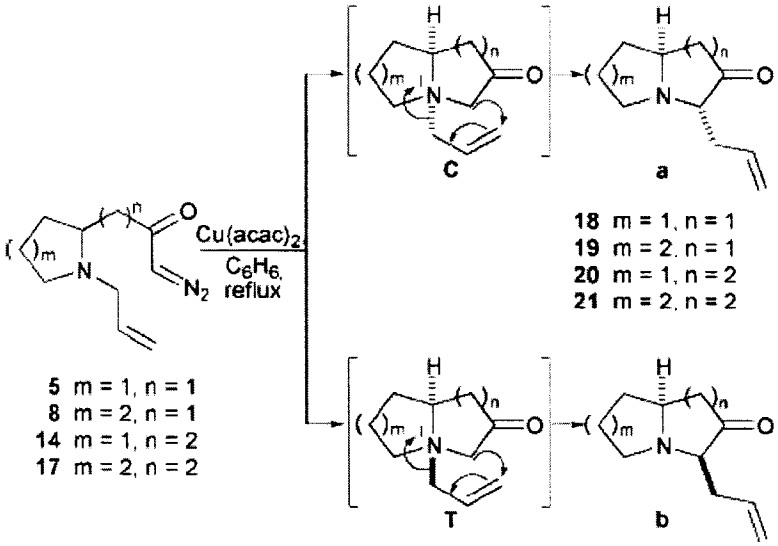


Substrate	R	n	Catalyst	Product (Ratio)	Yield (%)
27	CH_3	0	$Cu(acac)_2$	**34** (1:1)	70
27	CH_3	0	$Rh_2(OAc)_4$	**34** (1:1)	62
28	CH_2CHCH_2	0	$Cu(acac)_2$	**35** (1.7:1)	84
28	CH_2CHCH_2	0	$Rh_2(OAc)_4$	**35** (2:1)	83
33	CH_2CHCH_2	1	$Cu(acac)_2$	**36** (1:1)	72
33	CH_2CHCH_2	1	$Rh_2(OAc)_4$	**36** (1:1)	70

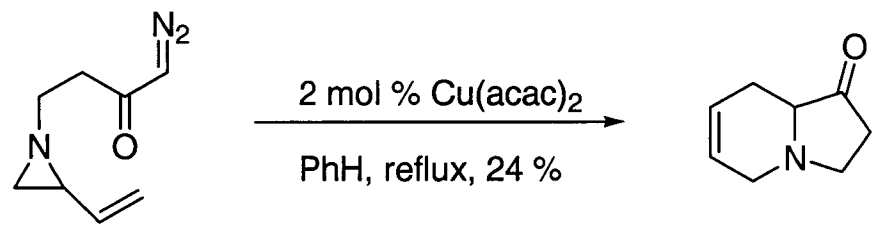
Poor diastereoselectivity from acyclic amines

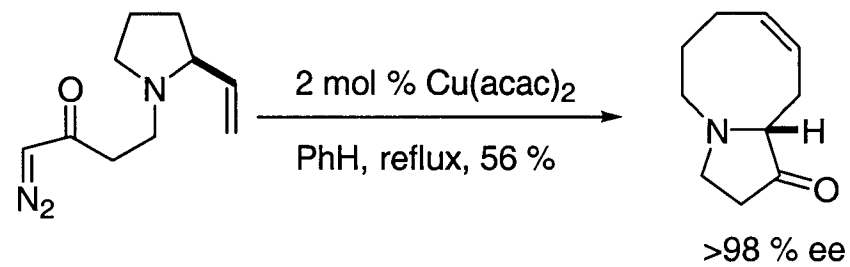
Clark, J. et Al. *JCS Perkin I*, **2001**, 3312
Clark, J. et Al. *JCS Perkin I* **2001**, 3325

Scope of 2,3 Rearrangements



Substrate	Product ratio	Yield (%)
5	**18a** only	65
8	**19a** only	62
14	**20a**:**20b** 3.5:1	66
17	**21a**:**21b** 6:1/1:6	61

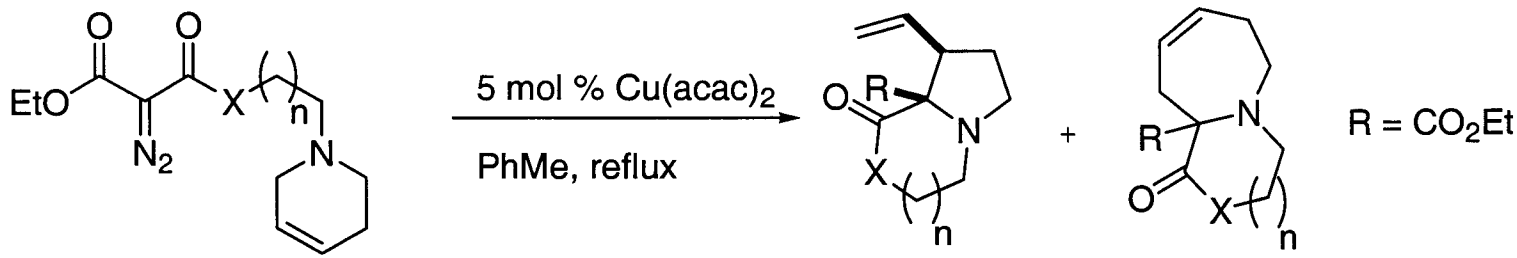




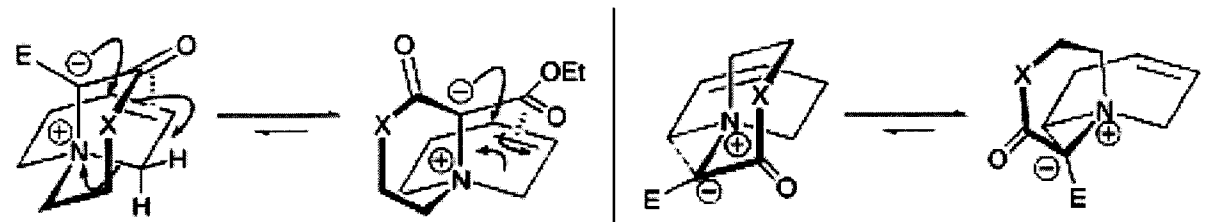
Formation of bicyclic amines proceed with good diastereoselectivity

Clark, J. et Al. *JCS Perkin I*, **2001**, 3312
Clark, J. et Al. *JCS Perkin I* **2001**, 3325

Endo vs Exo in Spirocyclic Ylides



n = 1 X = C	60 % (2.3 : 1 dr)	8 %
n = 1 X = O	54 % (1.3 : 1 dr)	23 %
n = 2 X = C	42 % (1 : 1 dr)	43 %
n = 2 X = O	43 % (1.5 : 1 dr)	43 %



***endo*-anion A** ***endo*-anion B**

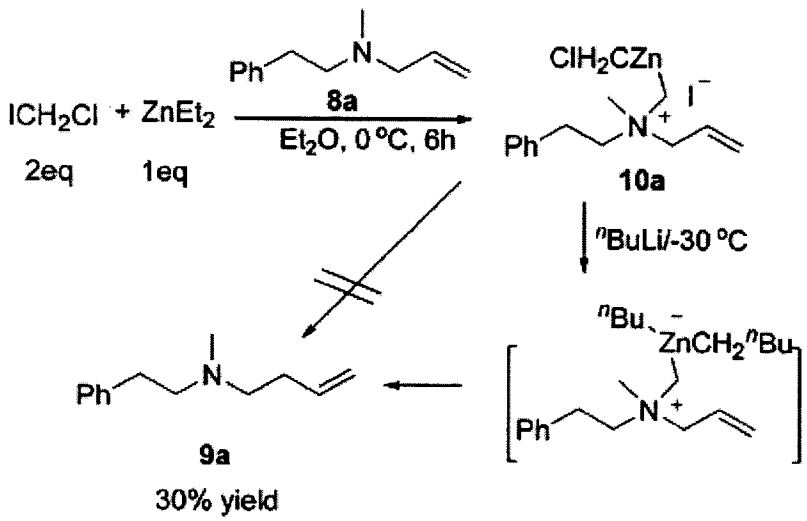
Anion in proximity to alkene → [2,3]

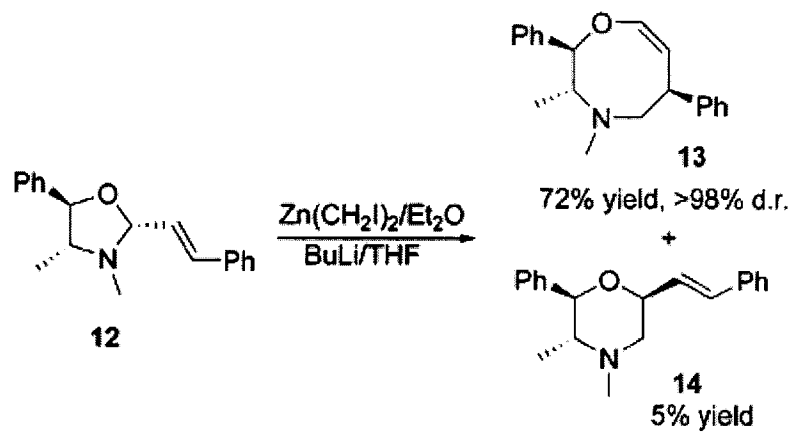
***exo*-anion C** ***exo*-anion D**

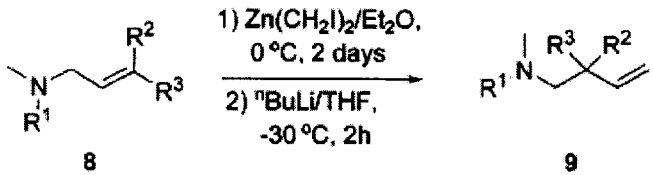
Anion distant from alkene → [1,2]

Roberts, E.; Sancon, J.; Sweeney, J. *Org. Lett.*, ***2005***, *2075*

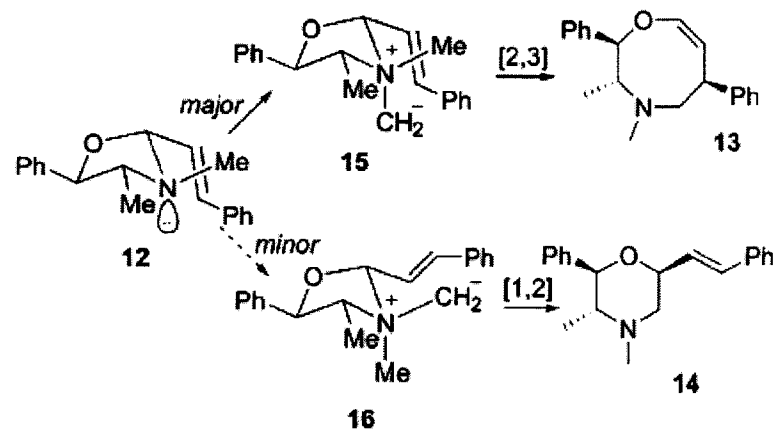
Zn - Complexed Ylides







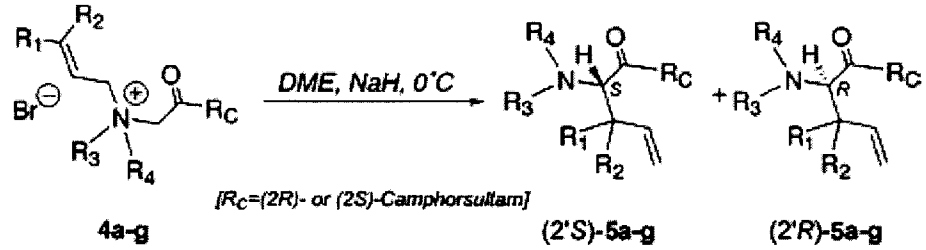
substrate	R^1	R^2	R^3	yield (%)
8a	$Ph(CH_2)_2$	H	H	70
8b	$Ph(CH_2)_2$	CH_3	CH_3	50
8c	$Ph(CH_2)_2$	H	Ph	76
8d	$PhCH_2$	H	H	30[b]



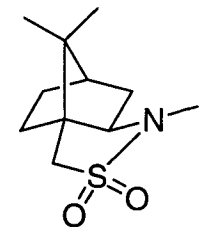
Zn ylides serve as stable rearrangement precursors

Aggarwal, V. et. Al. *Org. Lett.* **2003**, 1757

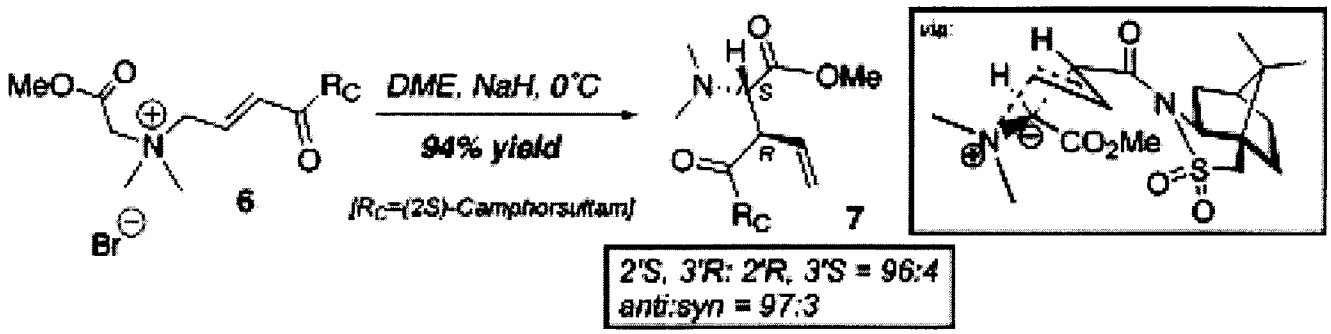
Chiral Auxiliary Approach



R_C =

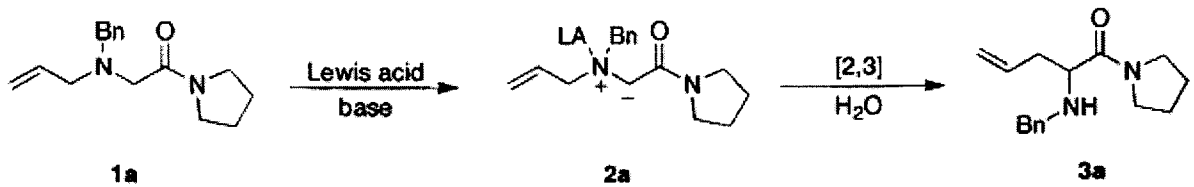


entry	salt	R^1	R^2	R^3	R^4	yield 5 (%)	anti:syn	2'R:2'S
1	4a[b]	H	H	Me	Me	99		2:98[a]
2	4b[c,d]	H	H	Me	allyl	99		97:3[e]
3	4c[c,d]	H	H	allyl	allyl	86		97:3[e]
4	4d[d]	H	H	Bn	allyl	80		>99:1[e]
5	4e[d]	Me	H	Me	Me	86	>99:1	96:4[a]
7	4f[d]	Me	Me	Me	Me	70		97:3[a]
8	4g[d]	MeO_2C	H	Me	Me	64[f]	>99:1	>99:1[a]



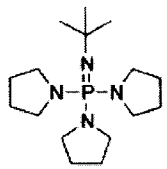
Sweeney, J. et Al. *JACS*, **2005**, 1066

Lewis Acid Mediated Rearrangement

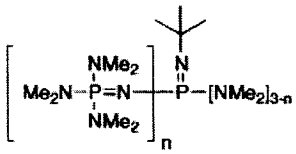


1a **2a** **3a**

All runs 16-20 h in THF, 1.2 equiv LA and base

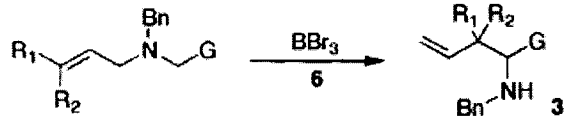


BTPP (**4**); pK_{BH^+}=~26



P_2-t-Bu (**5**): n=1; pK_{BH^+}=~33
P_4-t-Bu (**6**): n=3; pK_{BH^+}=~42

LA	Base	Temp.	Yield
BF_3	LDA	-78 -> rt	0
BF_3	KHMDS	-20	12
BF_3	*i*-Pr_2NEt	reflux	57
BF_3	**4**	-20	11
BF_3	**6**	-20	35
BBr_3	**6**	-20	66

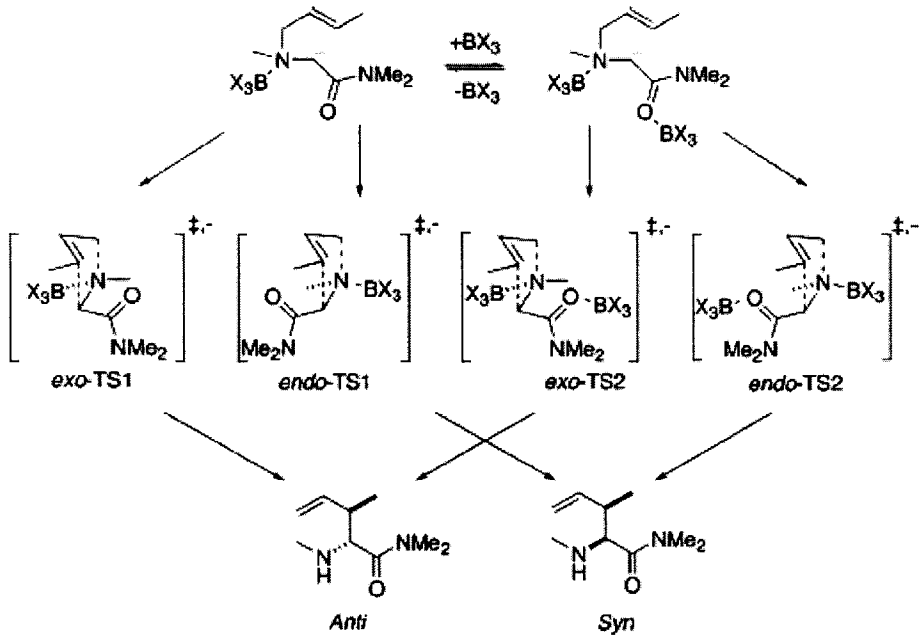


Entry	Substrate	R^1	R^2	G	Yield of 3 (%)[b]	*Syn*:*anti*[c]
1	1b	Me	H	$CONC_4H_8$	71 (20)	>20:1
2	1c	Ph	H	$CONC_4H_8$	62 (32)	11:1
3	1d	H	Me	$CONC_4H_8$	56 (33)	6:5
4	1e	Me	Me	$CONC_4H_8$	60 (31)	–

Circumvents need for quaternization

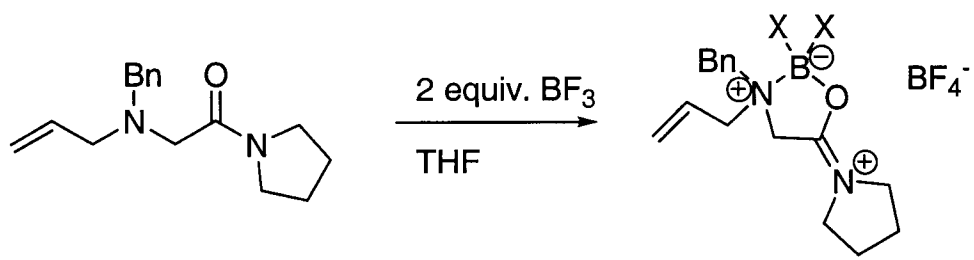
Bild, J.; Somfai, P. *Tetrahedron Lett.* **2003**, 3159

Understanding Selectivity



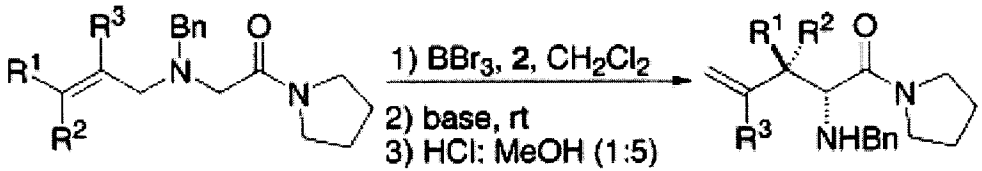
LA	TS	$\Delta G^{\ddagger}$	$\Delta\Delta G^{\ddagger\,b}$
BF_3	*exo*-**TS1**	18.7	
	endo-**TS1**	19.9	1.2
	exo-**TS2**	19.6	
	endo-**TS2**	19.4	−0.2
BBr_3	*exo*-**TS1**	25.5	
	endo-**TS1**	27.8	2.3

[a] Solvation effect included in the free energy. [b] Calculated diastereoselectivity, $\Delta\Delta G^{\ddagger} = \Delta G^{\ddagger}(\text{endo}) - \Delta G^{\ddagger}(\text{exo})$.

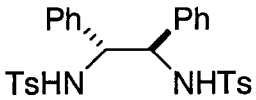


Blid, J.; Brandt, P.; Somfai, P. *JOC*, **2004**, 3043

Asymmetric LA-Mediated Rearrangement



2a =



entry	ligand/equiv	BBr_3 (equiv)	base/equiv	yield of **3a** (%)[b]	ee (%)[c]
1	**2a**/1.2	1.4	4/1.0	22 (55)	85 (*R*)
2	**2a**/1.2	1.2	4/2.0	39 (59)	97 (*R*)
3	**2a**/2.0	2.0	4/1.0	18 (78)	97 (*R*)
4	**2a**/2.0	2.0	4/2.0	79 (0)	96 (*R*)
5	**2a**/2.0	2.0	Et_3N/5.0	87 (3)	97 (*R*)

	yield (%)[b]	*anti*:*syn*[c]	ee (%)[d] *anti*:*syn*
R^1 = Me	**3b**/82	79:21	96 (2*R*,3*R*):75 (2*R*,3*S*)[e]
R^2 = Me	**3c**/85	20:80	82 (2*R*,3*R*):98 (2*R*,3*S*)[e]
R^1 = CH_2OBn	**3d**/70	88:12[f]	93:n.d.[f,g]
R^2 = CH_2OBn	**3e**/71	29:71[f]	98:99[f]
R^1 = $SiPhMe_2$	**3f**/52	95:5[f]	99:n.d.[f,g]
R^1 = Ph	**3h**/92	67:33	97:77[f]
R^2 = Ph	**3i**/65[j]	30:70	94:88[f]
R^1, R^2 = Me	**3j**/64		96[f]
R^3 = Me	**3k**/80		99[f]

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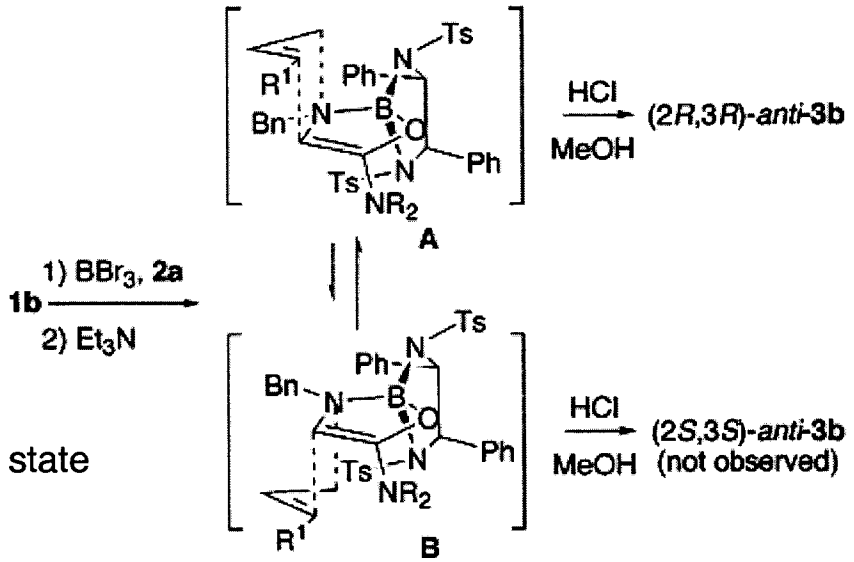
Origins of Enantioselectivity

:

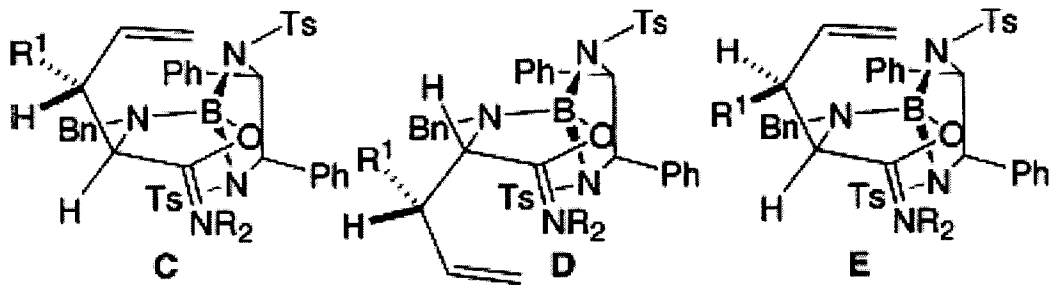
Kinetic:

Minor diastereomer
from endo transition state



Thermodynamic:

Minor diastereomer from
equilibration of **D**



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Summary

- Oxonium Ylides
  - Variable selectivity in substrates with existing stereocenters
  - Moderate enantioselectivity in both 1,2- and 2,3- rearrangements of cyclic substrates
- Ammonium Ylides
  - 1,2- rearrangements provide good selectivity only in rigid systems
  - Recent work on enantio- and diastereo-selective 2,3- rearrangements show good potential for synthesis of both cyclic and acyclic amines
  - Most applicable to synthesis of N- containing polycyclic systems