Control and Amplification of Chirality

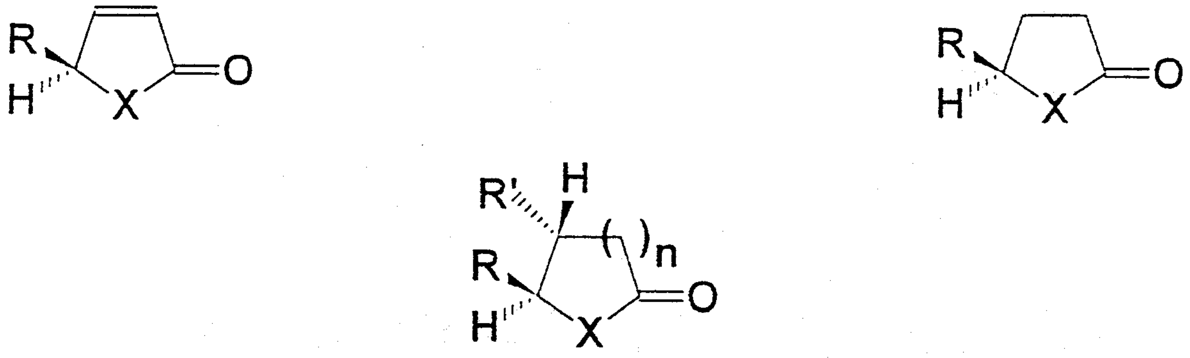
Heterocyclic

lipase-Pd-catalysis

Carbocyclic

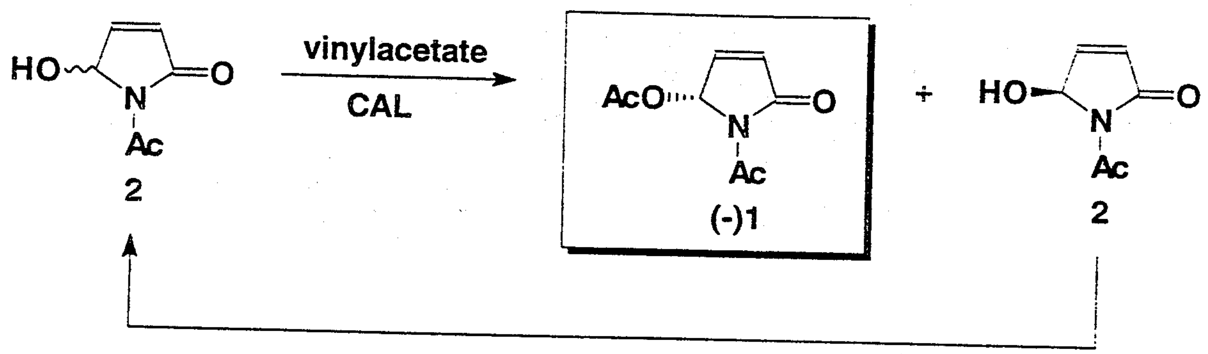
catalytic 1,4-addition

Chemoenzymatic route to chiral heterocycles



X = O, NR''   n = 0, 1

Enzymatic esterification of hydroxypyrrolinones

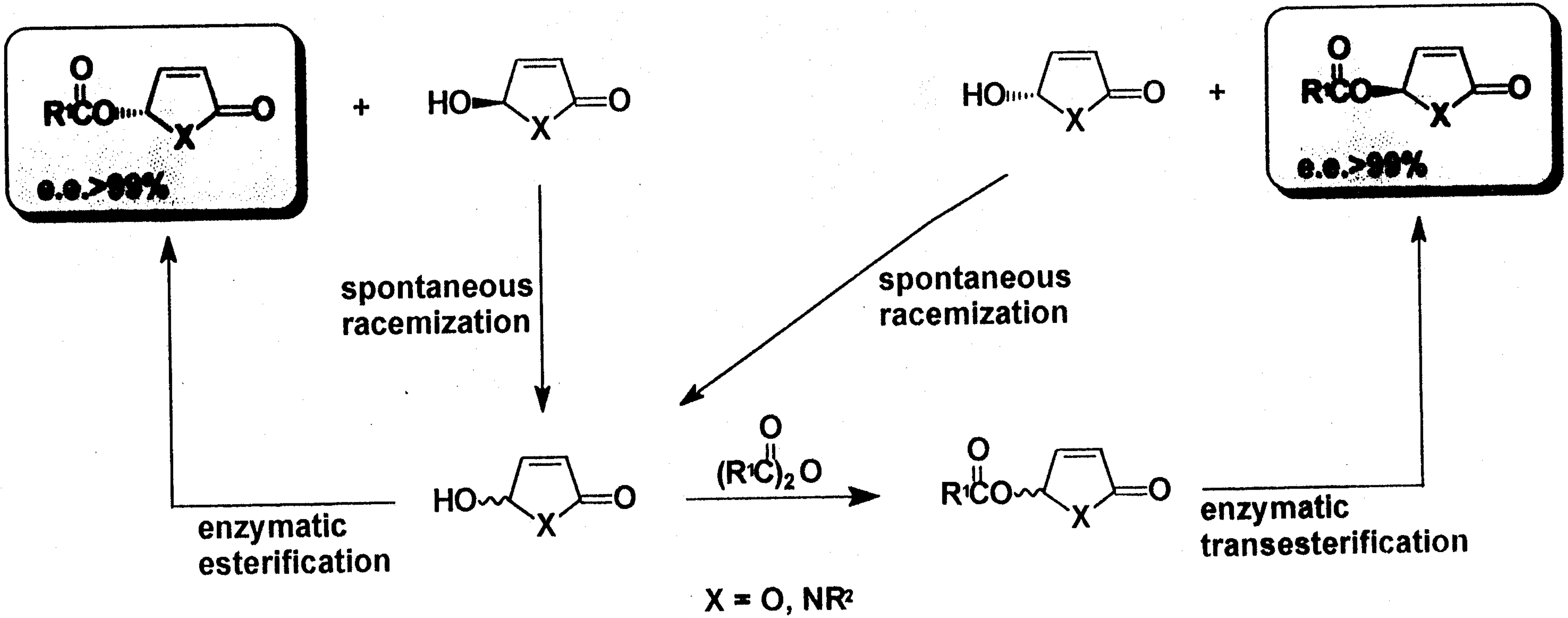


Influence of the temperature

solvent	temperature (^0C)	time (hours)	conversion (%)	e.e. (%)
hexane	22	168	53	>99
hexane	40	72	99	>99
acetone:hexane (1:1)	56	18	100	>99
hexane	69	18	100	>99

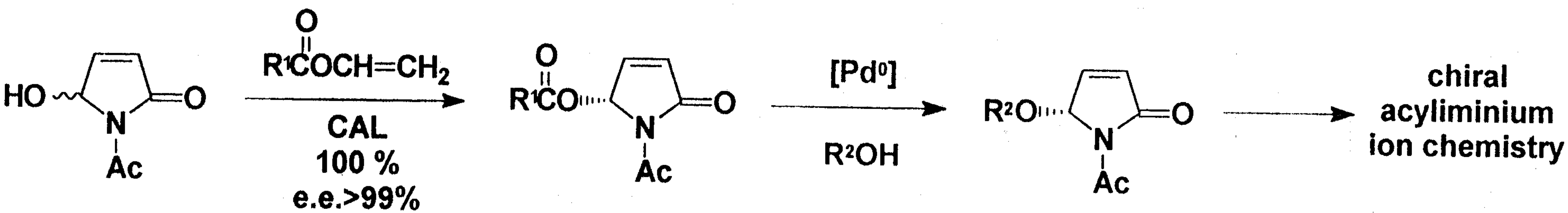
YMATIC SYNTHESIS SCHEME

Both enantiomers of an acyloxypyrrolinone can be obtained with the use of a single enzyme, simply by variation of procedure.



Deen van der, H.; Cuiper, A.D.; Hof, R.P.; Oeveren van, A.; Feringa, B.L.; Kellogg, R.M. *J. Am. Chem. Soc.*, 1996, 118, 3801.

ATALYZED ALLYLIC SUBSTITUTION



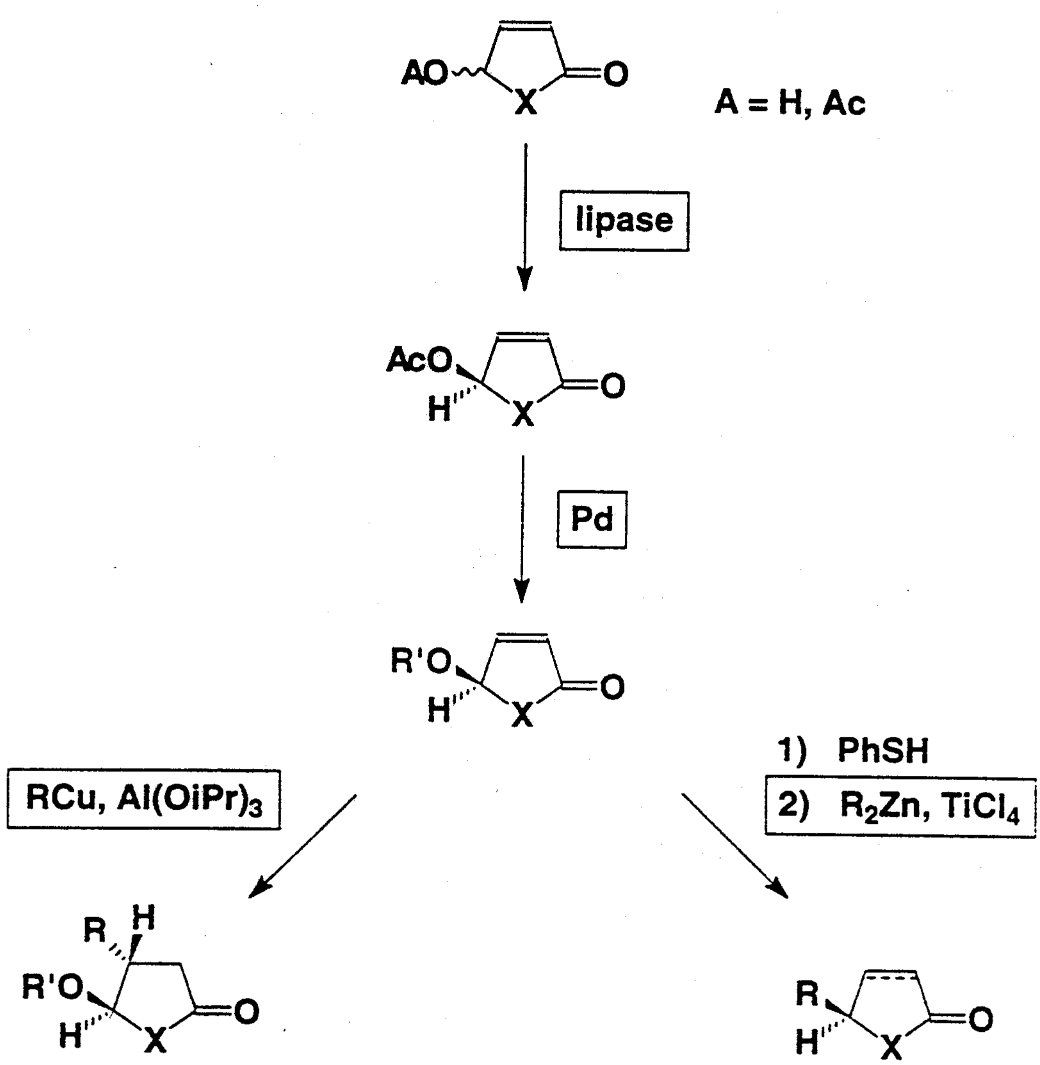
1

(-) 2

(-) 3

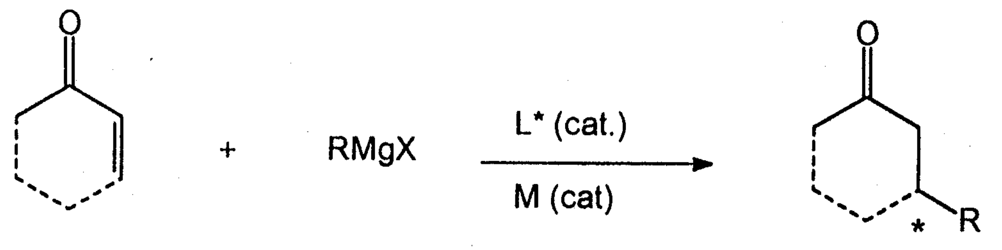
(7

Multimetallic Approach to Heterocycles



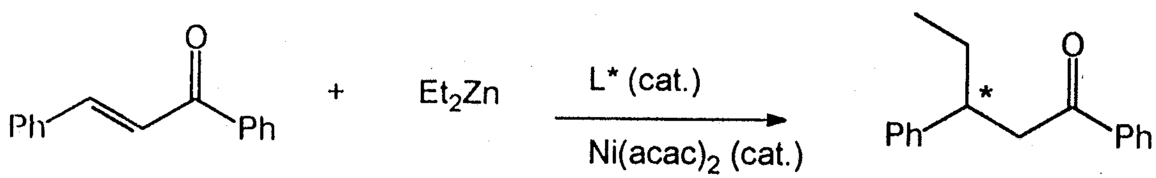
Catalytic enantioselective conjugate addition of organometallic reagents

RuG



yield > 80%
e.e. 15-85%

c.f.: Lippard, v. Koten, Pfaltz, Spescha, Tomioka



yield > 80%
e.e. 40-90%

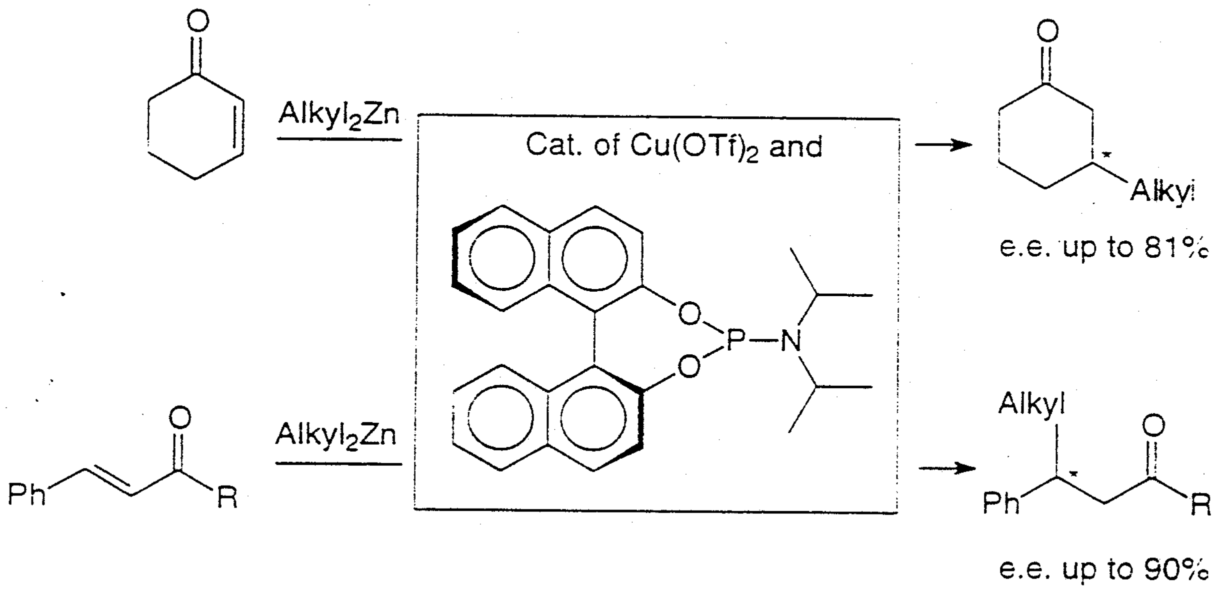
c.f.: Soai, Bolm, Feringa

Reviews:

N. Krause and A. Gerold *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 186.

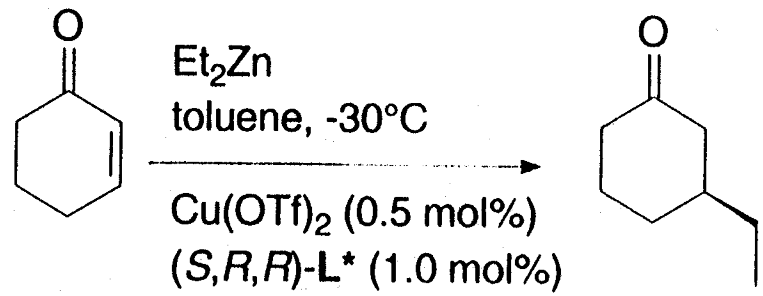
B.L. Feringa, A.H.M. De Vries, in *Advances in Catalytic Processes, Vol 1*, JAI Press, Connecticut, **1995**, p. 151.

COPPER -PHOSPHORAMIDITE CATALYST

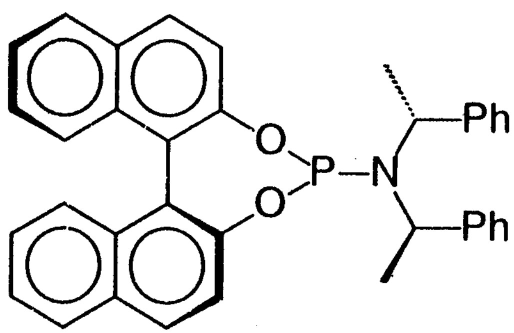


- new class of monodentate ligand
- excellent chemoselectivity
- relatively high e.e. for cyclic and acyclic enones
- the possibility to start with alkenes

Catalytic 1,4-Addition to cyclohexenone

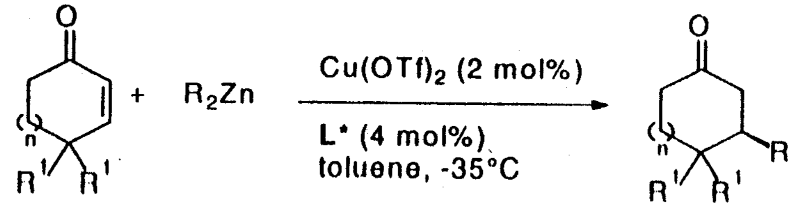


95% yield
e.e. > 98%

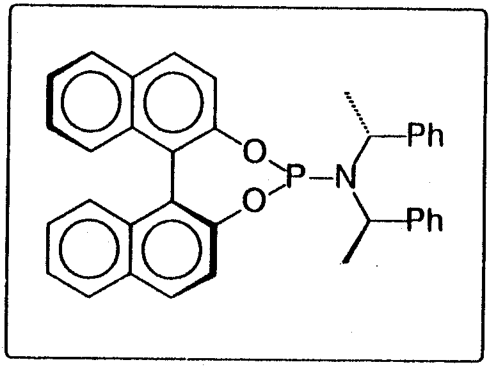


(*S*,*R*,*R*)-**L***

Conjugate Addition to Cyclic Enones

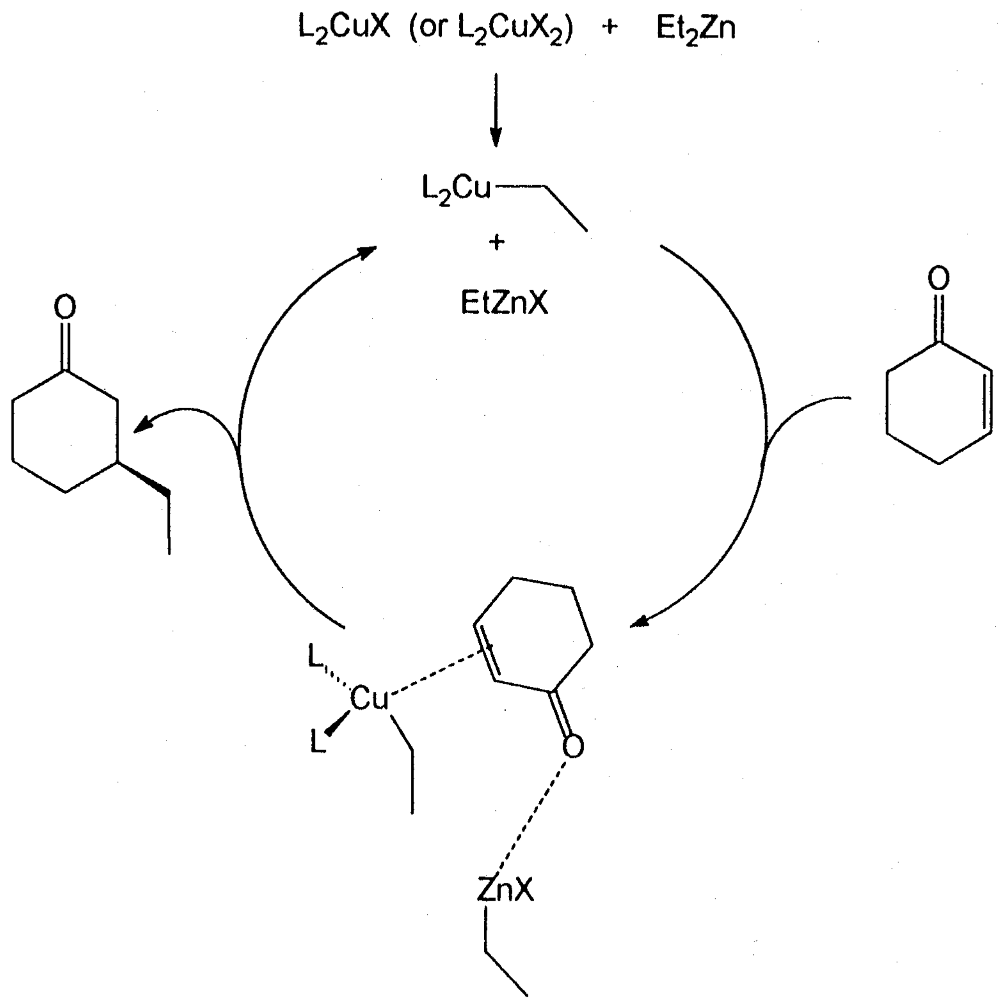


R	R[1]	n	yield (%)	e.e. (%)
C_2H_5	H	1	94	>98
C_2H_5	H	0	75	10
C_2H_5	H	2	95	>98
C_2H_5	H	3	95	97
C_2H_5	CH_3	1	74	>98
C_2H_5	C_6H_5	1	93	>98
CH_3	H	1	72	>98
CH_3	CH_3	1	68	>98
C_7H_{15}	H	1	95	95
i-C_3H_7	H	1	95	94
$(CH_2)C_6H_5$	H	1	53	95
$(CH_2)_5OAc$	H	1	77	95
$(CH_2)_3CH(OC_2H_5)_2$	H	1	91	97



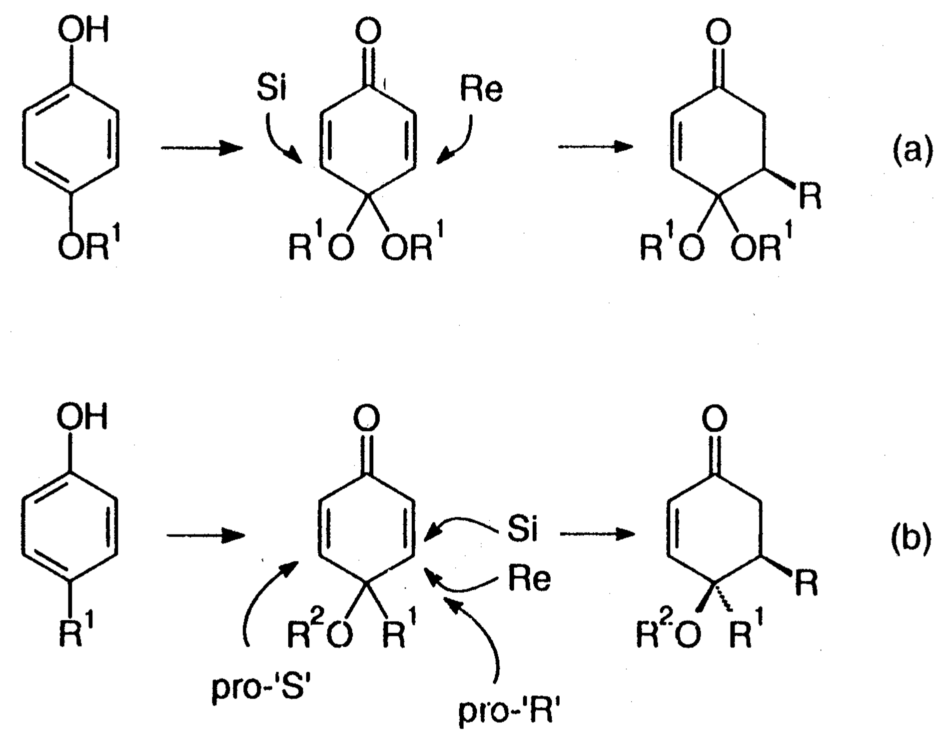
Proposed catalytic cycle

RuG

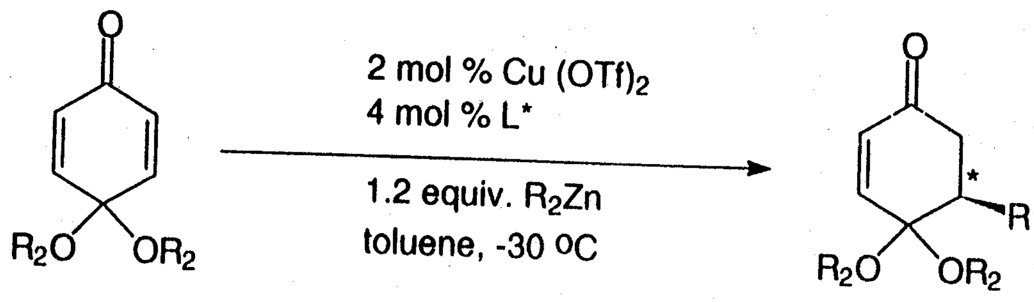


11

Cyclohexadienones

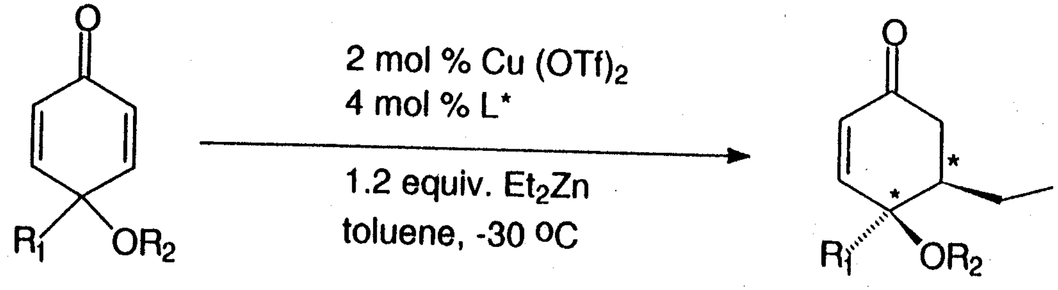


Conjugate addition to dienones with $R_1=R_2$



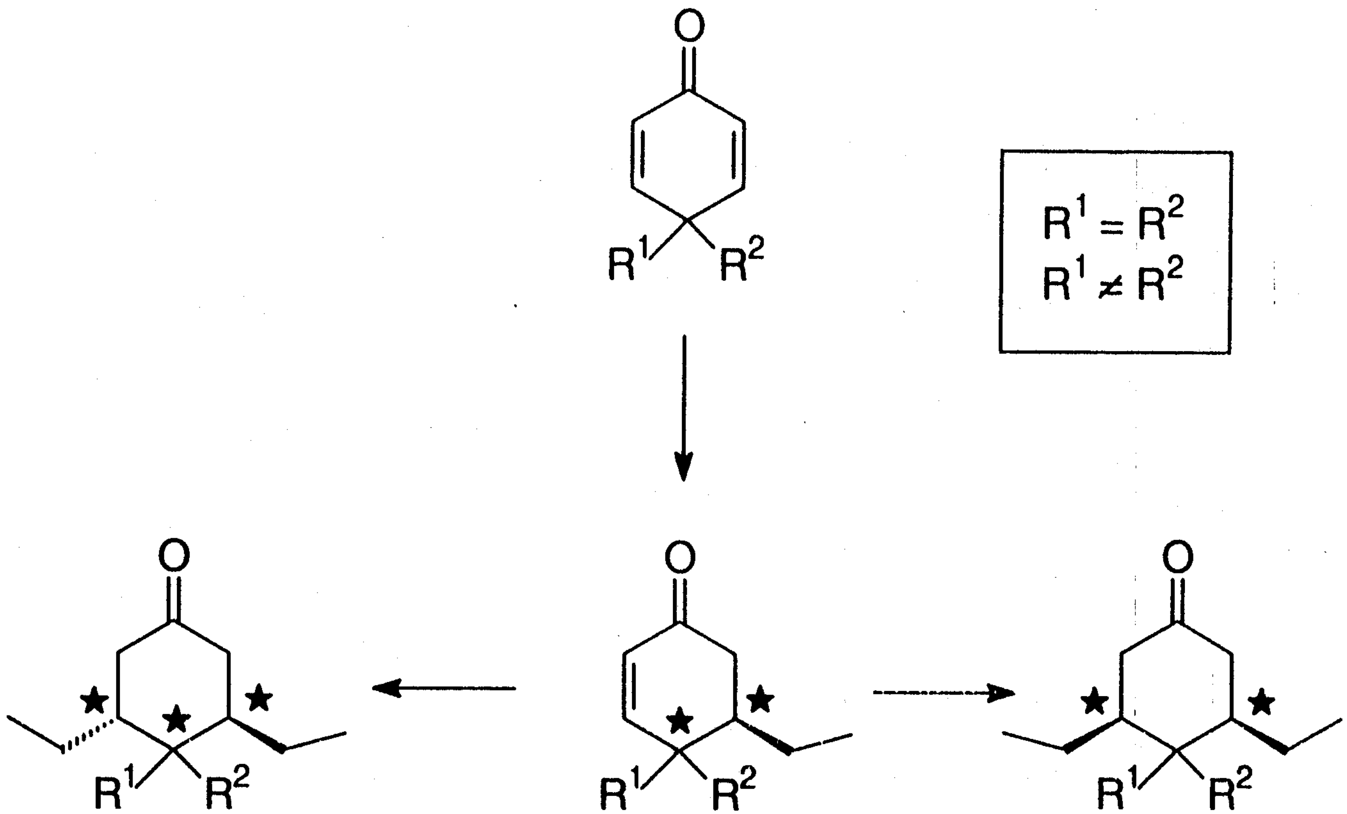
Entry	R_2	R_2	R	Yield (%)	Ee (%)
1	Me	Me	Et	65	97
2	Me	Me	Me	76	99
3	Et	Et	Et	59	92
4	$-CH_2CH_2-$		Et	68	92
5	$-CH_2CH_2CH_2-$		Et	62	89
6	$-CH_2C(Me)_2CH_2-$		Et	75	85

Conjugate addition to dienones with $R_1 \neq OR_2$

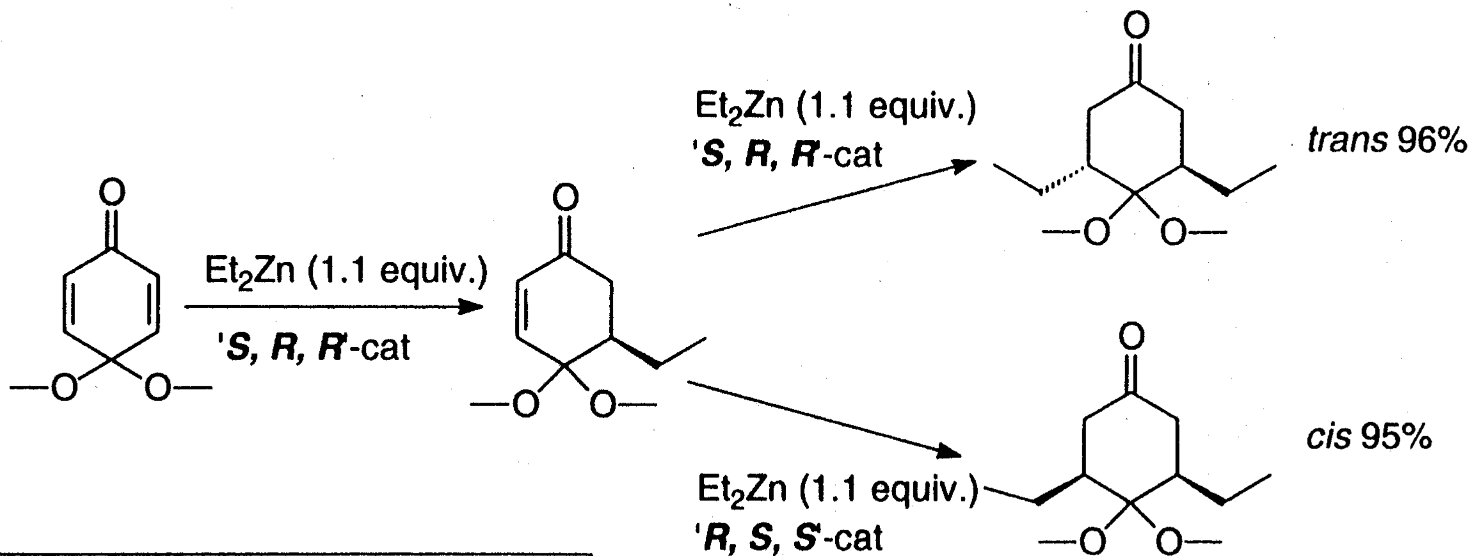


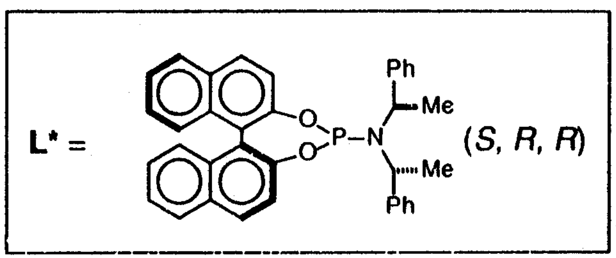
Entry	R_1	OR_2	Yield (%)	Dr	Ee major (%)	Ee minor(%)
1	Me	OMe	60	90/10	97 *(cis)*	85
2	CH_2Ph	OMe	53	97/3	93 *(cis)*	nd
3	$-CH_2CH_2CH_2O-$		66	99/1	65 *(cis)*	nd
4	OCH_2Ph	OMe	58	1/1	98	98

Catalytic Route to 3,4,5-Trisubstituted Cyclohexanones



Sequential Et_2Zn Addition
R^1=R^2





Conditions: 1mmol substrate, 2 mol% $Cu(OTf)_2$, 4.5 mol% L*, 5 ml toluene, 1.1 equiv. Et_2Zn, -25 ºC, 16 h.