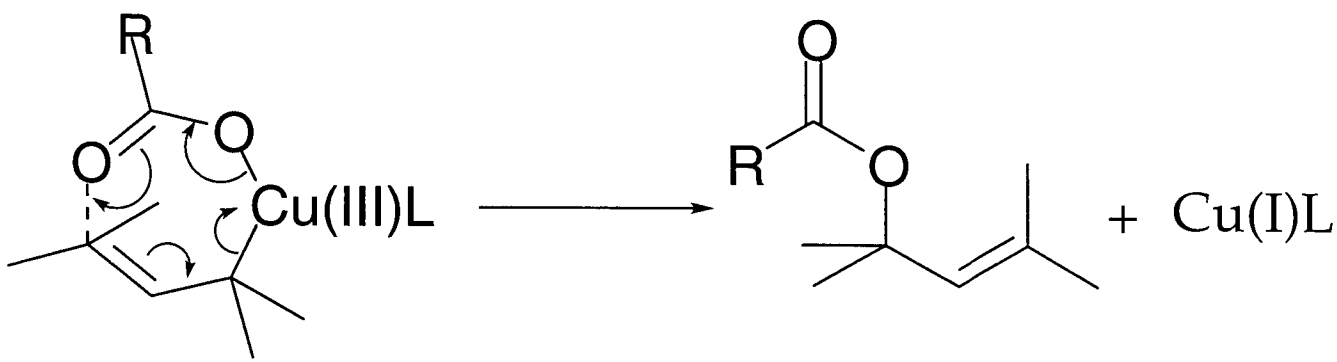
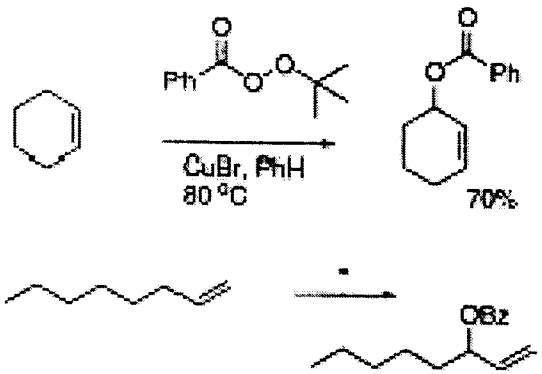
7-30-02
Yu Fan

Copper Catalyzed Allylic Oxidation
Kharasch-Sosnovsky Reaction

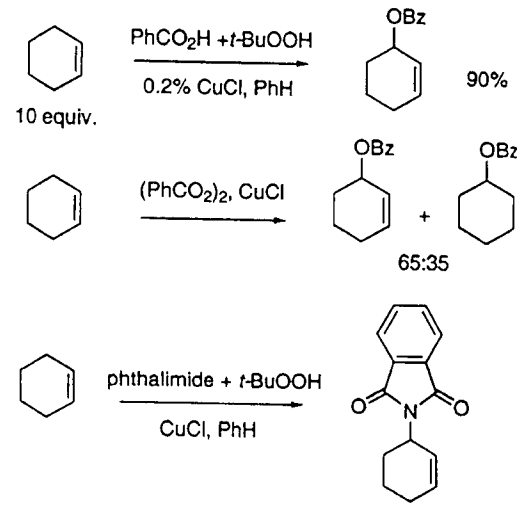


Initial Discovery



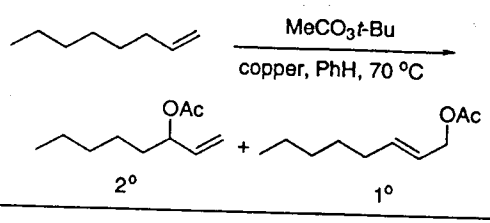
Kharasch, M. S., Sosnovsky, G. *JACS*. **1958**, *80*, 756

Terminal olefin as major products.



Kharasch, M. S.; Fono, A. *JOC*, **1958**, *23*, 324
Kharasch, M. S.; Fono, A. *JOC*, **1958**, *23*, 326

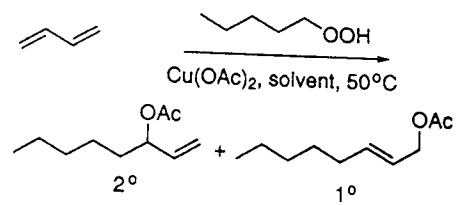
Effect of Copper Source on Selectivity



Entry	Copper	2°/1°
1	CuCl	86:14
2	$Cu(OAc)_2$	89:11
3	$Cu(OAc)_2$/pyr	70:30

Walling, C.; Zavitsas, A. A. *JACS*, **1963**, *85*, 2084

Copper complex has different selectivity.



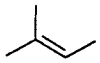
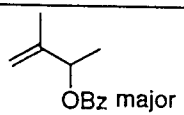
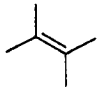
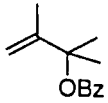
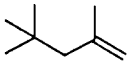
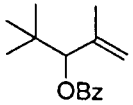
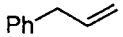
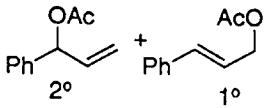
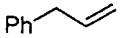
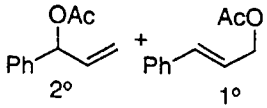
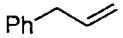
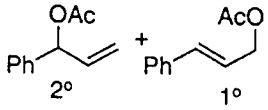
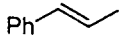
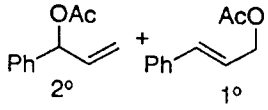
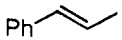
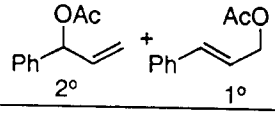
Entry	Solvent	ε	2°/1°
1	EtOAc/AcOH	6.02	86:14
2	CH_3CN/AcOH	36.7	80:20
3	HCO_2H	58	80:20[a]
4	H_2O/AcOH	78.5	78:22[b]
5	AcOH/pyr	12.3	66:34

[a] Formate esters are formed.
[b] Alcohols formed

Kochi, J. K.; Mains, H. E. *JACS*, **1965**, *30*, 1862

Solvent has little effect on selectivty.

Substrate Scope-Acyclic Alkenes

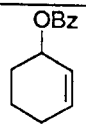
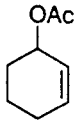
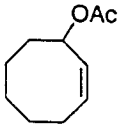
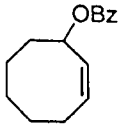
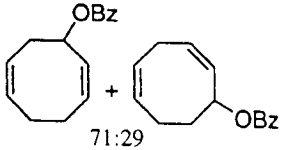
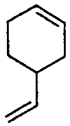
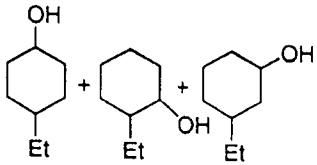
Substrate	Conditions	Product	Yield (%)
	$PhCO_3t$-Bu, $Cu(O_2CR)_2$, PhH, 70°C		71
	$PhCO_3t$-Bu, $Cu(O_2CR)_2$, PhH, 70°C		78
	$PhCO_3t$-Bu, CuBr, PhH		37
	CH_3CO_3t-Bu, CuCl, 70°C	 (71:29)	
	$Cu(OAc)_2$	 (67:33)	
	t-BuOOH, AcOH, CuCl	 (53:47)	
	CH_3CO_3t-Bu, CuCl, 70°C	 (100:0)	
	t-BuOOH, AcOH, CuCl	 (52:48)	

With acyclic alkenes, terminal olefin products predominate.

Andrus, M. B.; Lashley, J. C. Tetrahedron, 2002, 58, 845

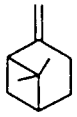
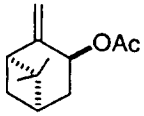
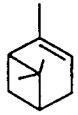
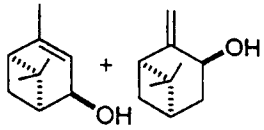
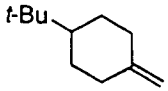
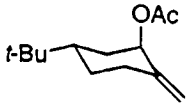
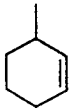
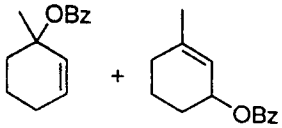
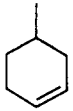
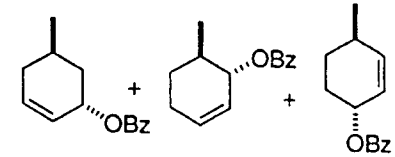
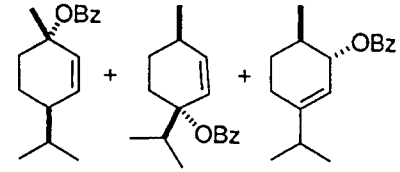
Substrate Scope-Cyclic Alkenes

Table 5. Cyclic alkene substrates for allylic oxidation

Substrate	Conditions	Product	Yield (%)
	$PhCO_3t$-Bu, CuBr, PhH		80
	AcOH, t-BuOOH, CuCl		88
	CH_3CO_3t-Bu, CuBr, PhH		38
	$PhCO_3t$-Bu, Cu–Na-HSZ-320 zeolite		68
	$PhCO_3t$-Bu, $Cu(O_2CR)_2$	 71:29 98:2	96
	$PhCO_3t$-Bu, Cu–Na-HSZ-320 zeolite		82
	(1) $PhCO_3t$-Bu, CuBr, PhH; (2) H_2, Pd/C; (3) NaOH	 3:2:2	36

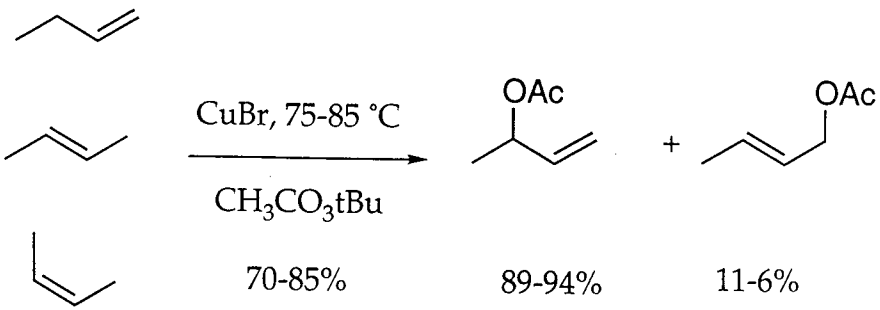
Andrus, M. B.; Lashley, J. C. Tetrahedron, 2002, 58, 845

Chiral Substrates

Substrate	Conditions	Product	Yield (%)
 $[\alpha]_D$ -80°	$PhCO_3t$-Bu, CuBr, PhH	 $[\alpha]_D$ 0°	85
	CH_3CO_3t-Bu, CuBr, PhH	 85%	90, *trans*
	CH_3CO_3t-Bu, CuBr, PhH/NaOH		50, 30
	CH_3CO_3t-Bu, CuBr, PhH/NaOH		26
	$PhCO_3t$-Bu, $Cu(O_2CR)$, PhH		28, 29
	$PhCO_3t$-Bu, $Cu(O_2CR)$, PhH	 29% (4:1) 16% (1.5:1) 9% (2:1)	
	$PhCO_3t$-Bu, $Cu(O_2CR)$, PhH	 34% (4:1) 26% (4:1) 13% (4:1)	

Diastereoselective allylic oxidation is possible.

Radical Chain Mechanism

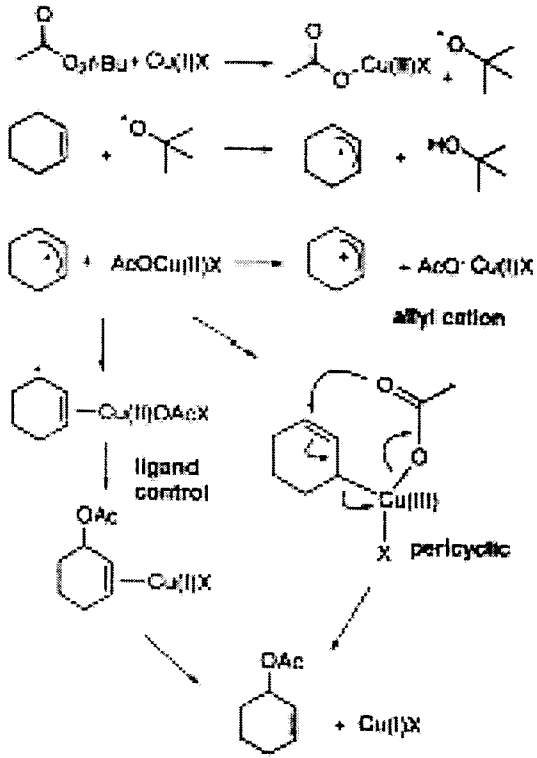


Kochi, J. K. *JACS. 1961*, **83**, 3102

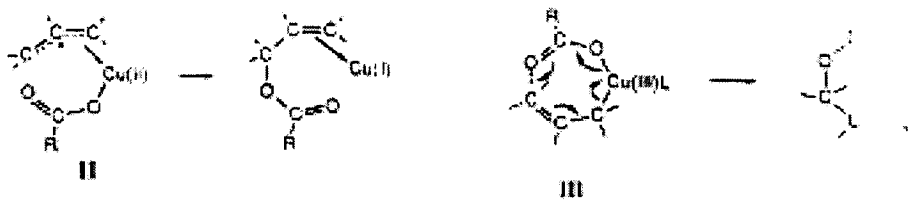
A common intermediate diverts to two products.

Kochi, J. K.; Mains, H. E. *JOC.* **1963**, *30*, 1862

Trapping experiment and isolation of by-product prove its existance.



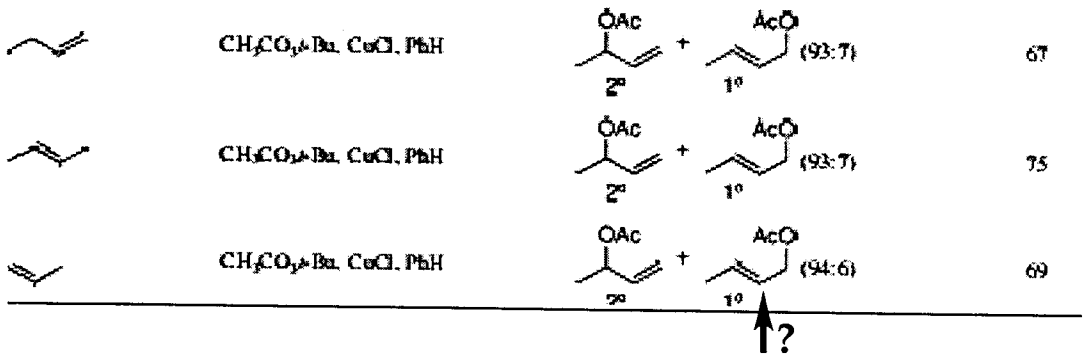
Which drawing is closer to the reality?



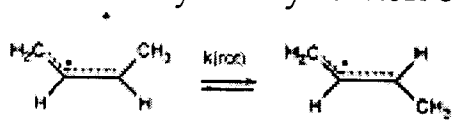
Beckwith, A. L. J.; Zavitsas, A. A. *JACS*, **1986**, *108*, 8230

How Cu(II) Oxidize Allyl Radical?

Product composition rechecked:



Configurational stability of allyl cation or radical:

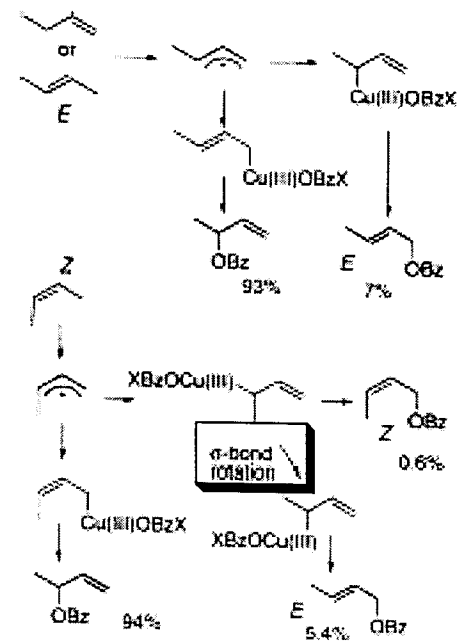


allylic compd	reagent	X	1-ene	*trans*-1-X-2-ene	*cis*-1-X-2-ene
1-butene	*t*-BuOCl[a]	Cl	31	41	28
trans-2-butene	*t*-BuOCl[a]	Cl	26	74	
cis-2-butene	*t*-BuOCl[a]	Cl	37		63
but-1-en-3-ol	conc HCl[b]	Cl	38	58	4
but-2-en-1-ol[c]	conc HCl[b]	Cl	31	56	13
3-chloro-but-1-ene[d]	H_2O[e]	HO	67	33	
trans-1-chloro-but-2-ene[d]	H_2O[e]	HO	56	44	
cis-1-chloro-but-2-ene[d]	H_2O[e]	HO	45	1	54

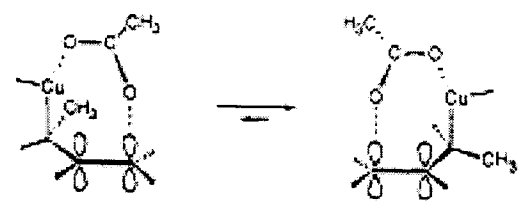
[a] At 70 °C, photolysis, in benzene solvent, radical reaction. [b] At 0 °C, ionic reaction. [c] Mixture of 70% trans and 30% cis isomers. [d] Brubacher, L. J.; Triendl, L.; Robertson, R. E. *J. Am. Chem. Soc.* **1968**, *90*, 4611–4616; hydrolysis postulated to proceed mostly through S_N1. [e] At 40 °C.

Under reaction conditions, allyl radical is configurationally stable.

Rationale for the product distribution:



Transition state geometry explains *trans*-product predominate.



VI (cis product) VII (trans product)

Beckwith, A. L. J.; Zavitsas, A. A. *JACS*, **1986**, *108*, 8230

Early Efforts toward Development of Enantioselective Allylic Oxidation

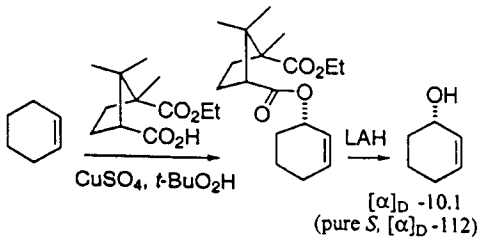


TABLE I

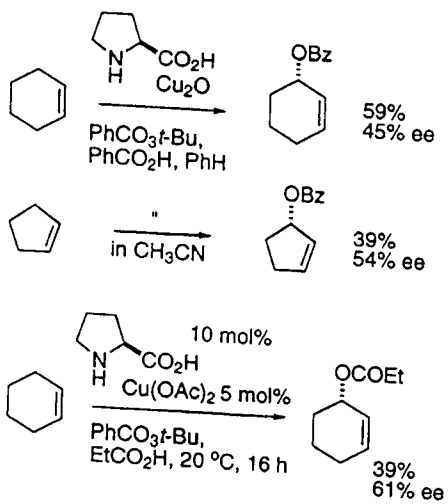
PEROXIDE REACTIONS

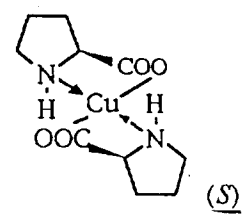
Olefin	Carboxylate	Conditions	Rotation of allylic alcohol degrees
Cyclohexene	III	2 days, 25°	−10.1
Cyclohexene	IV	16 hr., 50°	+10.1
Cyclopentene	III	2 days, 25°	−13.8
Cyclooctene	III	1 week, 65°	+5.85
Bicyclo-3,2,1-octene-2	III	2 days, 25°	−5.21
2-Methyl-2-butene	III	1 week, 25°	0
1-Octene	III	1 week, 70°	0
Cyclododecene	III	1 week, 25°	0

IV

Methyl Diacetyl tartarate

Denney, D. B. et al. *JOC.*, **1965**, *30*, 3151





Chiral copper complex could provide asymmetric induction.

Muzart, J. el al. *J. Mol. Cat. A.* **1991**, *64*, 381.
Muzart, J. et al. *Tetrahedron Asy.* **1995**, 6, 147-156.

Bisoxazoline Copper Complexes Catalysts

Substrate	L*	Solvent[a]	Time [days]	Temp. [°C]	Conversion [%]	Yield[b] [%]	ee[c] [%]
cyclopentene	2a	CH_3CN	4	23	57	74	74
	2a	CH_3CN	12	7	60	81	77
	2a	acetone	14	0	75	76	75
	2a	acetone	22	−20	67	66	82
	2b	CH_3CN	4	23	88	68	74
	2b	CH_3CN	12	7	65	65	79
	2b	CH_3CN	12	0	100	64	80
	2b	CH_3CN	22	−20	68	61	84
	2c	acetone	5	23	99	84	71
cyclohexene	2a	acetone	1	50	100	71	58
	2a	acetone	3	23	99	69	64
	2a	CH_3CN	9	23	91	64	61
	2b	CH_3CN	1	50	90	44	51
	2b	CH_3CN	7	23	63	68	60
	2b	CH_3CN	15	7	77	64	77
	2c	acetone	3	23	100	77	67
	3	CH_3CN	3	23	95	80	71
cycloheptene	2a	CH_3CN	2	50	87	57	69
	2a	CH_3CN	3	23	78	75	74
	2a	CH_3CN	14	7	63	44	82

[a] $CH_3CN/CHCl_3$ 3:1 or acetone/$CHCl_3$ 3:1. [b] Yield based on consumed perester. [c] Determined by HPLC on a chiral column (hexane/isopropanol 1000:1; 2-cyclohexenyl benzoate: Chiralcel OJ, 2-cyclopentenyl benzoate: Chiralcel OD, 2-cycloheptenyl benzoate: Chiralcel OD-H). All products show negative optical rotation values and, therefore, have (*S*)-configuration.[16]

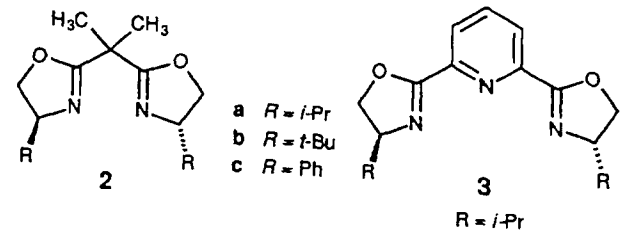
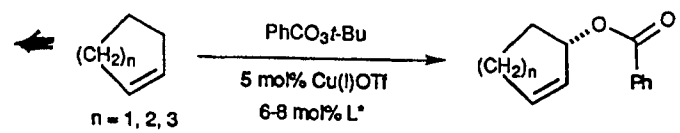
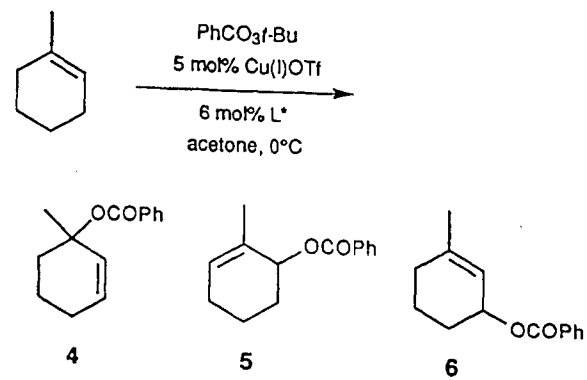


Table 1. Enantioselective allylic oxidation of cycloalkenes[12]



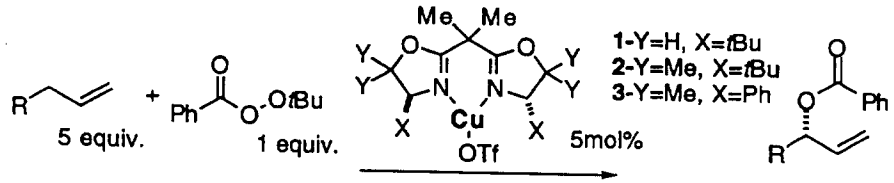


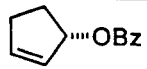
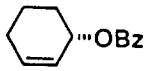
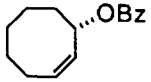
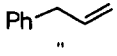
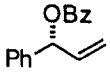
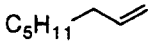
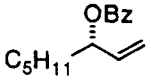
L*	Composition [%][a] 4	5	6	Enantiomeric Excess [%][b] 4	5	6
2a	9	50	42	90	63	13
2b	8	42	50	73	37	42

[a] Determined by GC (5% PhMe silicon). [b] Determined by HPLC (4 and 5: Chiralcel OJ, 6: Chiralcel OD).

Pfaltz, A. et al. *TL.*, **1995**, *36*, 1831.

Bisoxazoline-Copper Complexes Catalysts



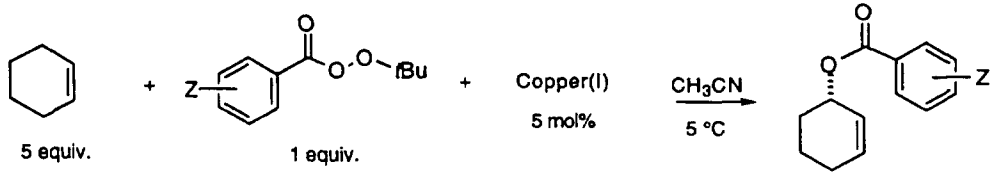
Entry[a]	Olefin	Product[b]	Catalyst	Solvent	Temp.[c]	%Yield[b]	%ee[d]
							
2	"	"	**1**	CH_3CN	-20°	44	70
3	"	"	**2**	"	-20°	41	42
4	"	"	**3**	"	-20°	49	**81**
							
5			**1**	CH_3CN	5°	62	67
6	"	"	**1**	"	-20°	43	**80**
7	"	"	**2**	"	-20°	49	67
8	"	"	**3**	"	5°	59	46
9	"	"	**3**	"	-20°	44	47
							
10			**1**	CH_3CN	-20°	44	13
11	"	"	**2**	"	-20°	43	0
							
12			**1**	PhH	55°	34	36
13	"	"	**1**	CH_3CN	5°	50	0
							
14			**1**	PhH	55°	50	30
15	"	"	**1**	CH_3CN	5°	13	0

[a] 0.5 mmol scale. [b] ^1H and ^{13}C NMR characterization. Isolated yields based on perester. [c] 5° C was maintained by a refrigerator. The freezer used for -20° C. [d] integration of ^1H NMR(500 MHz) signal for *o*-protons of the benzoate with chiral shift reagent $Eu(hfc)_3$ and compared to spectra of the racemic compound.

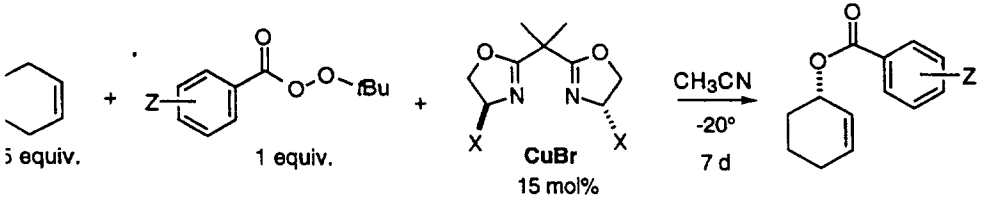
Andrus, M. B. et al. TL. 1995, 36, 2945.

Effects of Copper Source and Peresters

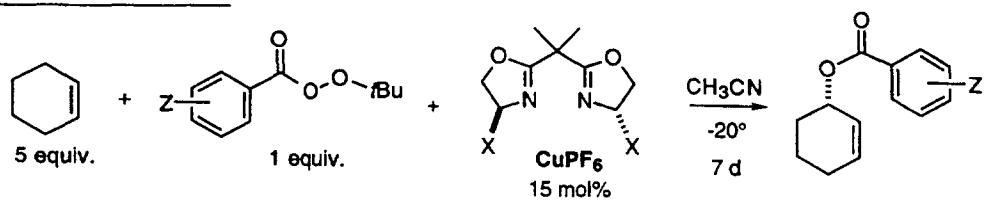
Table 2. Reaction of peresters and cyclohexene with copper(I) salts at 5 mol% without ligand at constant temperature (5 °C).



Perester	Copper(I)	Time (d)	Yield%
2 *m*-Cl	CuBr	5	42
"	$CuPF_6 \cdot (CH_3CN)_4$	5	61
3 *o*-Cl	CuBr	5	74
"	$CuPF_6 \cdot (CH_3CN)_4$	5	13
4 *p*-NO2	CuBr	5	23
"	$CuPF_6 \cdot (CH_3CN)_4$	5	15



Perester	Ligand	Yield%	ee%
1 *p*-Cl	X=*t*Bu	72	57
"	X=Ph	67	20
4 *p*-NO_2	X=*t*Bu	53	63
"	X=Ph	47	7



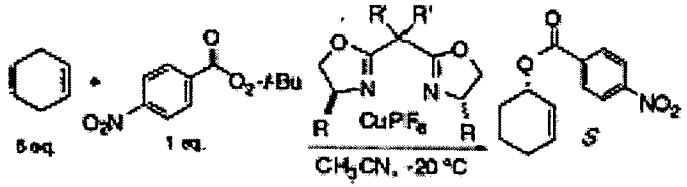
Perester	Ligand	Yield%	ee%
1 *p*-Cl	X=*t*Bu	73	75
"	X=Ph	83	75
2 *m*-Cl	X=*t*Bu	46	72
"	X=Ph	69	74
3 *o*-Cl	X=*t*Bu	67	73
"	X=Ph	78	71
4 *p*-NO_2	X=*t*Bu	60	76
"	X=Ph	71	76

No conclusive results

Andrus, M. B. et al. Tetrehedron 1997, 53, 16629.

Most Recent Results

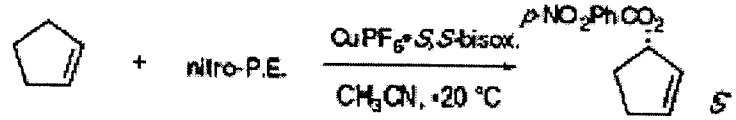
Table 1. Asymmetric Allylic Oxidation of Cyclohexene



entry	R	R′	time (d)[a]	% yield[b]	ee[c]
1	*t*-Bu	Me	7	61	84
2	–	Me	21	43	80[d]
3	Ph	Me	17	44	96
4	Bn	Me	6	30	71
5	*t*-Pr	Me	6	40	82
5	*t*-Bu	Et	16	25	16
6	Ph	Et	13	50	75
7	Bn	Et	12	50	53
8	*t*-Pr	Et	5	26	78

[a] Time in days, using a sealed vial placed in the freezer with stirring.
[b] Yields are for isolated, chromatographed materials based on the perester.
[c] Enantiomeric excesses were determined by chiral normal phase HPLC.
[d] Unsubstituted perester. *tert*-Butyl perbenzoate used.

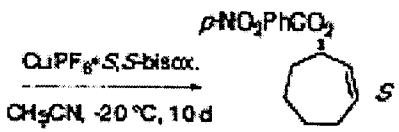
Table 2. Oxidation of Cyclopentene



entry	R	R′	time (d)[a]	% yield[b]	ee[c]
1	*t*-Bu	Me	10	52	79
2	Ph	Me	10	49	82
3	Bn	Me	10	25	75
4	*t*-Pr	Me	10	42	51
5	*t*-Bu	Et	10	31	38
6	Ph	Et	8	41	99
7	Bn	Et	8	28	80
8	*t*-Pr	Et	8	36	83

[a] Time in days, using a sealed vial placed in the freezer with stirring.
[b] Yields are for isolated, chromatographed materials based on the perester.
[c] Enantiomeric excesses were determined by chiral normal phase HPLC.

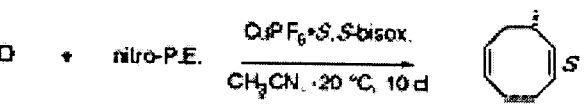
Table 3. Oxidation of Cycloheptene



entry	R	R′	% yield[a]	ee[b]
1	*t*-Bu	Me	3	95
2	ph	Me	23	56
3	*t*-Pr	Me	14	99
4	Ph	Et	12	86

[a] Yields are for isolated, chromatographed materials based on the perester.
[b] Enantiomeric excesses were determined by chiral normal phase HPLC.

Table 4. Asymmetric Oxidation of COD



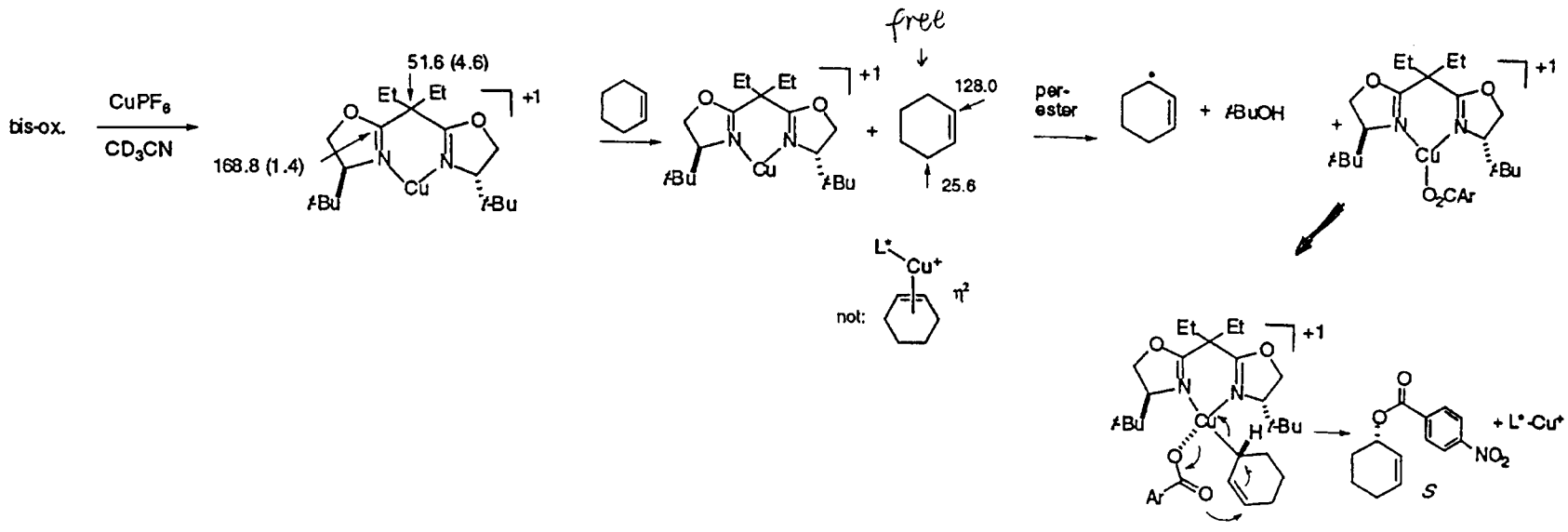
entry	R	R′	% yield[a]	ee[b]
1	*t*-Bu	Me	13	94
2	Ph	Me	46	74
3	*t*-Pr	Me	25	36
4	Ph	Et	34	59
5	*t*-Pr	Et	27	78

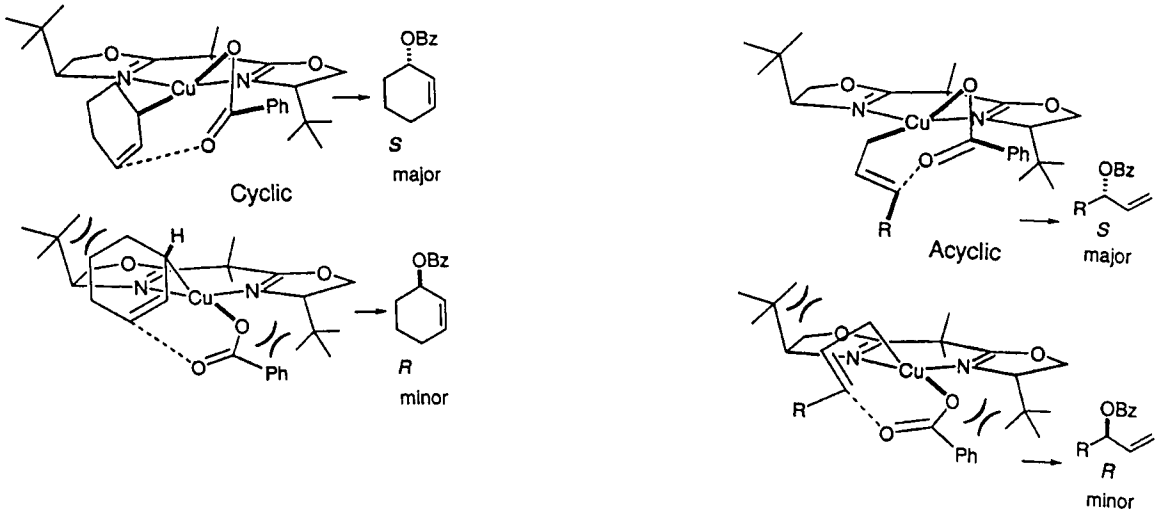
[a] Yields are for isolated, chromatographed materials based on the perester.
[b] Enantiomeric excesses were determined by chiral normal phase HPLC.

Screening catalyst for each substrate is necessary.

Andrus, M. B. et al. *JACS* **2002**, *124*, 8806.

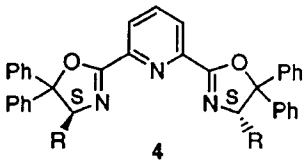
Catalyst Resting Sta.. and Transition State Model





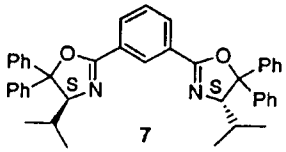
Andrus, M. B. et al. *JACS* **2002**, *124*, 8806.

Pybox-Copper Complex Catalyst

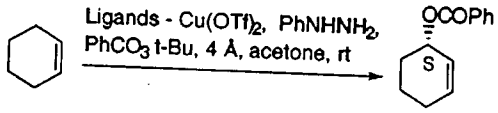


4

a: R = Isopropyl
b: R = Benzyl
c: R = Methyl
d: R = Phenyl



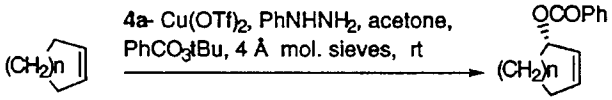
7



entry	ligand	time[b]	% yield[c]	% ee[d]
1	**4a**	24 h	73	75
2	**4b**	24 h	79	62
3	**4c**	02 d	69	23
4	**4d**	36 h	57	11
5	**7**	24 h	62	00

[a] The reaction was done at rt, which here refers to 18–20 °C. [b] h for hour and d for days. [c] Isolated yield. [d] Determined by HPLC on chiral columns.

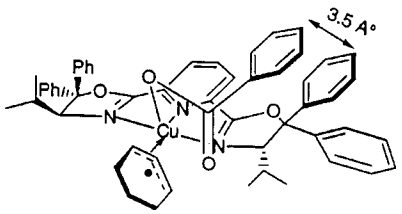
Table 6. Catalytic Enantioselective Allylic Oxidation of Olefins with Chiral 4a–Cu(I) Complex Reduced in Situ from 4a–Cu(OTf)$_2$ by Phenylhydrazine[a]



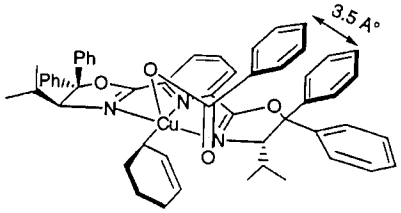
n = 1, 2, 3, 4 (*S*)-8

Entry	Olefins	Time[b]	% Yield[c]	% ee[d]
1.		04 h	80	60
2.		24 h	73	75
3.		24 h	42	82
4.		72 h	28	81

[a] The reaction was done at rt, which here refers to 28–30 °C. [b] h for hour. [c] Isolated yield. [d] Determined by HPLC on chiral columns and by 400 MHz ^{1}H NMR spectrum of a Mosher ester of the corresponding alochol.



13a

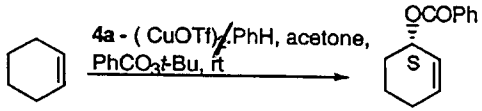


13b

Singh, V. K. et al. *JOC.* **1998,** *63,* 2961.

Additive Effects

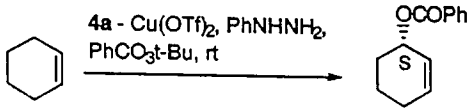
Table 2. Effect of Phenylhydrazine and 4 Å Molecular Sieves on Catalytic Enantioselective Allylic Oxidation of Cyclohexene with Chiral 4a–(CuOTf) Complex[a]



entry	$PhNHNH_2$	4 Å	time[b]	% yield[c]	% ee[d]
1	no	No	06 d	87	73
2	yes	No	05 h	78	70
3	no	Yes	21 d	88	86
4	yes	Yes	10 h	77	67

[a] The reaction was done at rt, which here refers to 18–20 °C. [b] h for hour and d for days. [c] Isolated yield. [d] Determined by HPLC on Chiracel OJ and OD-H columns.

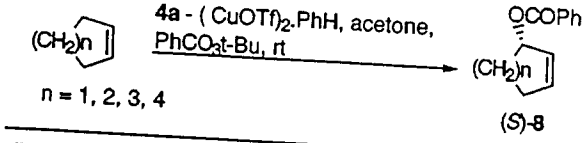
Table 5. Effect of Solvent and 4 Å Molecular Sieves on Catalytic Enantioselective Allylic Oxidation of Cyclohexene with Chiral 4a–Cu(I) Complex Reduced in Situ from 4a–Cu(OTf)$_2$ by Phenylhydrazine[a]



entry	solvent	4 Å	time[b]	% yield[c]	% ee[d]
1	benzene	no	24 h	55	28
2	benzene	yes	72 h	70	35
3	acetonitrile	no	10 d	43	70
4	acetonitrile	yes	15 d	58	80
5	acetone	no	24 h	65	71
6	acetone	yes	24 h	73	75
7	acetone	yes	30 d	78	79

[a] All the reactions, except entry 7, was done at rt, which here refers to 27–30 °C. The entry 7 was done at 10 °C. [b] h for hours and d for days. [c] Isolated yield. [d] Determined by HPLC on chiral

Table 3. Effect of Phenylhydrazine on Catalytic Enantioselective Allylic Oxidation of Olefins with Chiral 4a–(CuOTf) Complex[a]



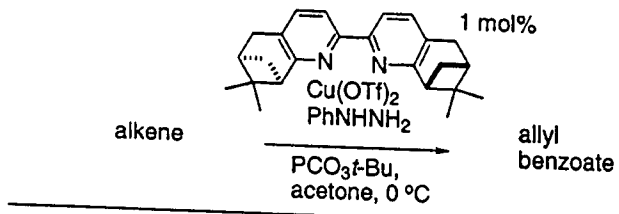
Entry	Olefins	$PhNHNH_2$	Time[b]	% Yield[c]	% ee[d]
1.		No	48 h	90	51
2.		Yes	03 h	62	54
3.		No	06 d	87	73
4.		Yes	05 h	78	70
5.		No	6.5 d	63	71
6.		Yes	06 h	35	72
7.		No	30 d	28	80
8.		Yes	24 h	26	81

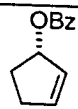
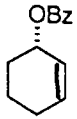
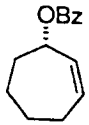
[a] The reaction was done at rt, which here refers to 18–20 °C. [b] h for hours and d for days. [c] Isolated yield. [d] Determined by HPLC on chiral columns and by 400 MHz ^{1}H NMR spectrum of a Mosher ester of the corresponding alochol.

Phenylhydrazind additive can effectively enhance reactivity without compromising selectivity.

Singh, V. K. et al. *JOC.* **1998,** *63,* 2961.

Chiral Bipydine Copper Complex



Alkene	Time (h)	Ester	Yield (%)	% ee
	12		80	59
	0.5		96	49
	0.5		88	62

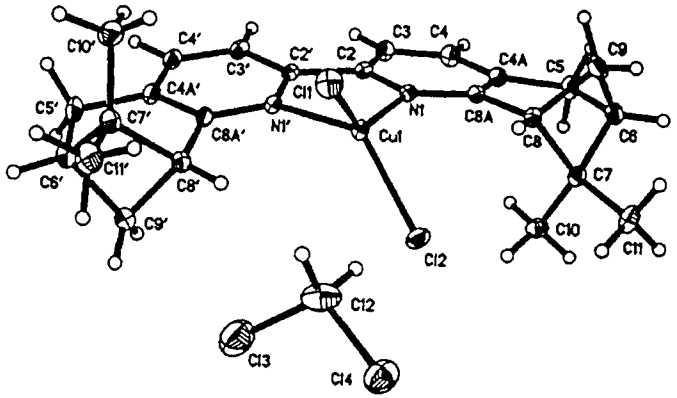


Figure 1. ORTEP diagram of **8**·CH_2Cl_2 showing the atom labeling scheme. Displacement parameters are shown at the 30% probability level. H atoms are shown as spheres of arbitrary radius.

Kocovsky, P. et al. *Org. Lett.* **2000,** *2,* 3047.

Chiral Phenanthroline Copper Complex

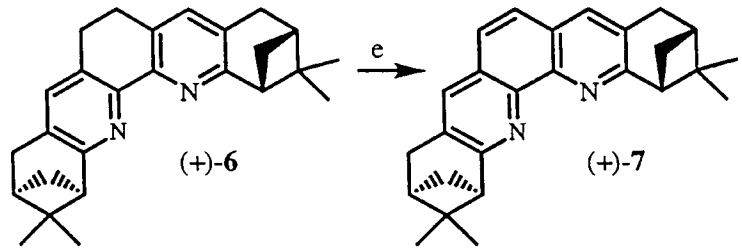
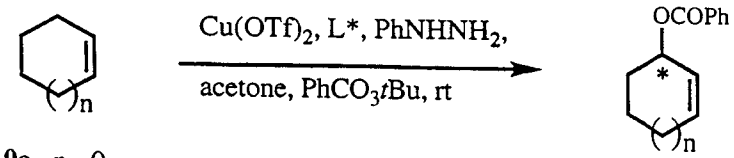


Table 1. Asymmetric allylic oxidation of cycloalkanes catalyzed by Cu(I)–L* complexes[a]



9a, n= 0
9b, n= 1
9c, n= 2
9d, n= 3

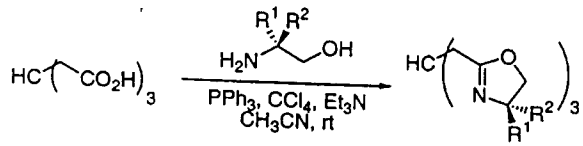
(S)-(-)-**10a**, n= 0
(S)-(-)-**10b**, n= 1
(S)-(-)-**10c**, n= 2
(S)-(-)-**10d**, n= 3

Entry	Olefin	Ligand	Time (h)	Yield (%)[b]	Ee (%)[c]
1	Cyclopentene	(+)-6	0.5	78	47
2	Cyclopentene	(+)-7	0.5	86	57
3	Cyclohexene	(+)-6	0.5	82	50
4	Cyclohexene	(+)-7	0.5	85	53
5	Cycloheptene	(+)-6	0.5	81	63
6	Cycloheptene	(+)-7	0.5	91	71
7	Cyclooctene	(+)-6	168	–	–
8	Cyclooctene	(+)-7	168	–	–

[a] The reaction were carried out at room temperature in Me_2CO in the presence of the catalyst (1 mol%), generated in situ by reduction of $Cu(OTf)_2$ with $PhNHNH_2$.[10]
[b] Isolated yields.
[c] Determined by chiral HPLC.[10] The assignment of the absolute configuration is based on the sign of the optical rotation: Ref. 12.

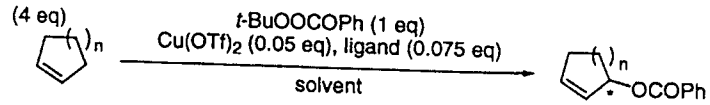
Chelucci, G. et al. *TL.* **2002,** *43,* 3601.

Tris(oxazoline) Copper Complex



	R^1	R^2	Yield (%)
4a	Ph	H	40
4b	4-$MeOC_6H_4$	H	45
4c	H	4-$CF_3C_6H_4$	36
4d	H	*i*-Pr	20

Table 1
Asymmetric allylic oxidation of cycloalkenes

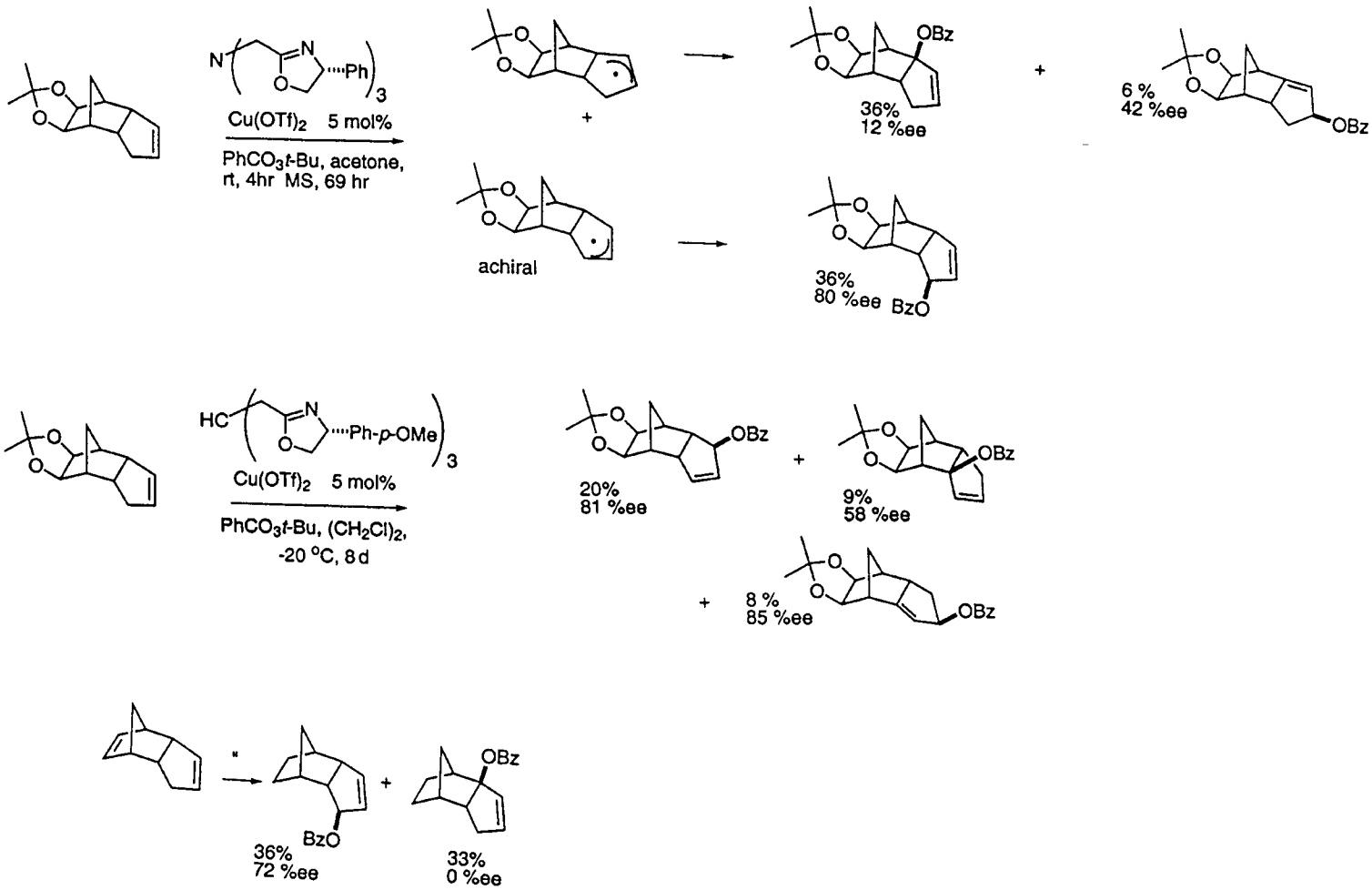


Entry	n	Ligand	Solvent	Temp. (°C)	Time (h)	Yield (%)[a]	ee (%)	Confign.[b]
1	1	**4a**	$(CH_3)_2CO$	rt	10	46	65[c]	*R*
2[d]	1	**3**	$(CH_3)_2CO$	rt	16	83	76[c]	*S*
3[d]	1	**4a**	$(CH_3)_2CO$	rt	46	77	31[c]	*R*
4	1	**4a**	CH_3CN	rt	21	69	63[c]	*R*
5	1	**4a**	$CH_3CO_2C_2H_5$	rt	8	57	45[c]	*R*
6	1	**4a**	CH_2Cl_2	rt	7	77	74[c]	*R*
7	1	**4a**	$(CH_2Cl)_2$	rt	7	78	76[c]	*R*
8	1	**4a**	$(CH_2Cl)_2$	0	48	80	83[c]	*R*
9	1	**4a**	$(CH_2Cl)_2$	-20	210	40[e]	87[c]	*R*
10	1	**4a**	C_6H_6	rt	7	77	34[c]	*R*
11	1	**4a**	C_6H_5Cl	rt	8	71	56[c]	*R*
12	1	**4b**	$(CH_2Cl)_2$	rt	6	71	80[c]	*R*
13	1	**4b**	$(CH_2Cl)_2$	0	48	73	85[c]	*R*
14	1	**4b**	$(CH_2Cl)_2$	-20	200	46[e]	89[c]	*R*
15	1	**4c**	$(CH_2Cl)_2$	0	48	77	51[c]	*S*
16	1	**4d**	CH_2Cl_2	rt	11	43	2[c]	*S*
17	2	**4b**	$(CH_2Cl)_2$	0	48	80	82[c]	*R*
18	2	**4b**	$(CH_2Cl)_2$	-20	200	50[e]	86[c]	*R*
19	3	**4b**	$(CH_2Cl)_2$	0	48	64	88[f]	*R*
20	3	**4b**	$(CH_2Cl)_2$	-20	200	13[e]	92[f]	*R*
21	4	**4b**	$(CH_2Cl)_2$	rt	48	24	81[c]	*R*
22	4	**4b**	$(CH_2Cl)_2$	0	200	25[e]	85[c]	*R*

a) Isolated yield. Yield was calculated based on the amount of *t*-butyl peroxybenzoate used.
b) Determined by comparison of the specific rotation (reference 7e).
c) Determined by HPLC analysis (DAICEL CHIRALCEL OD-H, hexane/2-propanol=1000:1).
[illegible] in the presence of MS-4A.

Katsuki, T. et al. *TL.* **2000,** *41,* 3941.

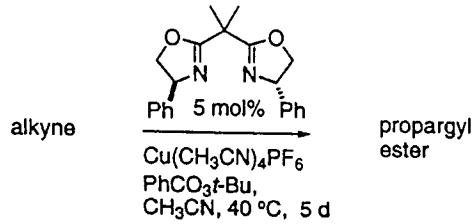
Attempted Desymmetrization

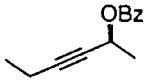
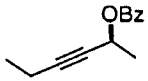
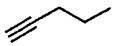
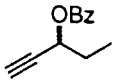
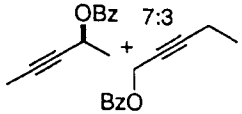
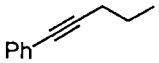
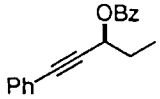
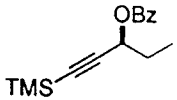


Desymmetrization of *meso* allyl radical potentially can efficiently set multiple chiral centers.

Katsuki, T. et al. *Tetrahedron.* **1997,** *53,* 6337.

Asymmetric Propargylic Oxidation



Substrate	Sub/perester	Ester	Yield (%)	% ee
	5:1		80	21
	1:1		38	21
	1:4		43[a]	20
	5:1	 7:3	73	15
	1:4		95[a]	51
	1:4		92[a]	46

[a] Yield based on alkyne.

Clark, J. S. et al. *TL.* **1998**, *39*, 4913.

Conclusions

1. Radical chain mechanism accounts for copper catalyzed allylic oxidation reactions.
2. Copper catalyzes this reaction through a Cu(I)-Cu(II)-Cu(III)-Cu(I) redox cycle.
3. High degree of enantioselection has been achieved.
4. A highly active and enantioselective allylic oxidation catalyst(s) still needs to be found.
5. Desymmetrization of meso allyl radical and propargylic oxidation provide room for new development.