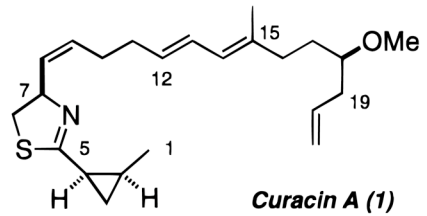
Iodomethylzinc Phosphates: Powerful Reagents for the Cyclopropanation of Alkenes

Andre B. Charette, Marie-Christine Lacasse and Cyril Poulard

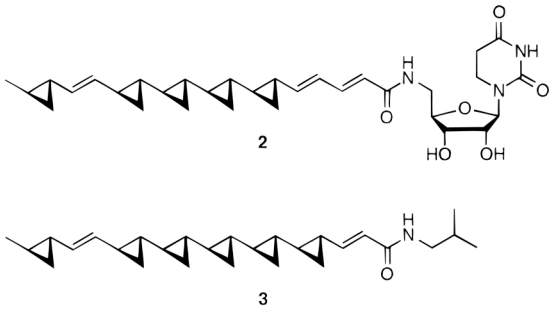
J. Am. Chem. Soc. ASAP

Natural Product Containing Cyclopropanes

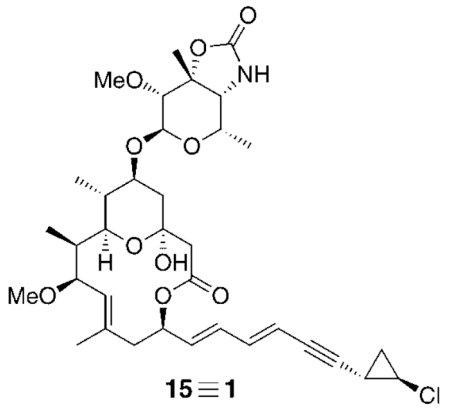


Curacin A (1)

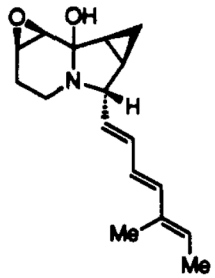
Figure 1. Curacin A, an antimitotic metabolite of the blue-green alga *L. majuscula*.



2-Anti-Fungal Agent FR-900848
3-Cholesteryl Ester Transfer Protein Inhibitor U-1006305



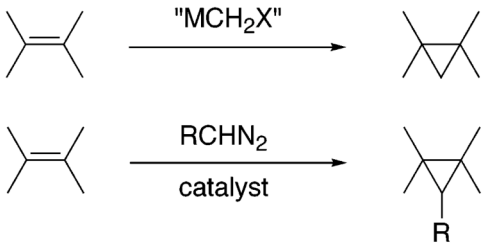
Anticancer Compound Callipeltoside

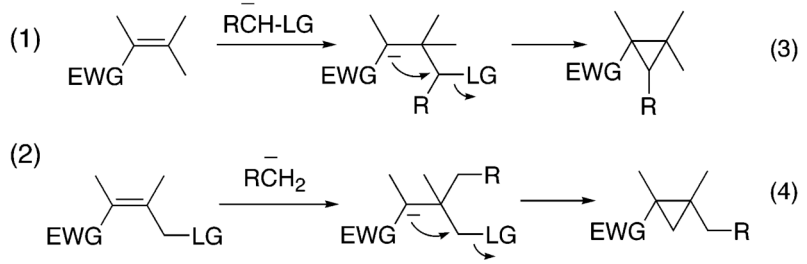


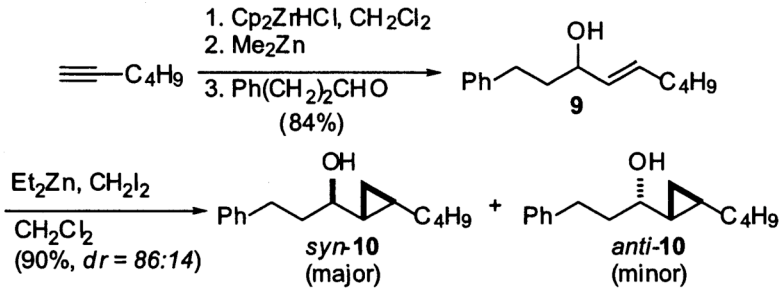
Antiboitic Compound Indolizomcyin

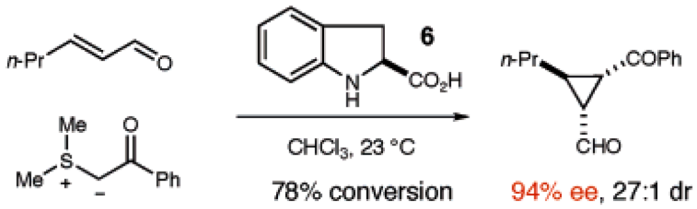
Wipf, P,; Xu, W., *J. Org. Chem.***1996**, 6556
Barrett, A.G.M., Kasdorf, K., *J. Am. Chem. Soc.* **1996**, 11030
Barrett, A.G.M., Hamprecht, D., *J. Am. Chem. Soc.* **1996**, 7863
Danishefsky, S.J.;Kim, G.; Chu-Moyer, M. Y.; Schulte, G. K., *J. Am. Chem. Soc.* **1993,** 30
Trost, B. M.; Dirat, O.; Gunzner, J. L., *Angew. Chem. Int. Ed.* **2002,** 841

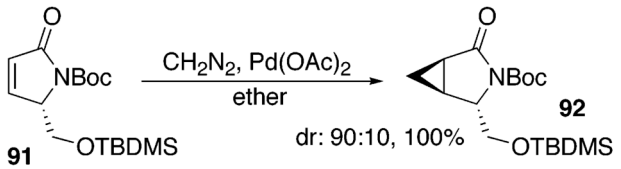
General Types of Cyclopropanation

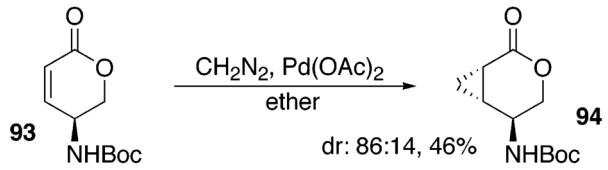


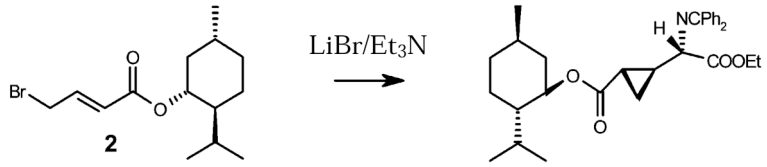








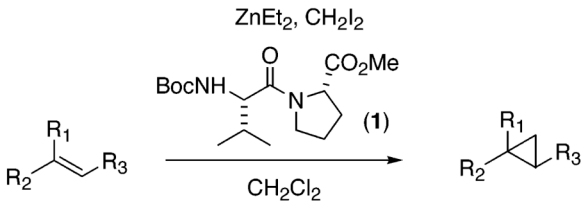


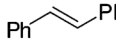
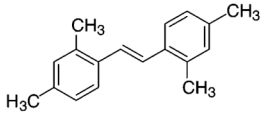
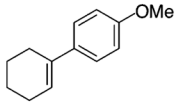
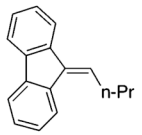
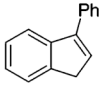
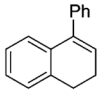


Wipf, P.; Kendall, C.; Stephenson, C. *J. Am. Chem. Soc.* **2003,** 761
Shimamoto, K.; Ishida, M.; Shinozaki, H.; Ohfune, Y. *J. Org. Chem.* **1991,** 4167
MacMillan, D.W.C.; Kunz, R. K., *J. Am. Chem. Soc.* **2005,** 3240
Chavan, S. P. *et. al., J. Am. Chem. Soc.* **2003,** 6817

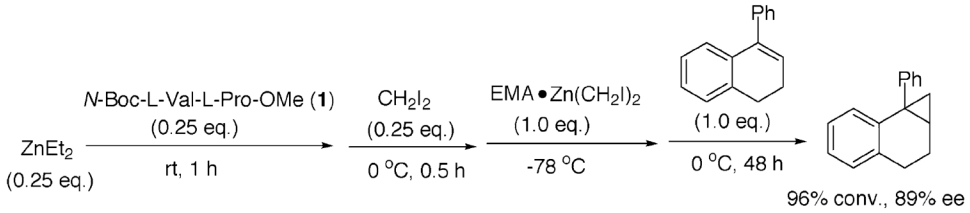
Shi Cyclopropanation

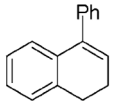
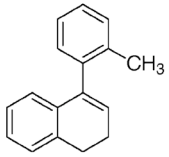
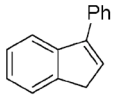
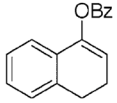
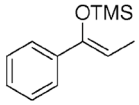
Stoichiometric Ligand



entry	substrate	yield (%)[d]	ee (%)
1		71	72[f]
2[b]		83	75[g]
3[c]		43	89[g]
4		71	75[g]
5[c]		78	90[f]
6		84	78[f] (98[h])
7		83	90[f] (99[h])

Catalytic Ligand

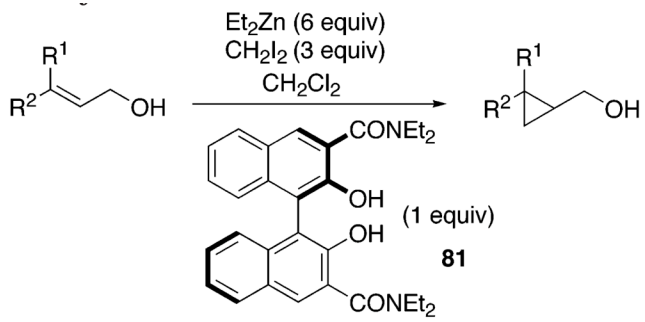


Entry	Substrate	Yield[b] (%)	ee[c] (%)
1		87	89
2		60	89
3		85	77
4		52	78
5		96	87

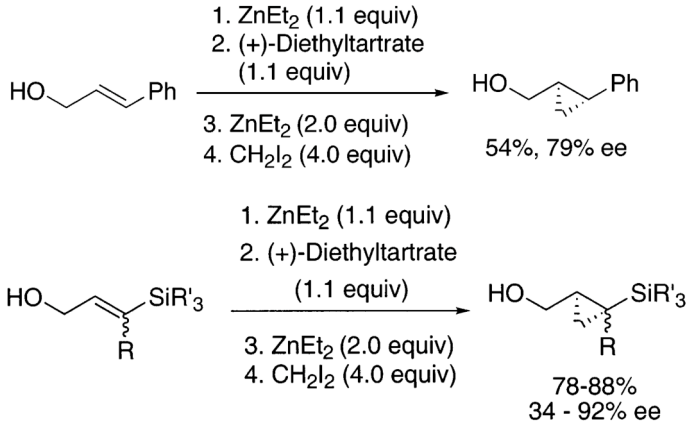
[a] The cyclopropanation was carried out with olefin (1.0 equiv), $ZnEt_2$ (1.25 equiv), CH_2I_2 (2.25 equiv), ethyl methoxyacetate (1.0 equiv), dipeptide **1** (0.25 equiv), and ZnI_2 (0.25 equiv) in CH_2Cl_2 at 0 °C for 48 h except for entry 5, where the reaction was carried out at −40 °C for 72 h.

Shi, Y.; Long, J.; Yuan, Y., *J. Am. Chem. Soc.* **2003,** 13632
Shi, Y.; Long, J.; Du, H.; Li, K., *Tetrahedron Letters* **2005,** 2737

Stoichiometric Chiral Ligands

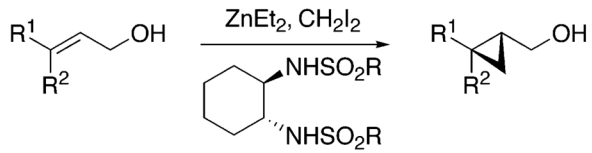


Entry	Substrate	Yield (%)	% ee
1	*p*-MeOC$_6$H$_4$	78	94
2	*p*-ClC$_6$H$_4$	50	90
3	Ph	65	89
4	TrO	64	88
5	TBDPSO	59	87
6	TrO	34	65



Katsuki, T.; Kitajima, H.; Aoki, Y.; Ito, K.; *Chem. Lett.* **1995,** 1113
Ukaji, Y.; Nishimura, M.; Fujisawa, T., *Chem. Lett.* **1992,** 2651
Ukaji, Y.; Sada, K.; Inomata, K., *Chem. Lett.* **1993**, 1227

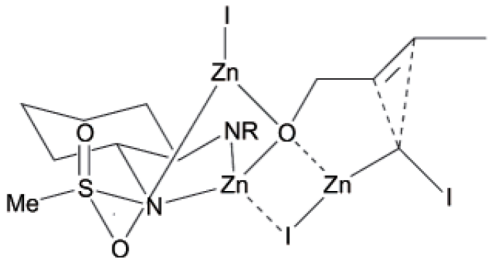
Catalytic Chiral Ligands



82 R = *p*-$NO_2C_6H_4$-
83 R = CH_3

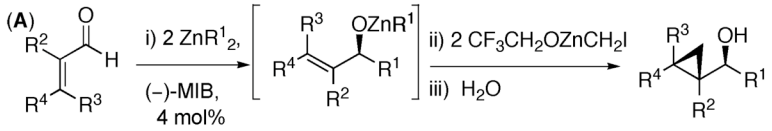
			ee (%); yield (%)	
entry	R^1	R^2	catalyst **82**	catalyst **83**
1	Ph	H	76; 82	89; 92[a]
2	H	Ph	75; 71	81; 81
3	$PhCH_2CH_2$	H	82; 100	89; 88
4	$BnOCH_2$	H	36; 70	
5	$TrOCH_2$	H	80; 86	
6	H	$BnOCH_2$	13; 36	
7	H	$TrOCH_2$	65; 77	
8	Bu_3Sn	H	86; 94	
9	Me_2PhSi	H	81; 83	
10	H	Bu_3Sn	66; 75	
11	H	Me_2PhSi	59; 67	
12	H	$PhCH_2CH_2$	72; 93	72; 93

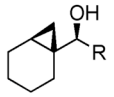
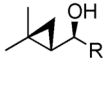
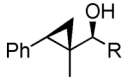
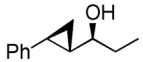
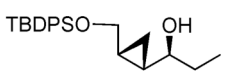
[a] In situ generation of ZnI_2.



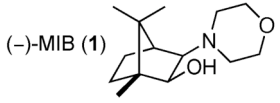
Kobayashi, S.; Imai, N.; Ohno, M.; Shibasaki, M., *Tetrahedron* **1995,** 12013
Lebel, H.; Marcoux, J. F.; Molinaro, C.; Charette, A. B., *Chem. Rev.* **2003,** 977

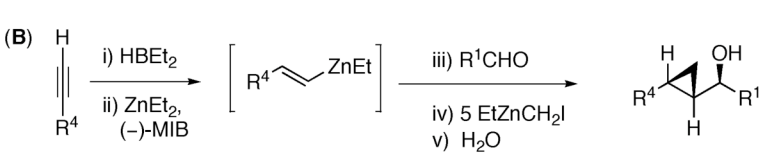
Tandem Cyclopropanation Reactions

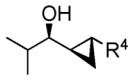
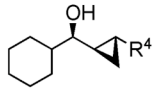


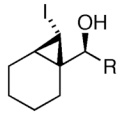
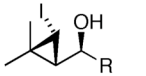
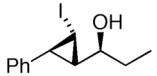
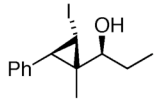
entry	ZnR_2	cyclopropyl alcohol	ee (%)	dr [a]	yield (%)
1	Et[b]		99	>20:1	90
2	-$(CH_2)_4$iPr[c]		97	>20:1	66
3	-$(CH_2)_5$OTBDPS[c]		98	>20:1	75
4	Me[c]		99	>20:1	76
5	Et		95	>20:1	78
6	-$(CH_2)_4$iPr[c]		96	>20:1	64
7	Me[c]		95	>20:1	85
8	Et		96	>20:1	90
9	Et		89	>20:1	87
10	Et		98	>20:1	80
11	Et		91	>20:1	91

[a] Determined by crude ^{1}H NMR analysis. [b] Stereochemistry assigned by X-ray analysis. See the Supporting Information. [c] With 5 equiv of $ZnEt_2$, 5 equiv of CF_3CH_2OH, and 5 equiv of CH_2I_2.



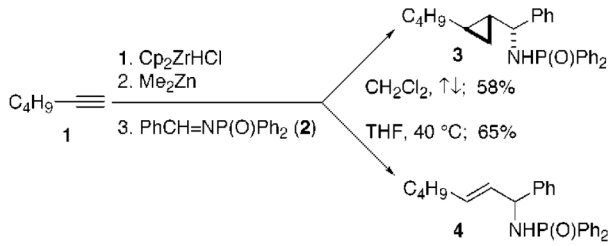


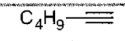
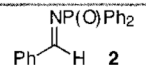
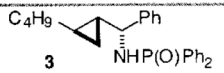
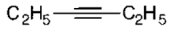
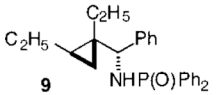
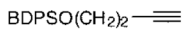
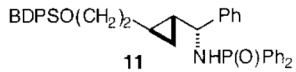
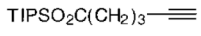
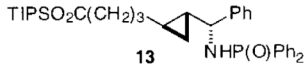
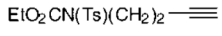
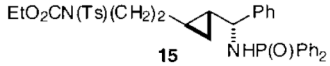
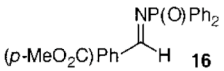
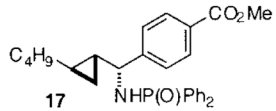
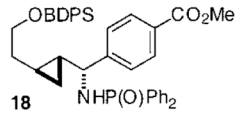
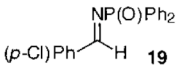
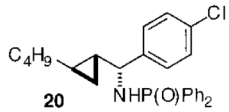
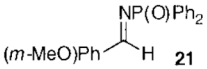
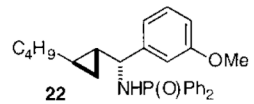
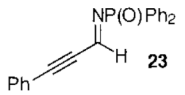
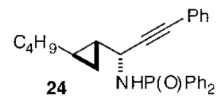
entry	cyclopropyl alcohol	R^4	ee(%)	dr[a]	yield (%)
1		Ph	99	>20:1	75
2		nBu	92	>20:1	71
3		tBu	87	>20:1	78
4		Ph	99	>20:1	78
5		nBu	93	>20:1	84
6		tBu	96	>20:1	74
7		$(CH_2)_4Cl$[b]	94	>20:1	80
8		CH_2CH_2OTr	93	>20:1	73

entry	$ZnR^1{}_2$	cyclopropyl alcohol	ee (%)	dr [a]	yield (%)
1	Et[b]		99	>20:1	68
2	-$(CH_2)_5$OTBDPS		98	>20:1	70
3	Me		99	>20:1	78
4	Et[b]		95	>20:1	62
5	-$(CH_2)_4$iPr		96	>20:1	60
6	Et		89	>20:1	70
7	Et		96	>20:1	56
8	Et		98	>20:1	74

Walsh, P. J.; Kim, H. Y.; Lurain, A. E.; Garcia-Garcia, P.; Carroll, P. J., *J. Am. Chem. Soc.* ASAP, 9-2-05

Tandem Cyclopropanation Reactions con'd



entry	alkyne	imine	amino cyclopropane	yield[a]
1	 **1**	 **2**	 **3**	74%
2	 **8**	**2**	 **9**	46%
3	 **10**	**2**	 **11**	68%
4	 **12**	**2**	 **13**	73%
5	 **14**	**2**	 **15**	45%
6	**1**	 **16**	 **17**	69%
7	**10**	**16**	 **18**	84%
8	**1**	 **19**	 **20**	65%
9	**1**	 **21**	 **22**	51%
10	**1**	 **23**	 **24**	44%

Wipf, P.; Kendall, C.; Stephenson, C. *J. Am. Chem. Soc.* **2001,** *5122*

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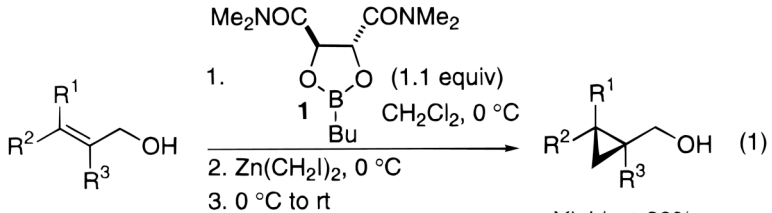
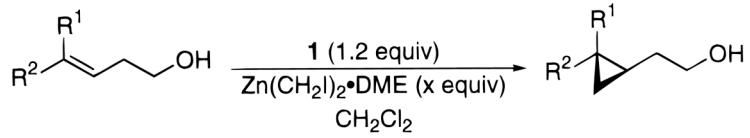


(1)

Yields: ≥80%
91-94% ee

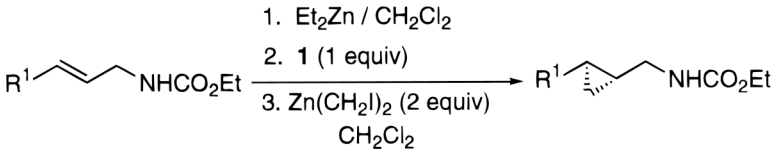
entry	R_1	R_2	R_3	proc[a]	yield,[b] % (**cpd**)	ee,[c] %
1	H	Ph	H	A	>98 (**5**)	93[d]
				B	95 (**5**)	94[d]
2	H	3-MeOPh	H	B	>98 (**6**)	93[d]
3	H	Pr	H	A	80 (**7**)	93[e]
4	H	$PhCH_2CH_2$	H	B	90 (**8**)	94[f]
5	H	$BnOCH_2$	H	B	87 (**9**)	94[f]
6	H	Bu_3Sn	H	A	82 (**10**)	ca. 90[g]
				B	88 (**10**)	ca. 90[g]
7	H	I	H	C	83 (**11**)	90[h]
8	Bu_3Sn	H	H	B	73 (**12**)	ca. 90[g]
9	I	H	H	C	71 (**13**)	83[e]
10	CH_3CH_2	H	H	A	90 (**14**)	93[h]
				D	>98[i] (**14**)	ca. 87[g]
11	$TBDPSOCH_2$	H	H	A	80 (**15**)	91[h]
12	$BnOCH_2$	H	H	A	93 (**16**)	91[f]
				B	92 (**16**)	91[f]
13	CH_3	CH_3	H	A	85 (**17**)	94[h]
14	H	Ph	CH_3	A	96 (**18**)	85[d]
				B	80 (**18**)	82[d]
15	H	CH_3CH_2	CH_2OTIPS	B	>98 (**19**)	89[e]
16	CH_3	CH_3	CH_2OTIPS	B	85 (**20**)	88[h]
17	H	$-CH_2CH_2CH_2CH_2-$		B	84 (**21**)	60[h]

[a] Procedure A (*with <1.0 mmol*): 2 equiv of $Zn(CH_2I_2)$ at 0 °C, then rt for 2 h. Procedure B (*with <1.0 mmol*): 2 equiv of $Zn(CH_2I)_2$·DME at −10 °C, then rt for 8 h. Procedure C (*with <1.0 mmol*): 5 × 2 equiv of $Zn(CH_2I)_2$·DME at −10 °C. Procedure D: dioxaborolane **22** was used instead of **1**. [b] Unless otherwise noted, these



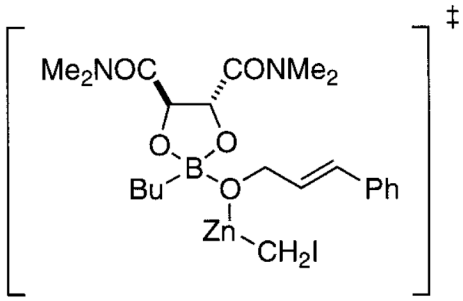
entry	R_1	R_2	x equiv	yield,[a] % (**cpd**)	ee, %
1	CH_3CH_2	H	2.0	90 (**43**)	82[b]
2	H	Ph	3.0	90 (**44**)	82[c]
3	Ph	H	4.0	86 (**45**)	81[c]

[a] Isolated yields. [b] Determined by ^{13}C NMR of the corresponding Mosher ester. [c] Determined by chiral HPLC.



entry	R_1	yield,[a] % (**cpd**)	ee,[b] %
1	Ph	21 (**46**)	53
2	$PhCH_2CH_2$	25 (**47**)	~55

[a] Isolated yields. [b] Determined by chiral HPLC.



Charette, A. B.; Juteau, H.; Lebel, H.; Molinaro, C., *J. Am. Chem. Soc.* **1998,** 11943c

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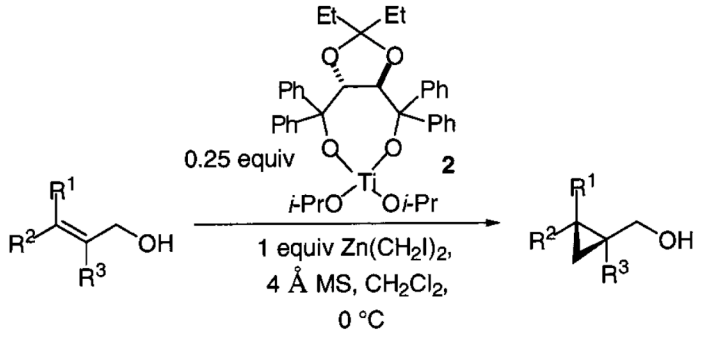
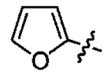
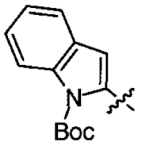


Entry	R^1	R^2	R^3	Yield[a] (%)	er	er K-D [h]
1 [g]	H	Ph	H	85	96 : 4 to 97 : 3 [b]	---
2 [g]	H	Ph	H	83	4 : 96 [b,f]	5 : 95
3 [h]	Ph	H	H	62	86 : 14 [b]	9 : 91
4 [g]	Me	Ph	H	80	94 : 6 [b]	13 : 87
5 [h]	H	Ph	Me	80	75 : 25 [b]	47 : 53
6 [g]	H	3,5-Me_2-Ph	H	86	96 : 4 [b]	---
7 [g]	H	2-napht	H	81	96 : 4 [c]	---
8 [h]	H	1-napht	H	80	92 : 8 [c]	---
9 [i]	H	*p*-Me-OPh	H	90	96 : 4 [b]	---
10 [g]	H	*p*-Cl-Ph	H	56	91 : 9 [c]	---
11 [h]	H	*p*-Cl-Ph	H	81	91 : 9 [c]	---
12 [h]	H	Pr	H	68	87 : 13 [d]	---
13 [h]	Pr	H	H	87	74 : 26 [e]	---
14 [h]	H	$PhCH_2CH_2$	H	63	80 : 20 [c]	5 : 95
15 [h]	H	Cyclohexyl	H	60	83 : 17 [d]	---
16 [h]	Me	Me	H	89	86 : 14 [e]	---
17 [g]	H		H	73	94 : 6 [b]	---
18 [g]	H		H	86	92 : 8 [c]	---

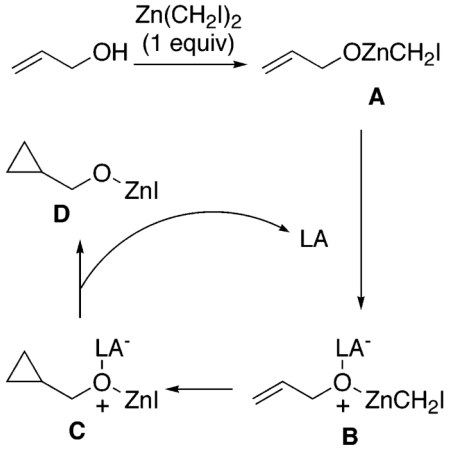


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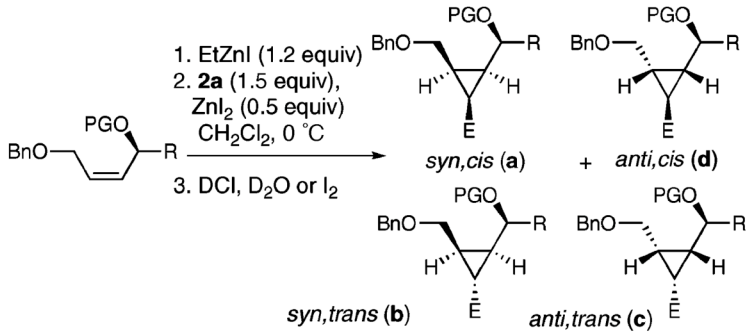
Table 1. Diastereoselective Zinco-Cyclopropanation of *cis*-Allylic Alcohols and Ethers



entry	R (PG)	dr (**a**:(**b** + **c** + **d**))	yield (%) (E = D)	yield (%) (E = I)
1	Me (H) (**5**)	>95:5	82 (**6**)	75 (**7**)
2	Et (H) (**8**)	>95:5	85 (**9**)	84 (**10**)
3	*i*-Pr (H) (**11**)	>95:5	86 (**12**)	87 (**13**)
4	*t*-Bu (H) (**14**)	>95:5	91 (**15**)	91 (**16**)
5	Ph (H) (**17**)	>95:5	62 (**18**)	58 (**19**)
6	Me (Bn) (**20**)	>95:5	86 (**21**)	77 (**22**)

Scheme 1

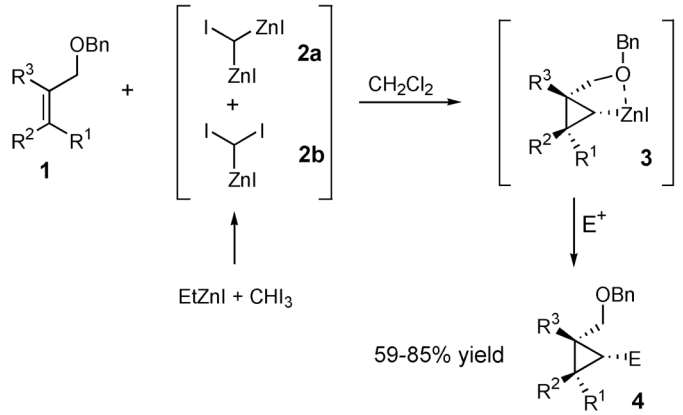
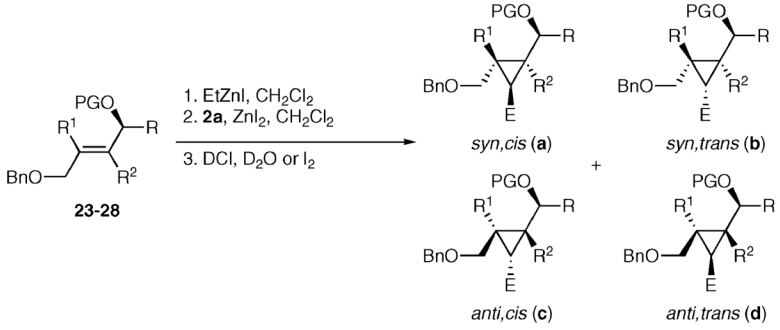


Table 2. Diastereoselective Zinco-Cyclopropanation of Trisubstituted Allylic Alcohols[a]



entry	PG	R	R^1	R^2	dr (*syn*:*anti*)	dr (*cis*:*trans*)	yield (%)
1	H	Me	H	H (**23**)	60:40		85 (**29**)[b]
2	H	*t*-Bu	H	H (**24**)	94:6	28:72	73 (**30**)[b]
3	TIPS	*t*-Bu	H	H (**25**)	>95:5	75:25	64 (**31**)[b]
4	H	Me	H	TMS (**26**)	<5:95	>95:5	68 (**32c**)
5	H	*t*-Bu	H	TMS (**27**)	<5:95	>95:5	77 (**33c**)
6	H	*t*-Bu	TMS	H (**28**)	>95:5	<5:95	84 (**34b**)
7	H	*t*-Bu	TMS	H (**28**)	>95:5	<5:95	81 (**35b**)

[a] In entries 2−6, cyclopropylzinc was quenched with D_2O (E = D). I_2 was used in entries 2 and 7 (E = I). H_2O was used in entry 1. [b] Combined yield of the diastereomers.

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Achiral Iodomethylzinc Phophates

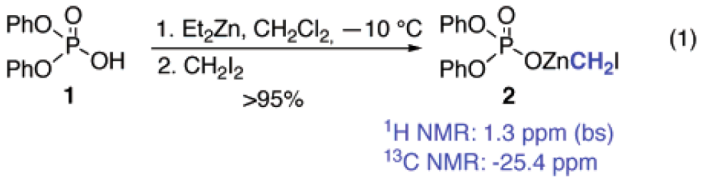
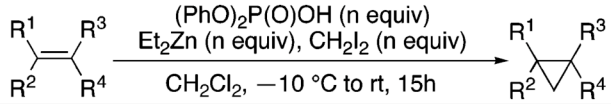
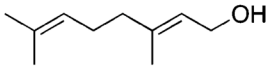
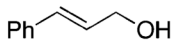
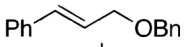
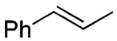


Table 1. Cyclopropanation Using Achiral Phosphoric Acid **2**



entry	substrate	product	n	yield (%)
1		**3**	1.2	> 95 (98%)[a,b]
2		**4**	1.2	> 95 (98%)[a]
3		**5**	1.2	> 95 (98%)[a]
4		**6**	1.5	95[c]
5		**7**	1.5	62[c]

[a] Determined by ^{1}H NMR using an internal standard. Isolated yield in parentheses. [b] Only the allylic alcohol double bond reacted. [c] Determined by GC analysis using an internal standard.

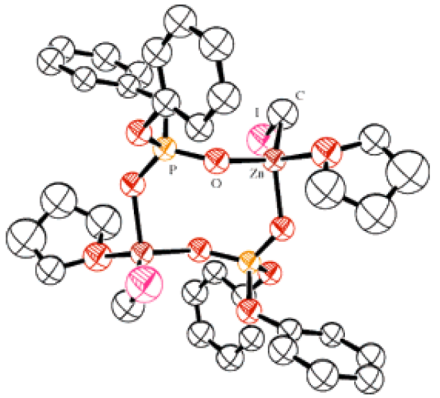
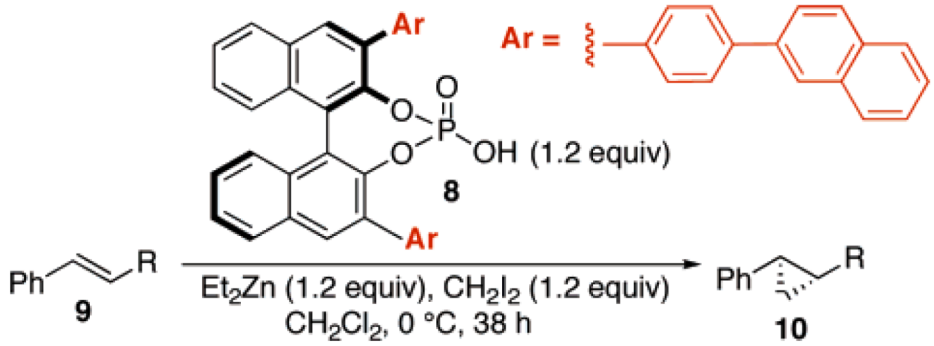


Figure 1. ORTEP drawing of **2**·THF dimer.

Chiral Stoichiometric Iodomethylzinc Phosphates

Table 2. Cyclopropanation with Chiral Phosphoric Acid **8**

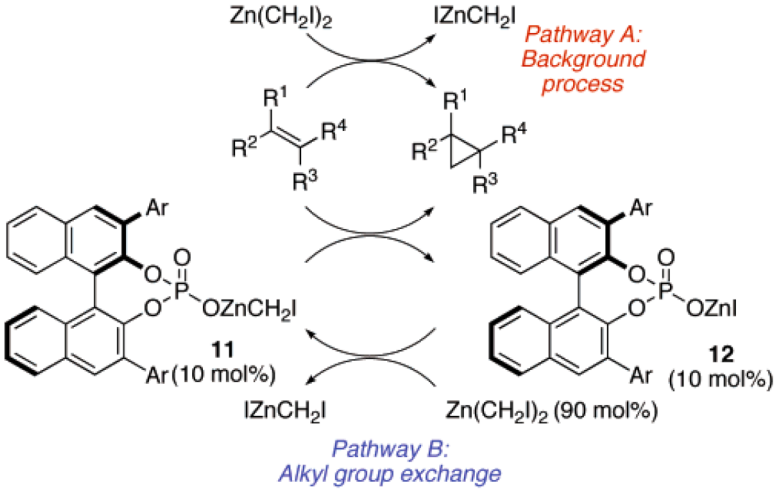


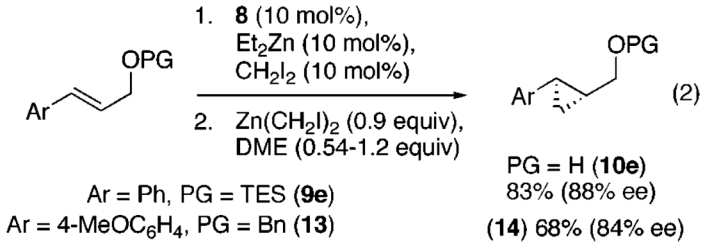
entry	R		yield (%)[a]	ee (%)[b]
1	CH_2OMe	**(9a)**	>95 (73)	91
2	CH_2OBn	**(9b)**	>95 (89)	90
3	CH_2OPMB	**(9c)**	95 (78)	85
4	CH_2OMOM	**(9d)**	75 (47)	90
5	CH_2OTES	**(9e)**	>95 (79)[c]	87
6[d]	CH_2OTES	**(9e)**	>95 (84)[c]	92
7	CH_2CH_2OBn	**(9f)**	>95 (85)	93
8	CH_2OZnEt	**(9g)**	>95 (80)	39[e]

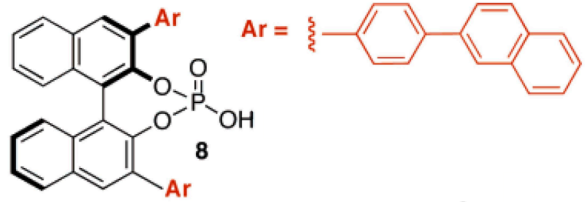
[a] Determined by ^1H NMR using an internal standard. Isolated yield in parentheses. [b] Determined by HPLC on chiral stationary phase. [c] The corresponding alcohol was obtained after deprotection with 1.0 M H_3PO_4 and NH_4F at 40 °C. [d] The reaction was performed at −20 °C for 48 h. [e] The opposite (*S*,*S*)-enantiomer was obtained.

Chiral Catalytic Iodomethylzinc Phosphates

Scheme 1. Catalytic Cycle for the Cyclopropanation Reaction







Conclusion

- The Charette group has reported a novel phosphate bound Zn reagent for the cyclopropanation of allylic alcohols. This reagent can be used in either stoichiometric or catalytic amounts to give moderate to good ee's and yields.
- The scope of both the stoichiometric and catalytic reaction needs to be expanded. The use of unfunctionalized olefins in this reaction would be an important improvement.
- Work is ongoing to develop a ligand which gives higher ee's in both reactions.