Control and Amplification of Chirality

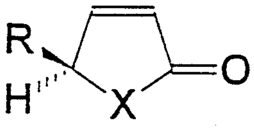
Heterocyclic

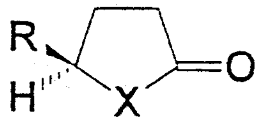
lipase-Pd-catalysis

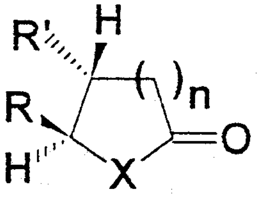
Carbocyclic

catalytic 1,4-addition

Chemoenzymatic route to chiral heterocycles

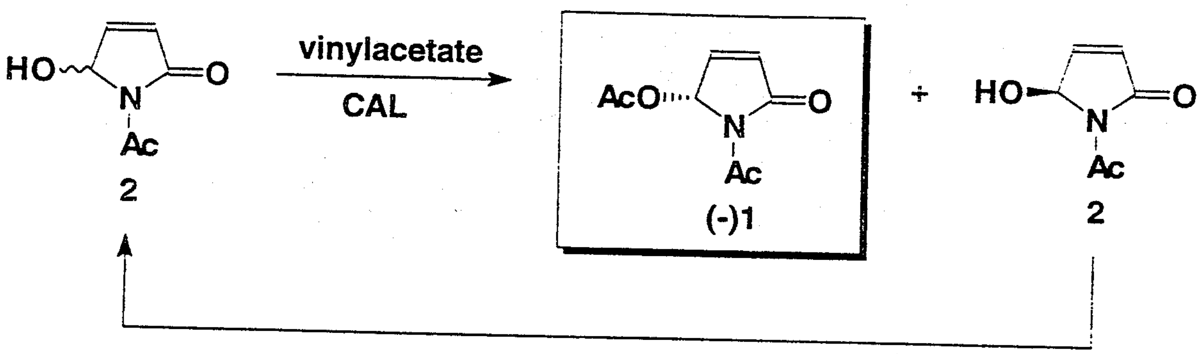






X = O, NR'' n = 0, 1

Enzymatic esterification of hydroxypyrrolinones

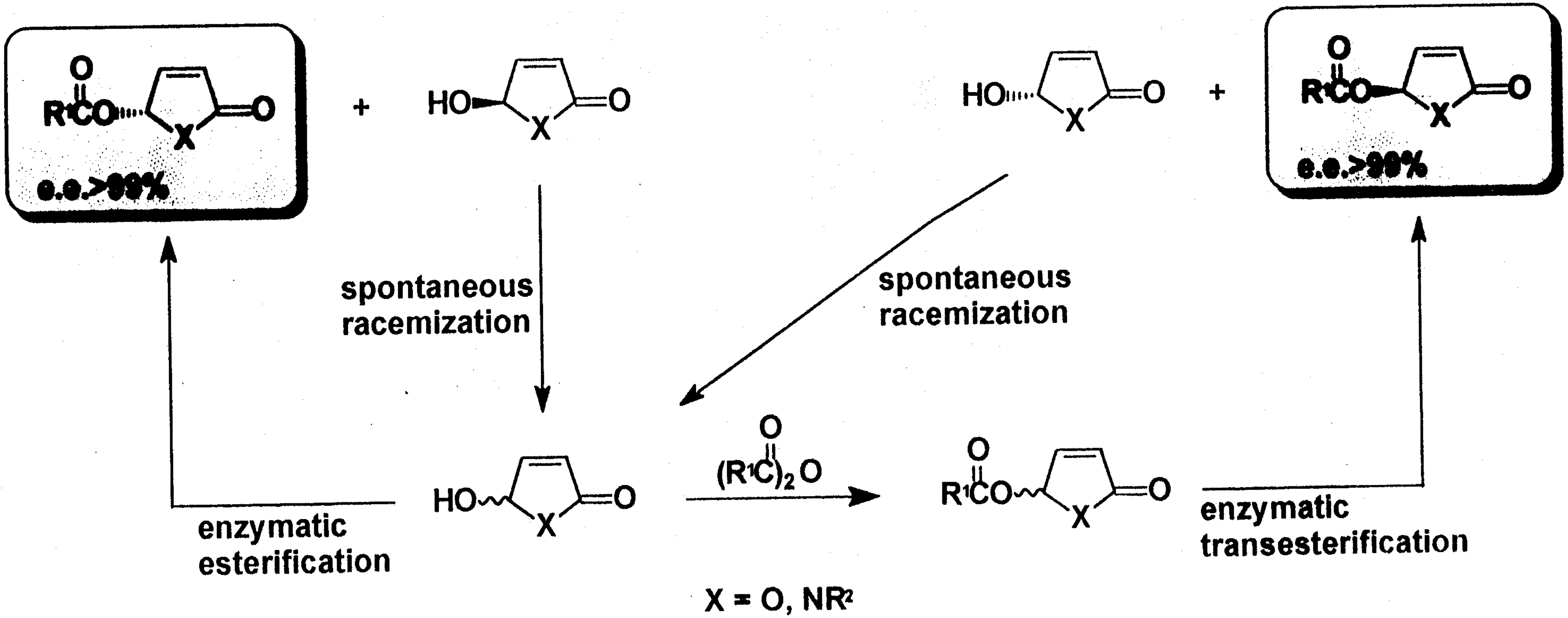


Influence of the temperature

solvent	temperature (°C)	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

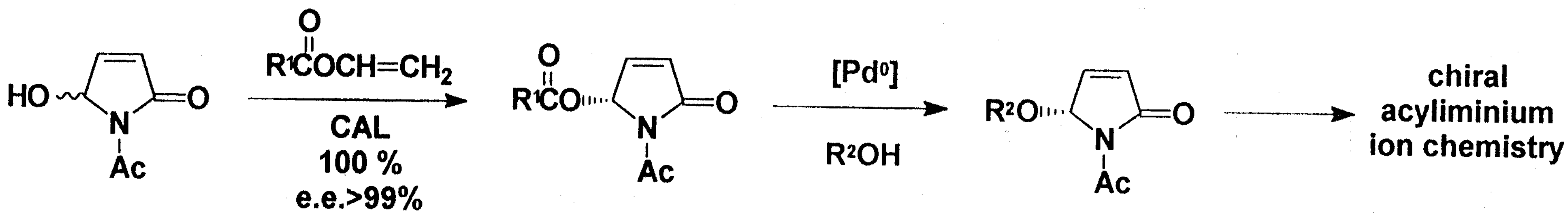
YMATIC SYNTHESIS SCHEME

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



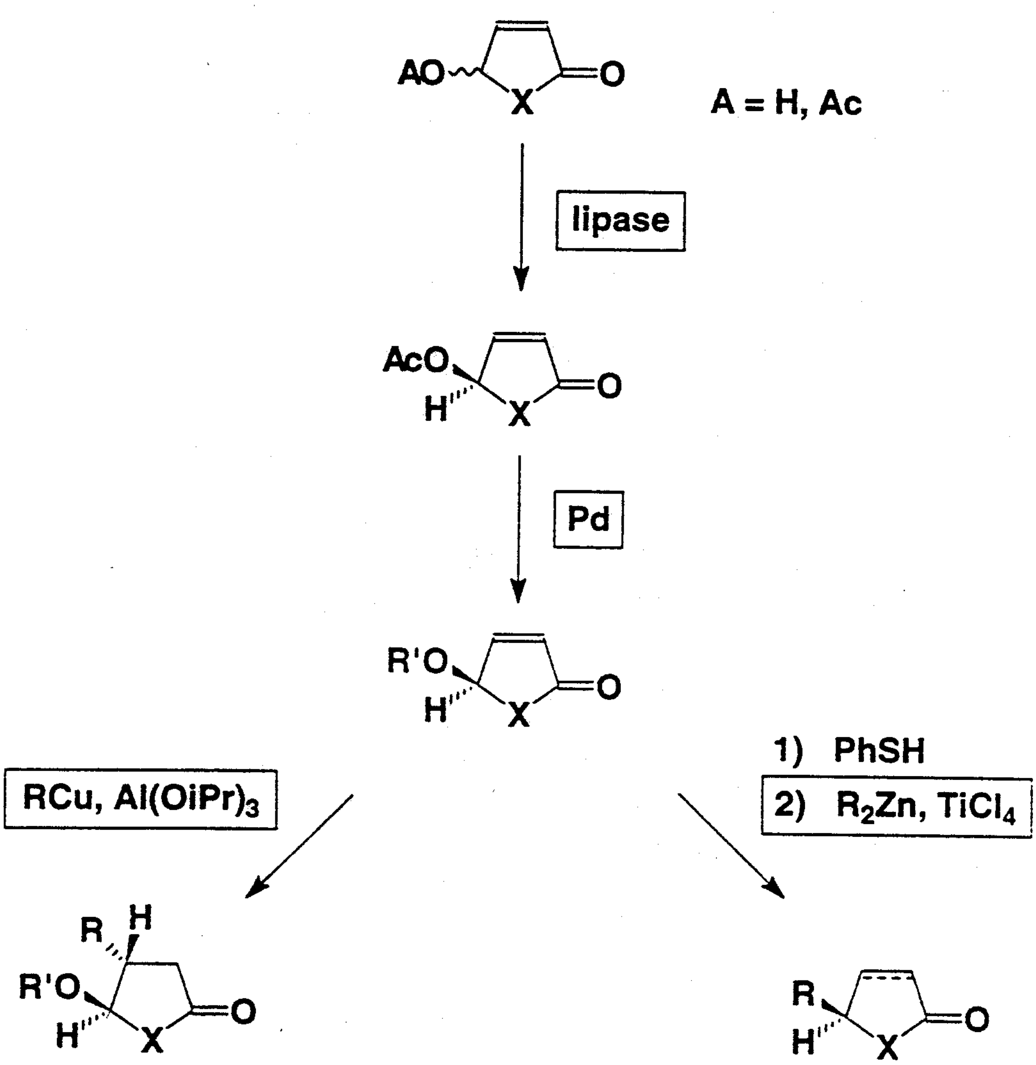
Deen van der, H.; Cuiper, A.D.; Hof, R.P.; Oeveren van, A.; Feringa, B.L.; Kellogg, R.M. *J. Am. Chem. Soc.*, 1996, 118, 3801.

ATALYZED ALLYLIC SUBSTITUTION



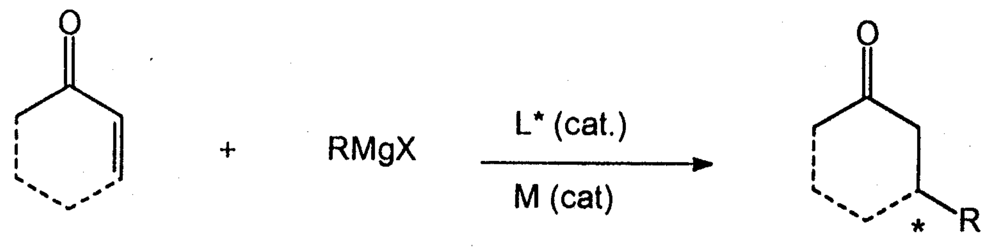
1 (-) 2 (-) 3

Multimetallic Approach to Heterocycles



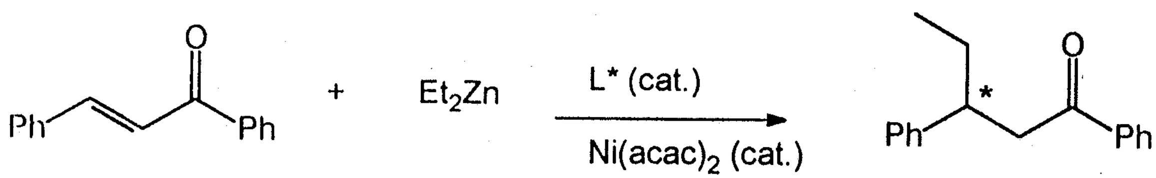
Catalytic enantioselective conjugate addition of organometallic reagents

RuG



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

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



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

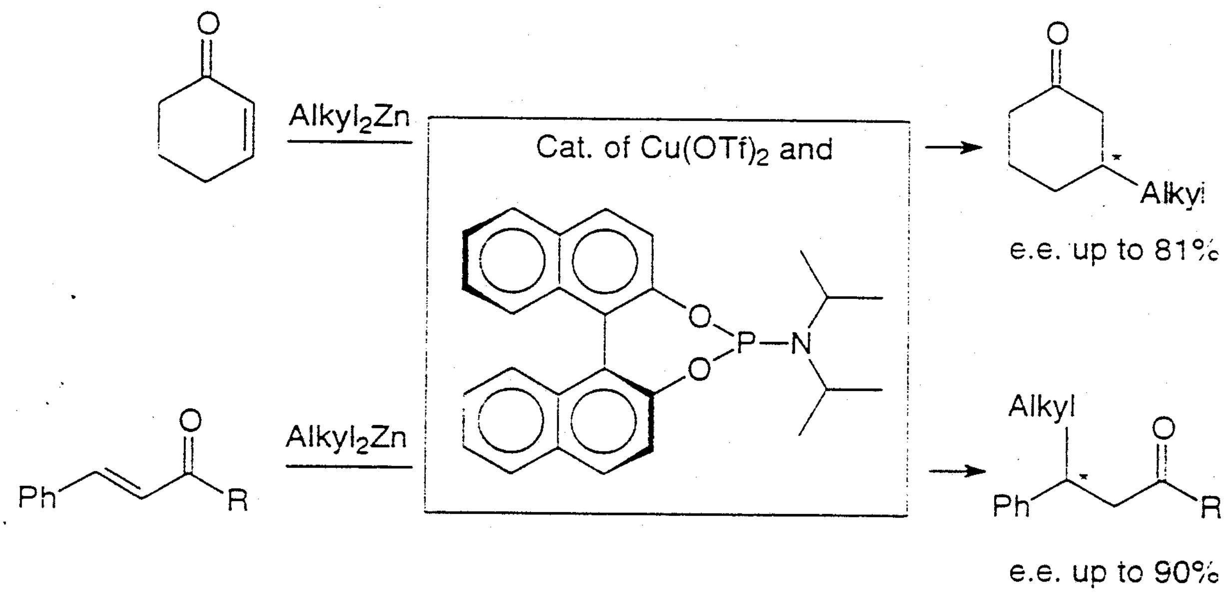
c.f.: Soai, Bolm, Feringa

Reviews:

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

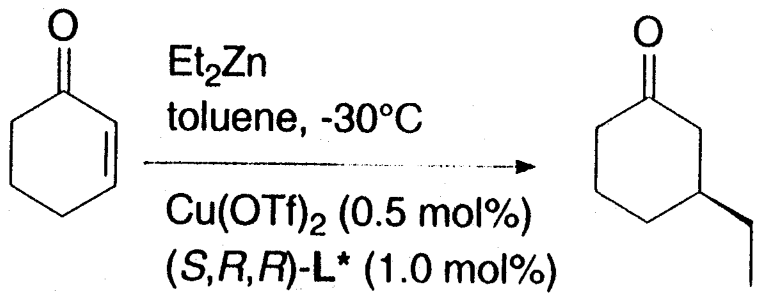
B.L. Feringa, A.H.M. De Vries, in *Advances in Catalytic Processes, Vol 1*, JAI Press, Connecticut, **1995**, p. 151.

COPPER -PHOSPHORAMIDITE CATALYST

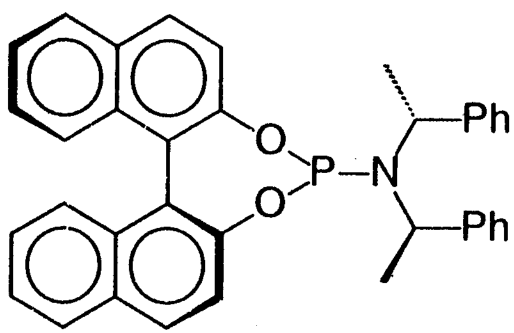


- new class of monodentate ligand
- excellent chemoselectivity
- relatively high e.e. for cyclic and acyclic enones
- the possibility to start with alkenes

Catalytic 1,4-Addition to cyclohexenone

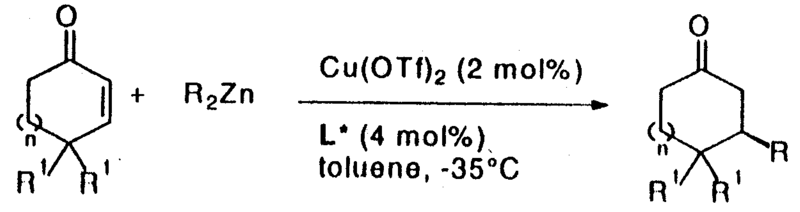


95% yield
e.e. > 98%

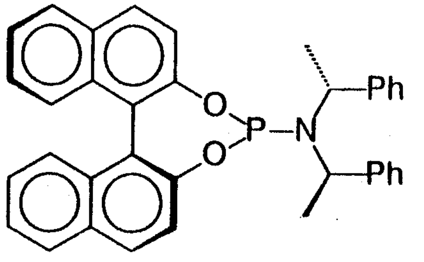


(*S*,*R*,*R*)-**L***

Conjugate Addition to Cyclic Enones

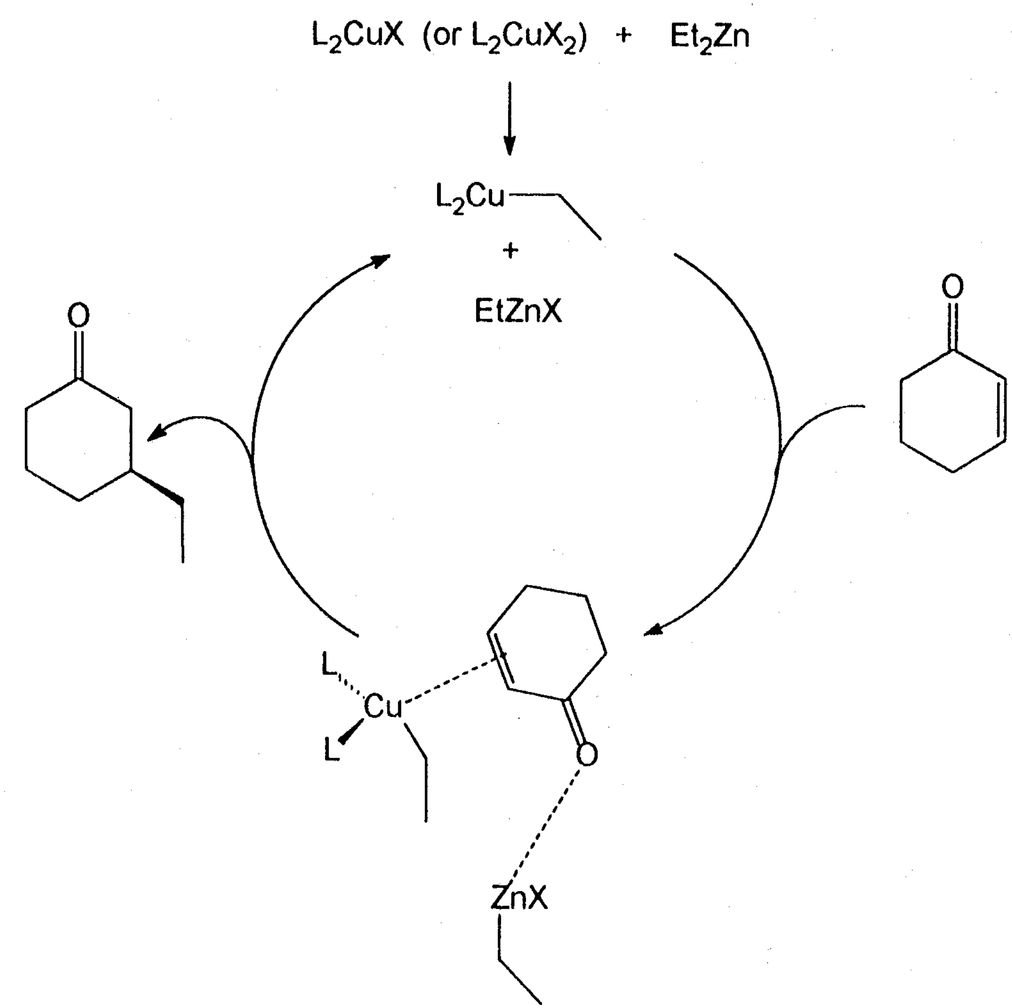


R	R^1	n	yield (%)	e.e. (%)
C_2H_5	H	1	94	>98
C_2H_5	H	0	75	10
C_2H_5	H	2	95	>98
C_2H_5	H	3	95	97
C_2H_5	CH_3	1	74	>98
C_2H_5	C_6H_5	1	93	>98
CH_3	H	1	72	>98
CH_3	CH_3	1	68	>98
C_7H_{15}	H	1	95	95
i-C_3H_7	H	1	95	94
$(CH_2)C_6H_5$	H	1	53	95
$(CH_2)_5OAc$	H	1	77	95
$(CH_2)_3CH(OC_2H_5)_2$	H	1	91	97

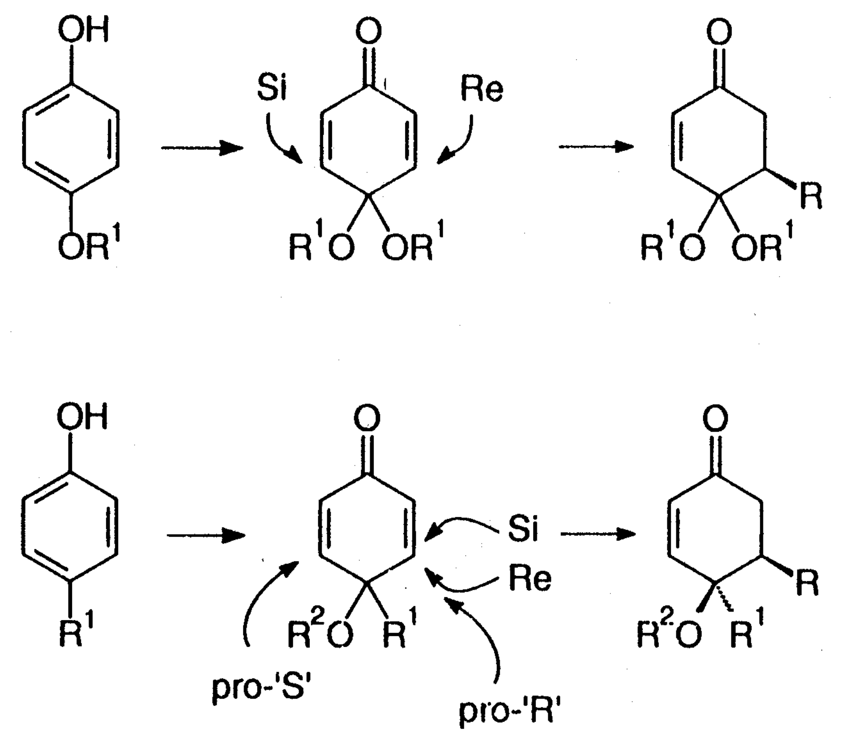


Proposed catalytic cycle

RuG



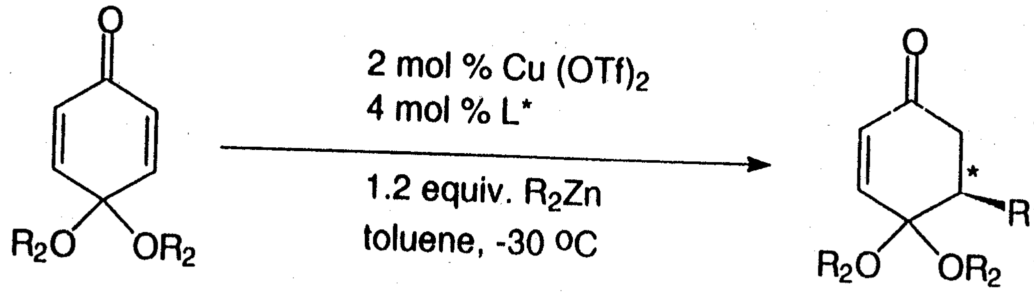
Cyclohexadienones



(a)

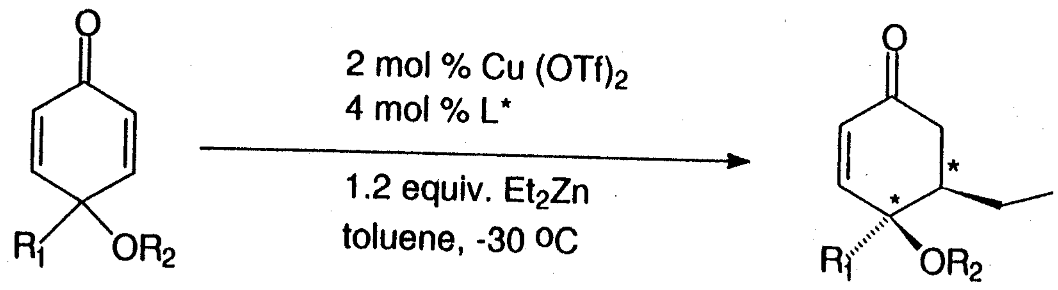
(b)

Conjugate addition to dienones with $R_1=R_2$



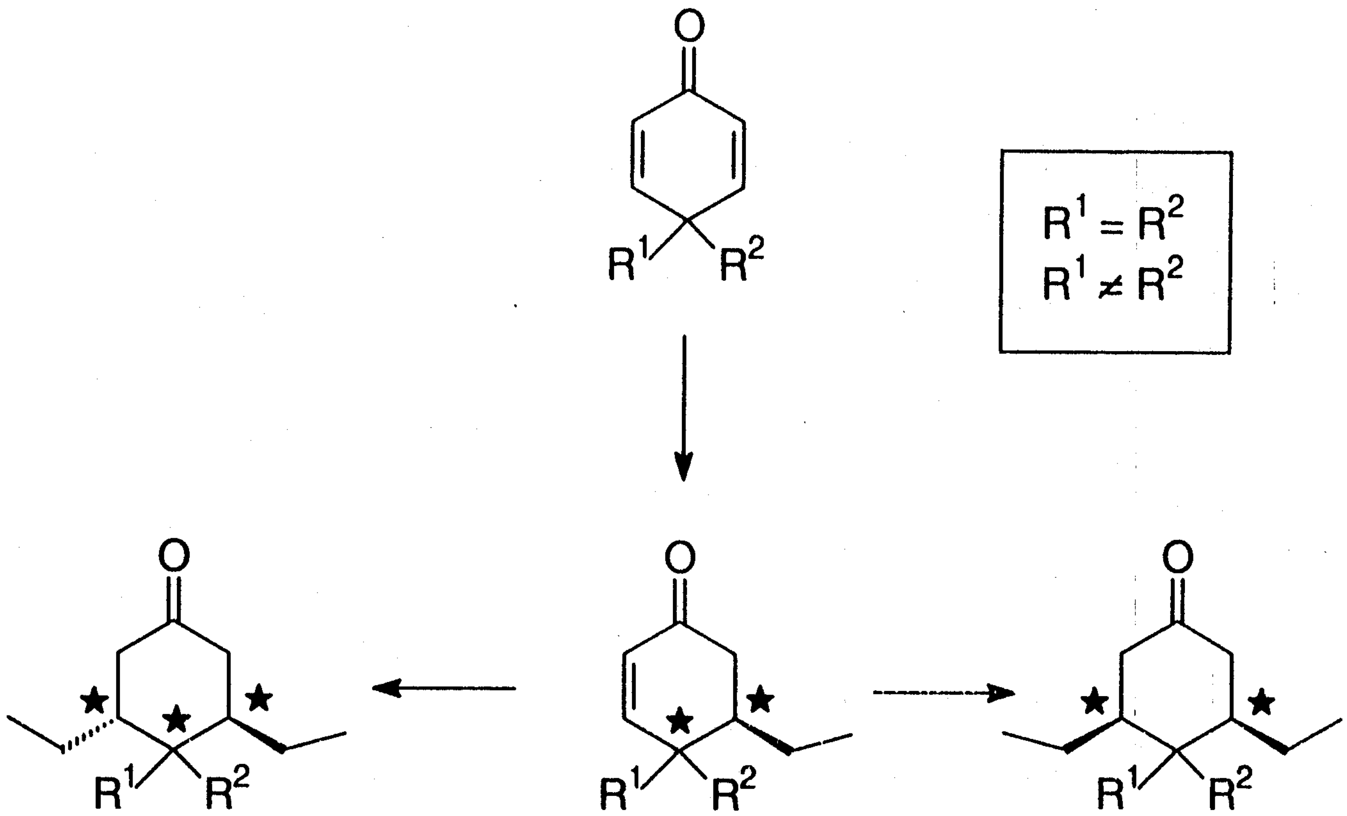
Entry	R_2	R_2	R	Yield (%)	Ee (%)
1	Me	Me	Et	65	97
2	Me	Me	Me	76	99
3	Et	Et	Et	59	92
4	$-CH_2CH_2-$		Et	68	92
5	$-CH_2CH_2CH_2-$		Et	62	89
6	$-CH_2C(Me)_2CH_2-$		Et	75	85

Conjugate addition to dienones with $R_1 \neq OR_2$

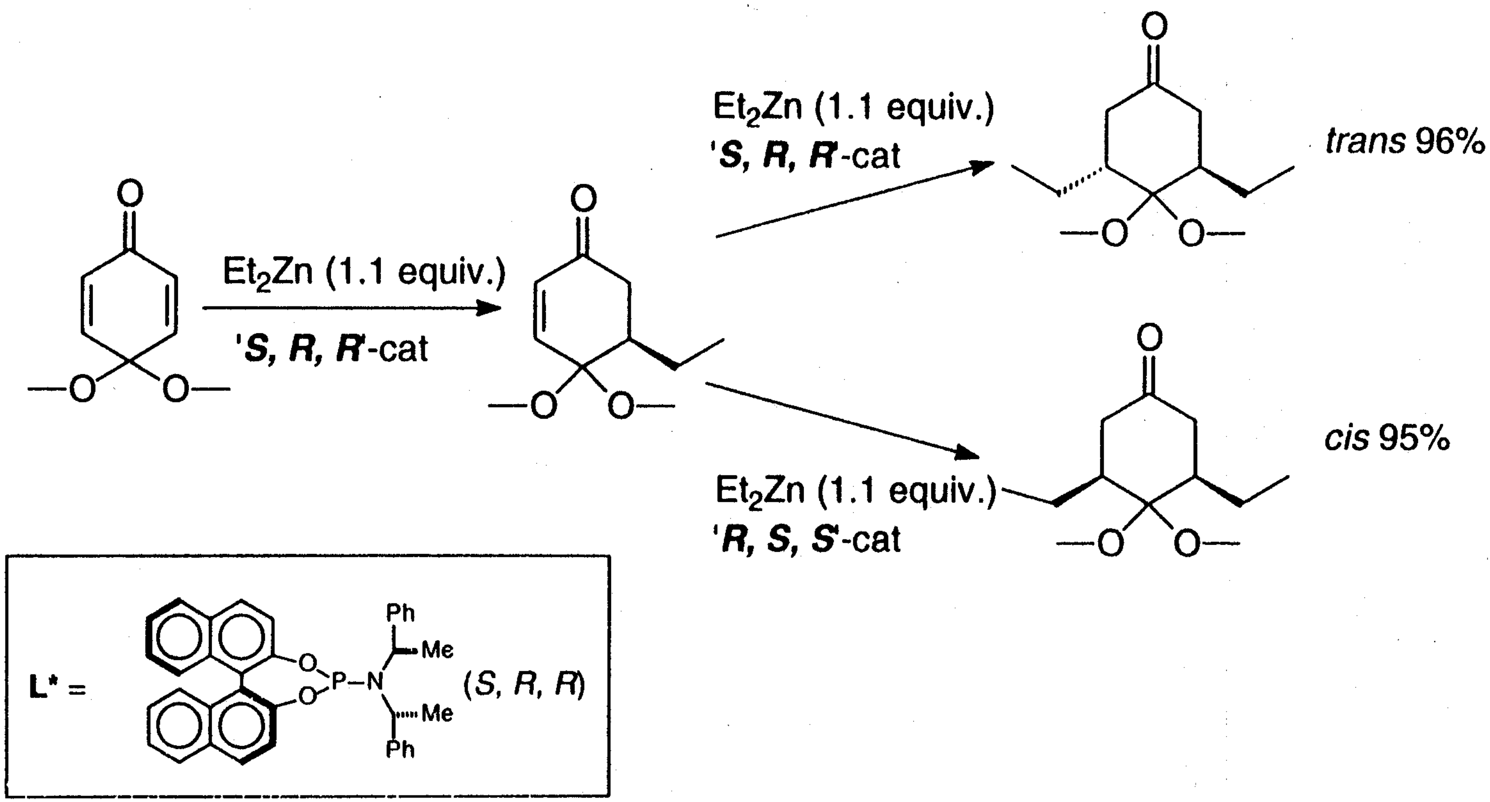


Entry	R_1	OR_2	Yield (%)	Dr	Ee major (%)	Ee minor(%)
1	Me	OMe	60	90/10	97 (*cis*)	85
2	CH_2Ph	OMe	53	97/3	93 (*cis*)	nd
3	$-CH_2CH_2CH_2O-$		66	99/1	65 (*cis*)	nd
4	OCH_2Ph	OMe	58	1/1	98	98

Catalytic Route to 3,4,5-Trisubstituted Cyclohexanones

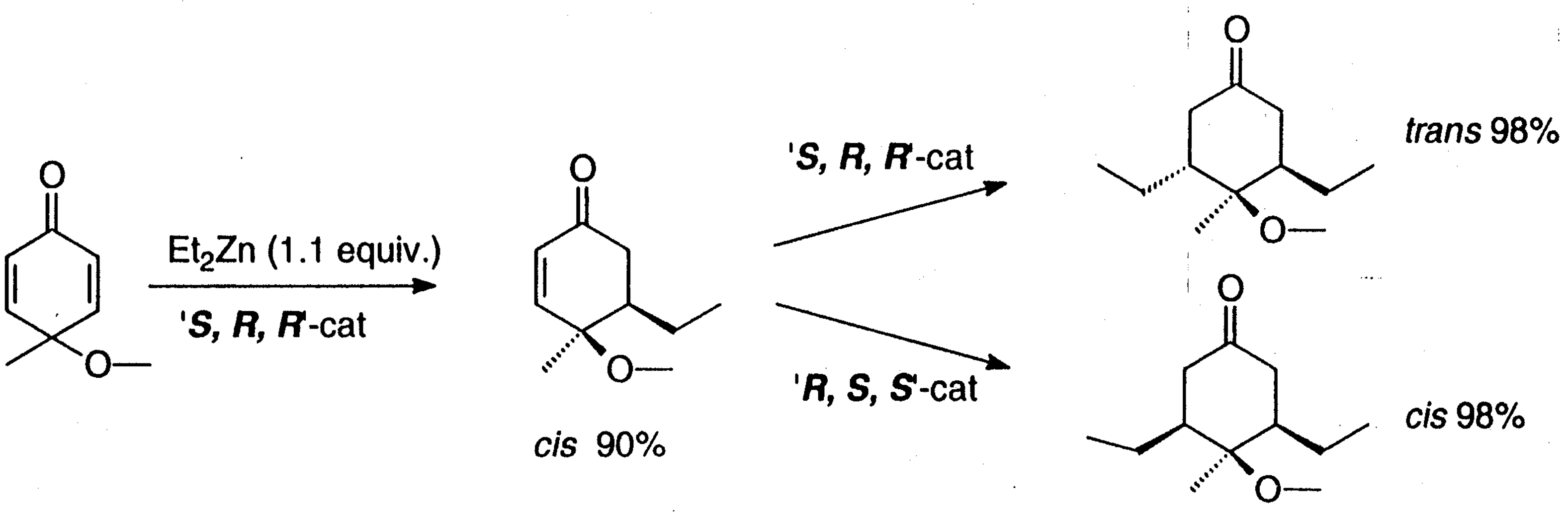


Sequential Et_2Zn Addition
$R^1=R^2$

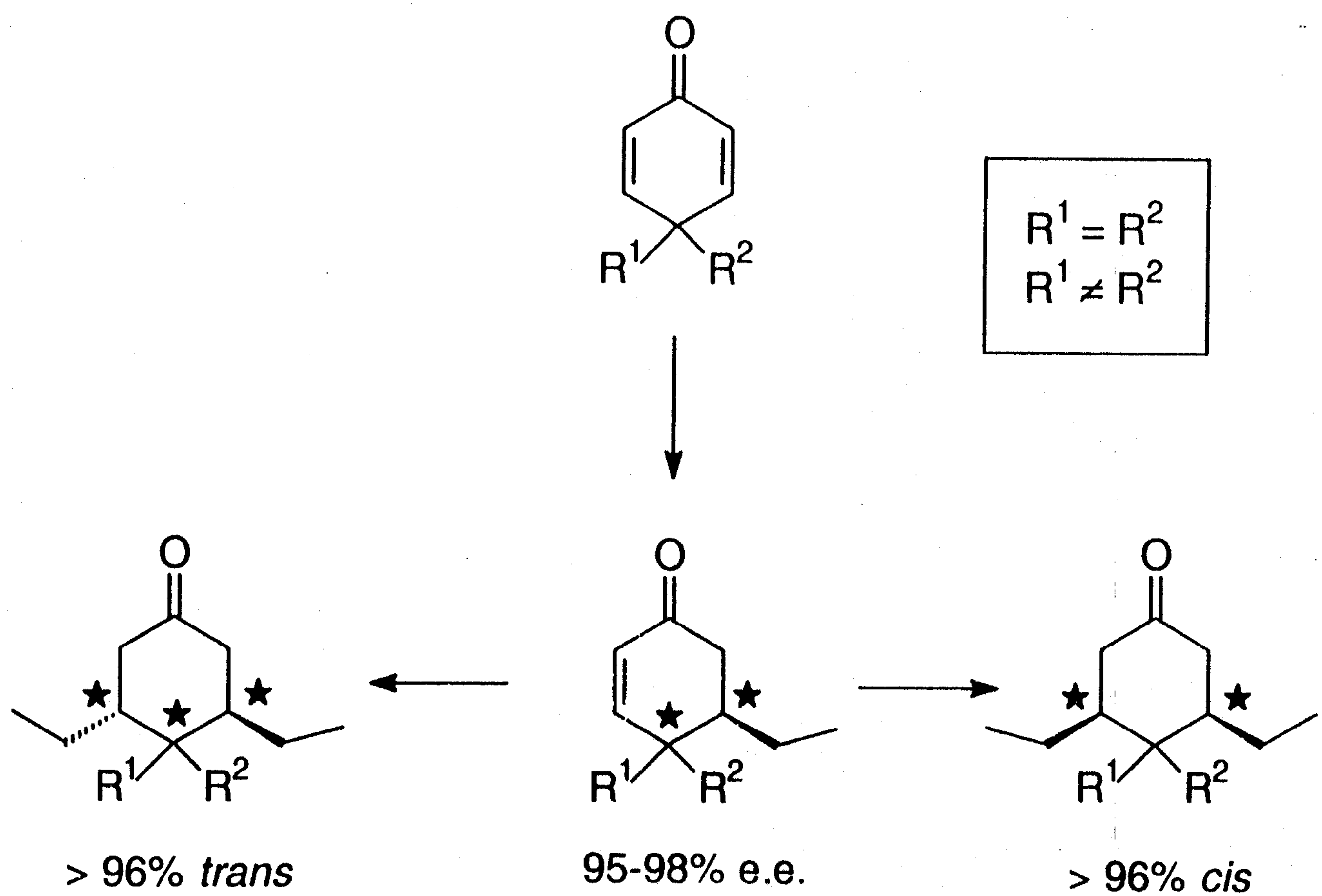


Conditions: 1mmol substrate, 2 mol% $Cu(OTf)_2$, 4.5 mol% L*, 5 ml toluene, 1.1 equiv. Et_2Zn, -25 ºC, 16 h.

Sequential Et_2Zn Addition
($R^1 \neq R^2$)

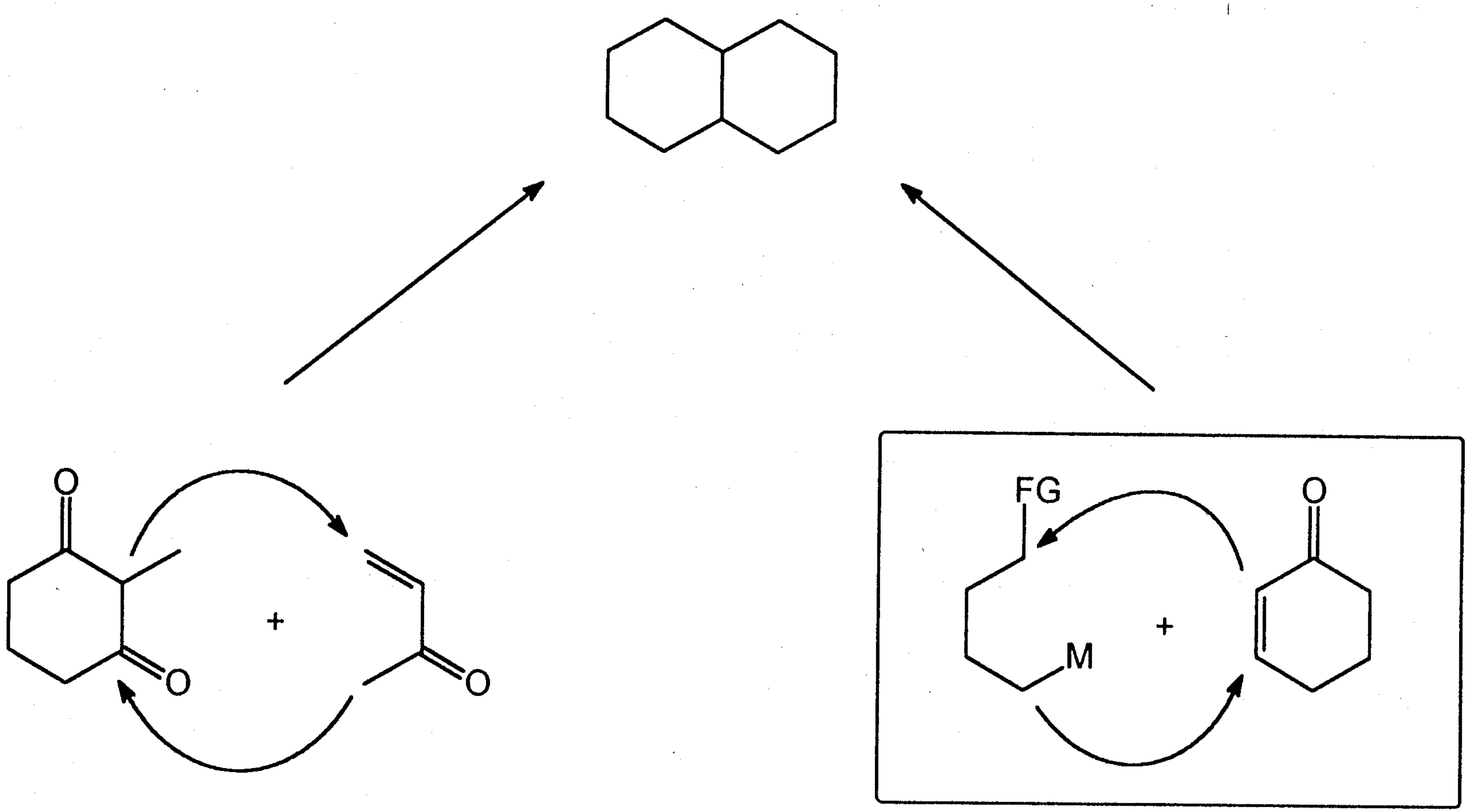


Catalytic Route to 3,4,5-Trisubstituted Cyclohexanones



Concept: alternative for enantioselective Robinson ring annulation?

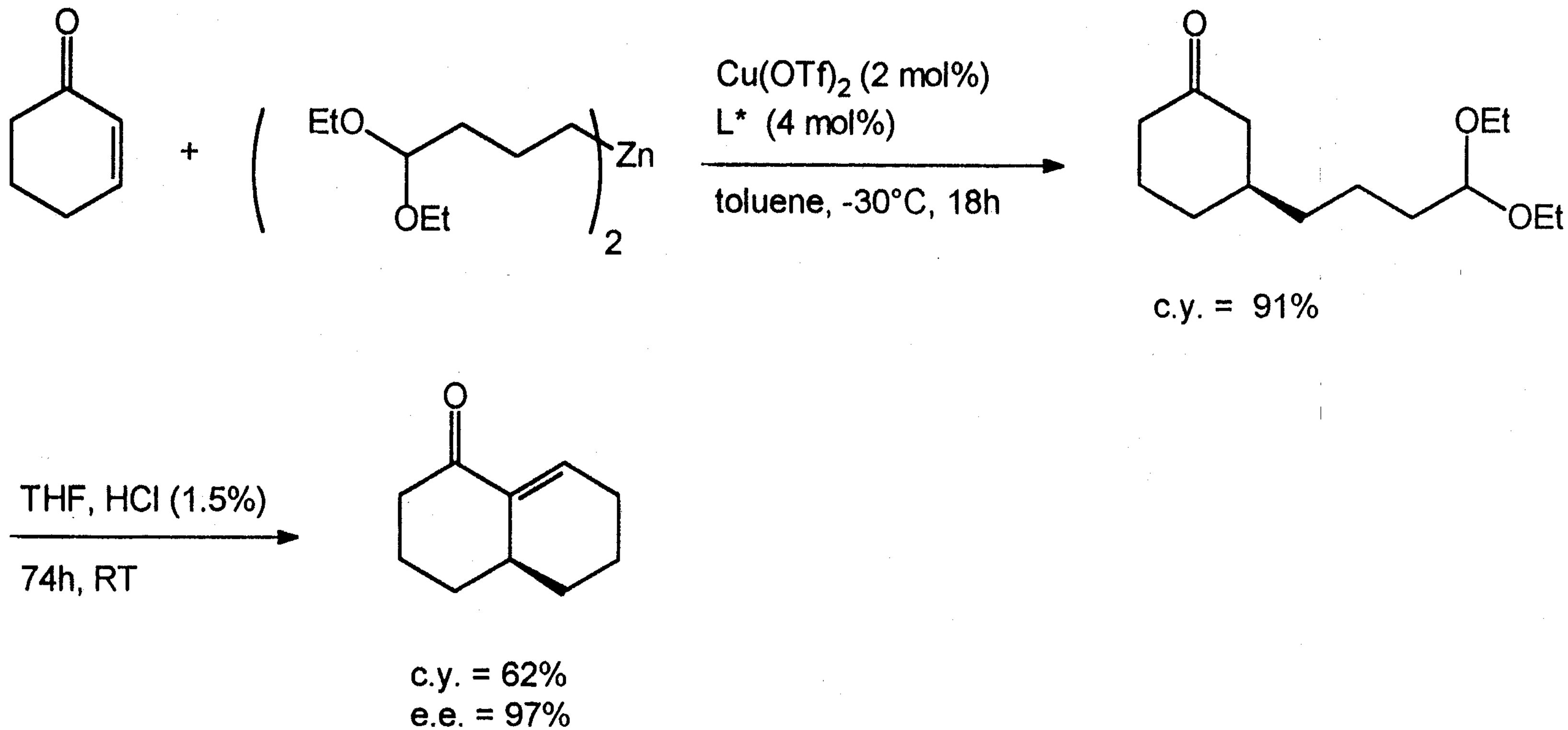
RuG



Robinson ring annulation

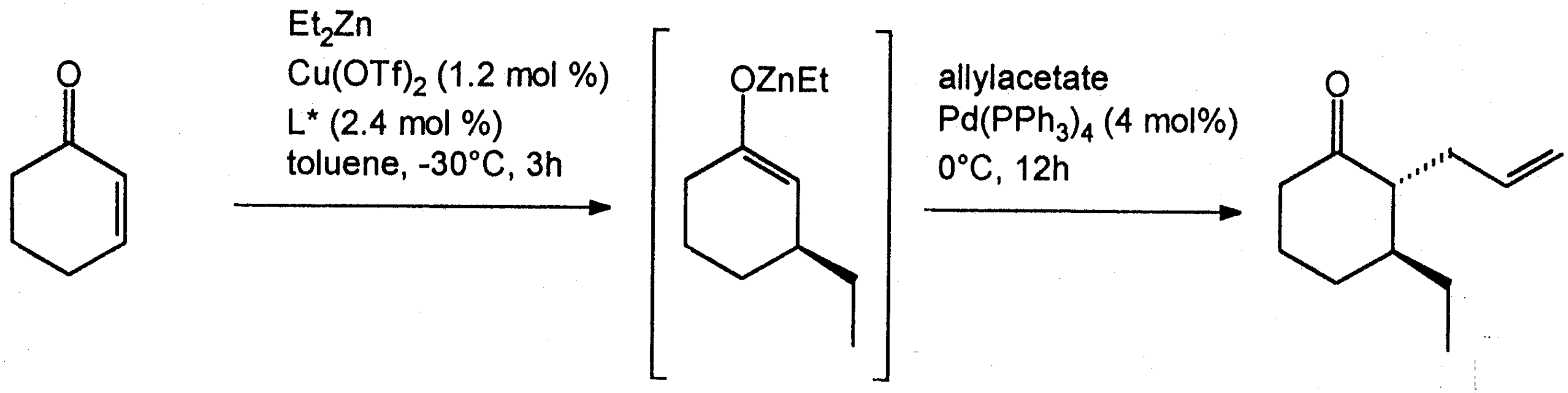
Novel ring annulation methodology (I)

RuG



Enantioselective catalytic tandem 1,4-addition-allylic substitution reaction

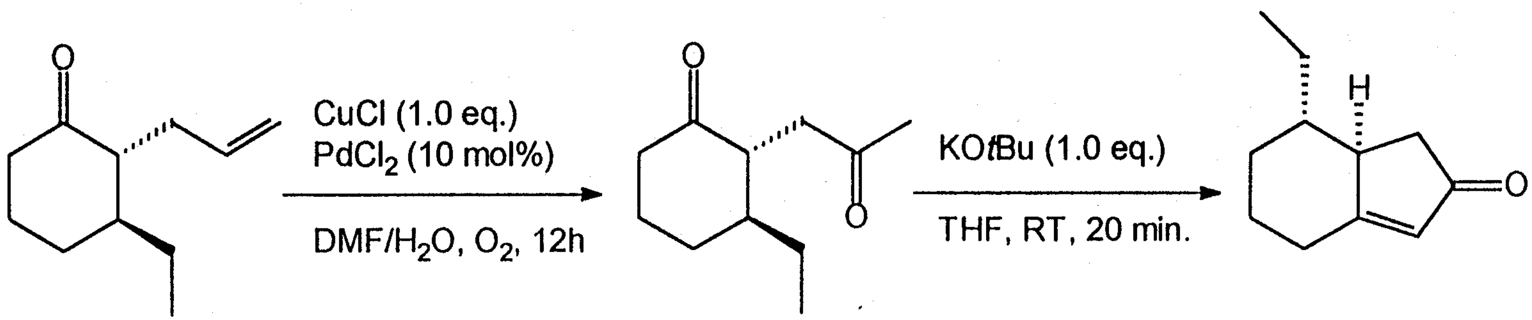
RuG



c.y. = 88%
e.e. = 96%
trans/cis = 9/1

Novel ring annulation methodology to form 5 membered ring systems (I)

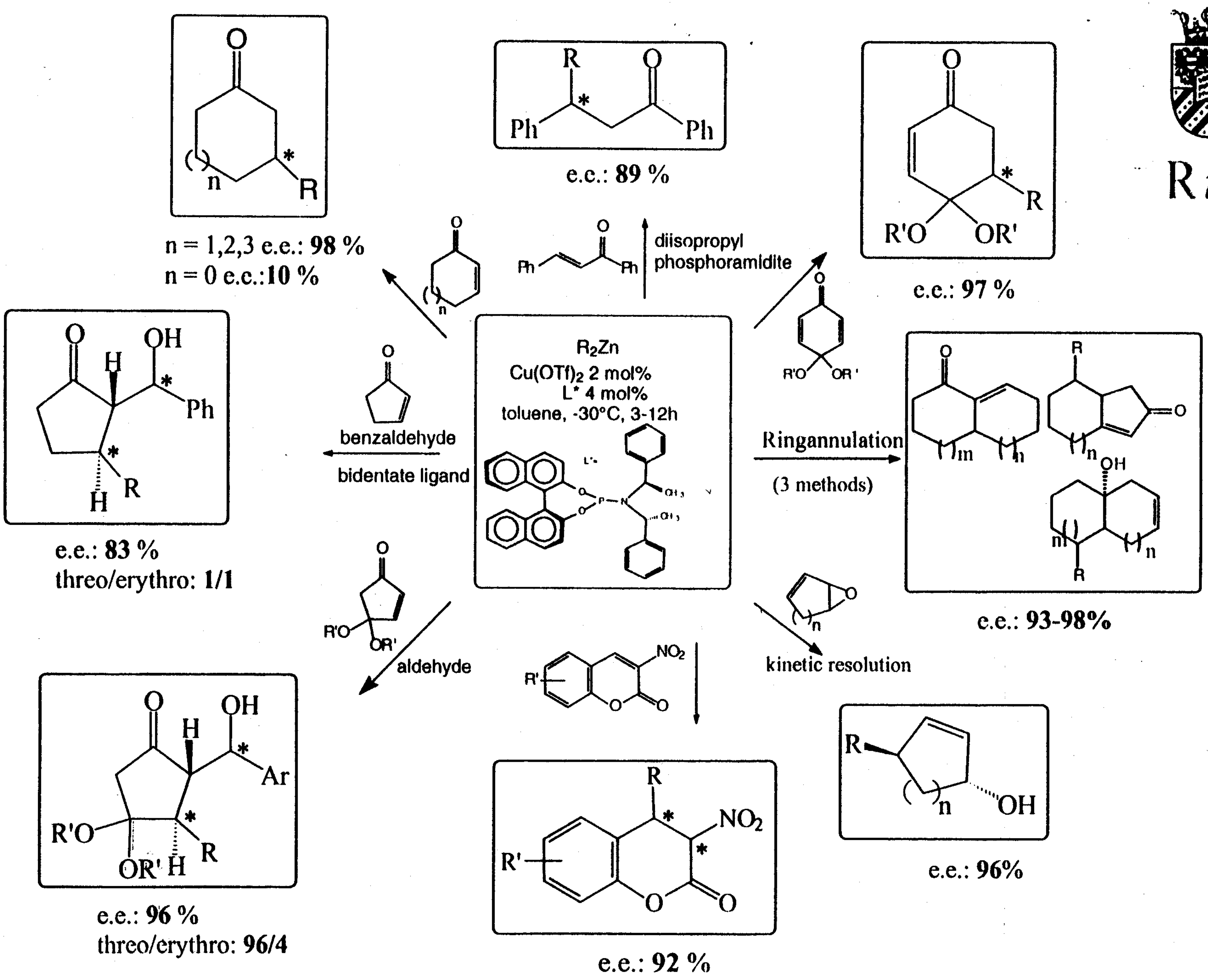
RuG



e.e. = 96%
trans/cis = 9/1

c.y. = 65%
e.e. = 96%
trans/cis = 35/1

c.y. = 56% (not optimised)
e.e. = 96%
trans/cis = 13/1



R2Zn
Cu(OTf)2 2 mol%
L* 4 mol%
toluene, -30°C, 3-12h
diisopropyl
phosphoramidite
e.e.: 89 %
n = 1,2,3 e.e.: 98 %
n = 0 e.e.:10 %
e.e.: 97 %
benzaldehyde
bidentate ligand
e.e.: 83 %
threo/erythro: 1/1
Ringannulation
(3 methods)
e.e.: 93-98%
aldehyde
e.e.: 96 %
threo/erythro: 96/4
e.e.: 92 %
kinetic resolution
e.e.: 96%
RuG