Use of Cp_2TiCl in Synthesis

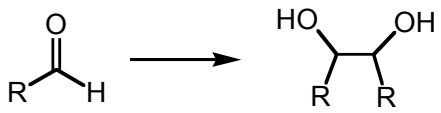
Reagent Control of Radical Reactions

Jeff Kallemeyn

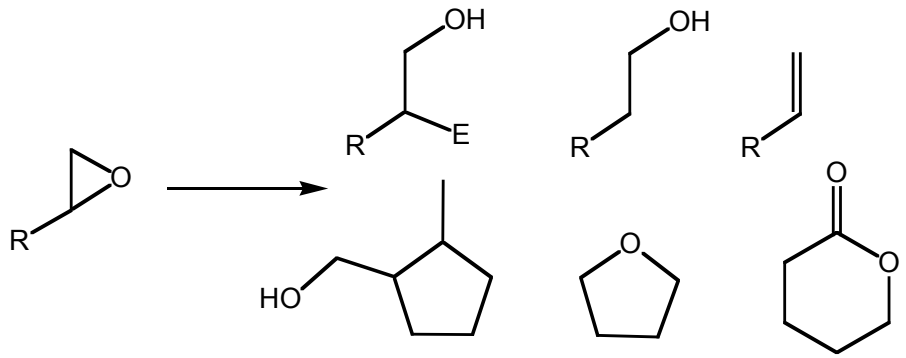
May 21, 2002

Reactions of Cp_2TiCl

1. Pinacol Coupling



2. Epoxide Opening



Chemoselectivity

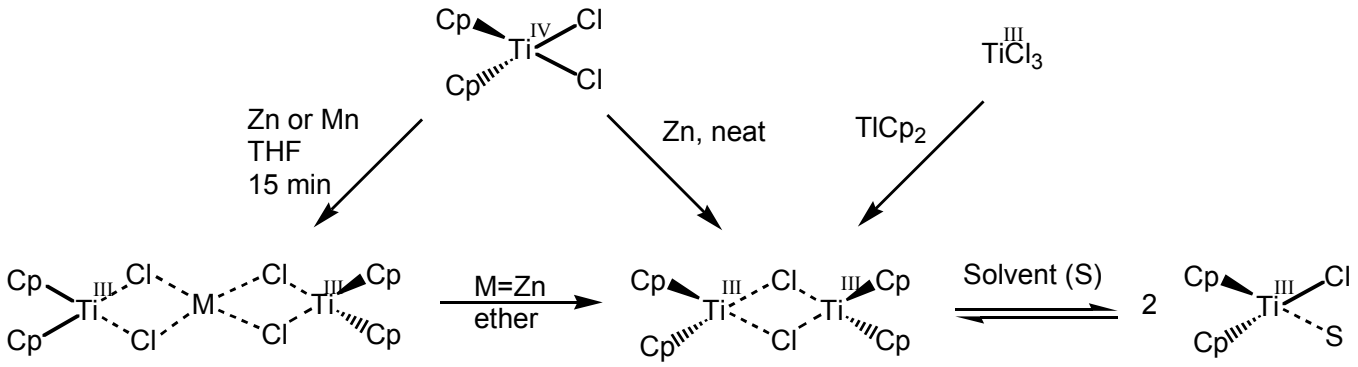
Activated aldehydes (aromatic, α,β-unsaturated) more reactive than aliphatic aldehydes.

Esters, nitriles, ketones unaffected.

Br, Cl, tosylate stable.

Mild radical initiator.

Preparation of Cp_2TiCl

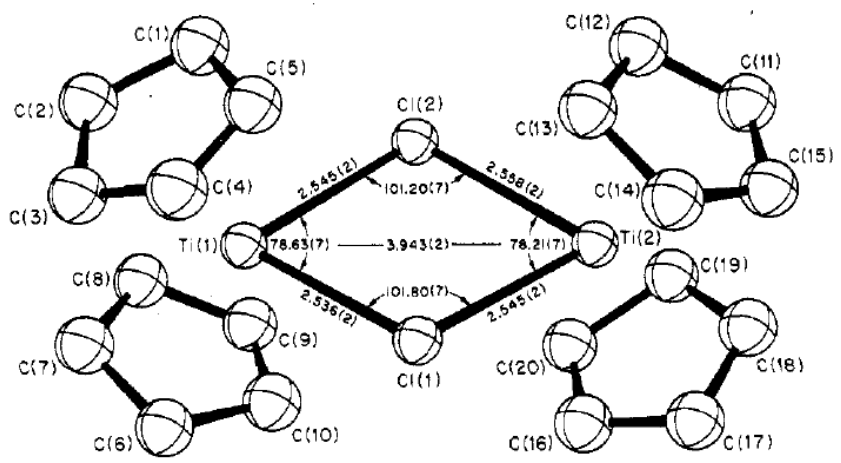


Ti(III): [Ar] $3d^1$

Cp_2TiCl generated by *in situ* reduction with Mn or Zn.

Both dimer and trimer work equally well in most cases.

In situ regeneration of Ti(III) possible allowing it to function catalytically.



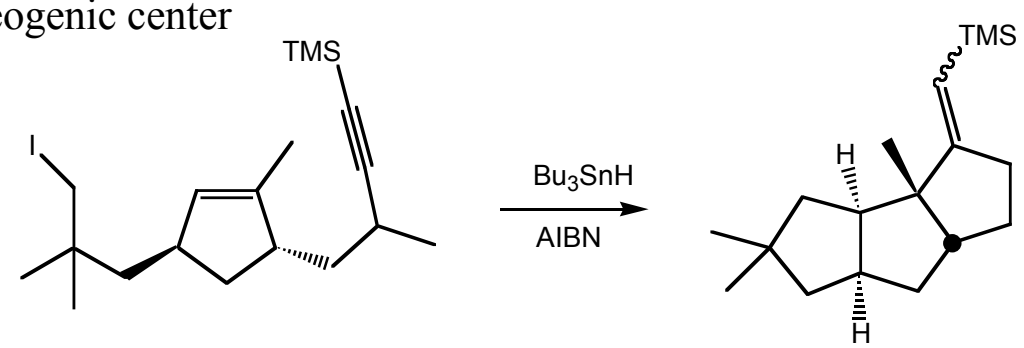
M-Ti-M : 132°

R. Jungst; D. Sekutiwski; J. Davis; M. Luly; G. Stucky, *Inorg. Chem*. **1977**, *16*, 1645.

Substrate Controlled Stereoselective Radical Reaction

Substrate directs the stereoselectivity of the reaction.

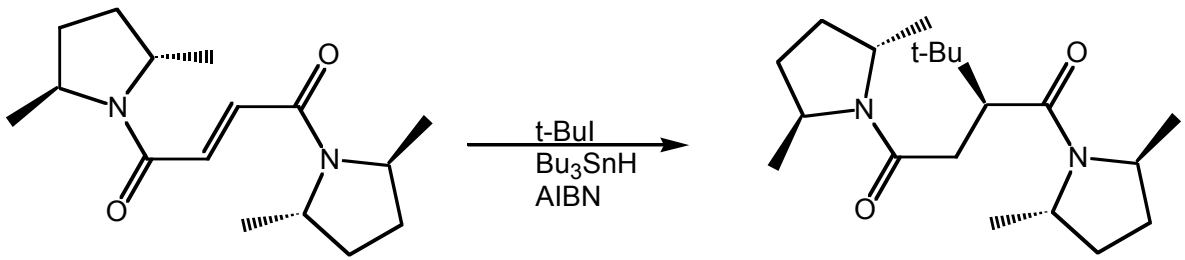
1. Substrate has stereogenic center



72% yield

D. Curran, D. Rakiewicz, *Tetrahedron,* **1985**, *41*, 3943.

2. Chiral Auxiliary

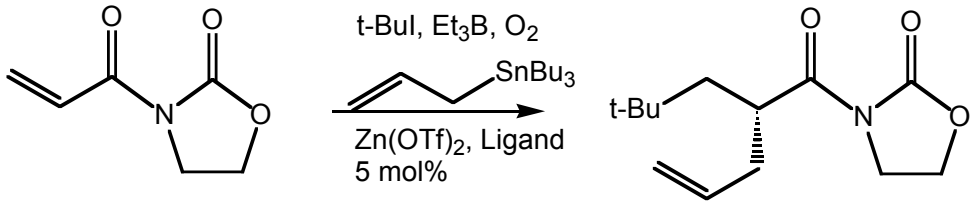


70% yield, 86-97% ee.

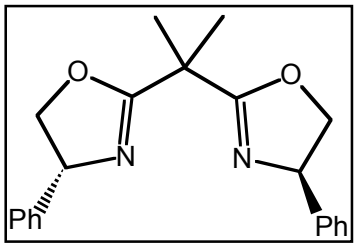
N. Porter, D. Scott, I. Rosenstein, B. Giese, A. Viet, H. Zeitz, *J. Am. Chem. Soc*. **1991**, *113*, 1791.

Reagent Controlled Stereoselective Radical Reaction

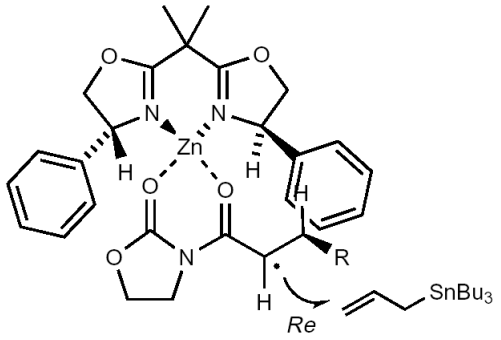
1. Complexation



92% yield, 90% ee



Ligand



Control Features:

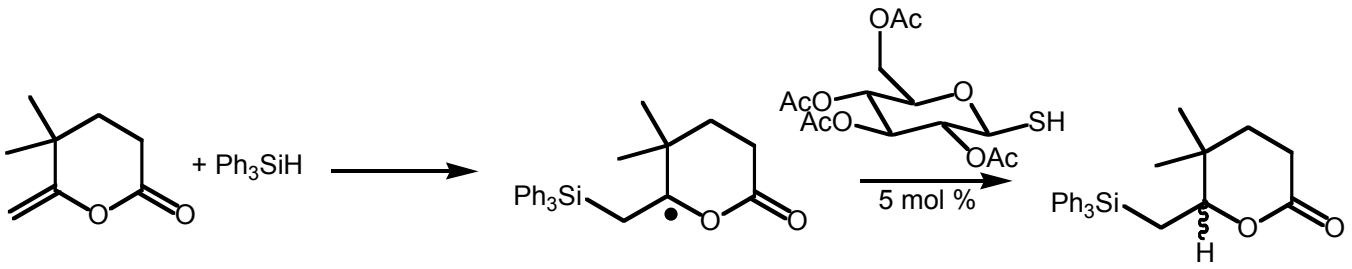
Chelation locks substrate into rigid conformation.

Chiral ligand allows only 1 face of radical to be accessible.

M. Sibi, N. Porter, *Acc. Chem. Res*. **1999**, 32, 163.

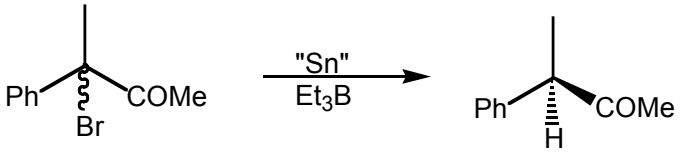
Reagent Controlled Stereoselective Radical Reaction

2. Chiral Hydrogen Source

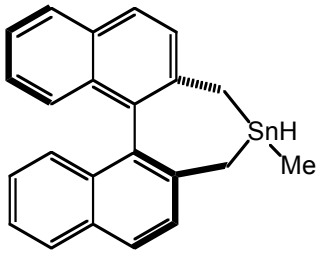


72% yield, 50% ee

M. Haque, B. Roberts, *Tetrahedron. Lett.* **1996**, *37*, 9123.



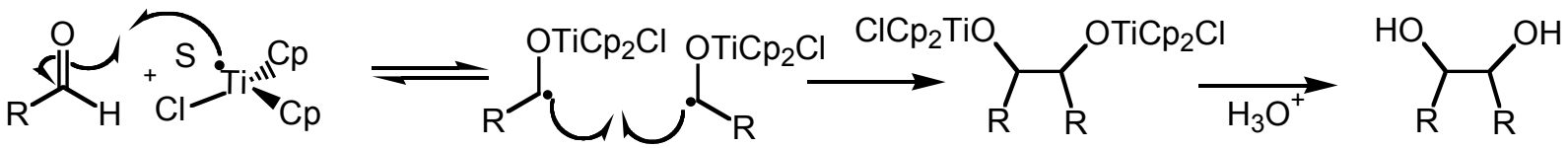
30% yield, 41% ee



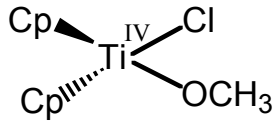
D. Nanni, D. Curran, *Tetrahedron Asymm*. **1996**, *37*, 2417.

3. Formation of radical: Cp_2TiCl

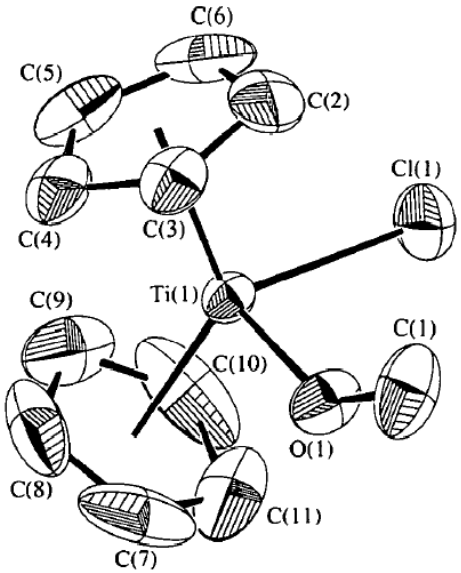
Pinacol Coupling



General Mechanism



Distorted Tetrahedral



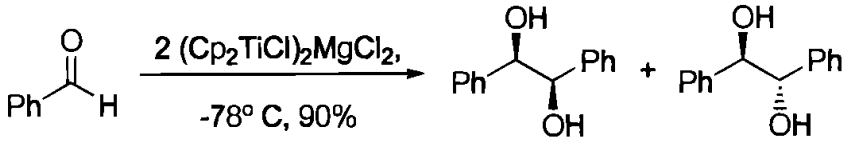
Bond Lengths and angles

Ti-O	1.839	Cl-Ti-O	93.8
Ti-Cl	2.412	O-Ti_M(1)	109.6
Ti-M	2.088	O-Ti-M(2)	105
Ti-M	2.093	Cl-Ti-M(1)	105
O-C	1.367	Cl-Ti-M(2)	106.3
		M(1)-Ti-M(2)	130.8
		Ti-O-C	141.4

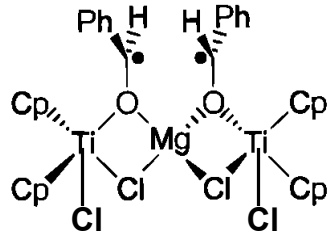
Y. Handa, J. Inanaga, *Tetrahedron Lett*. **1987**, *28*, 5717.

D. Gibson, Y. Ding, M. Mashuta, J. Richardson, *Acta Crys*. **1996**, *52*, 559.

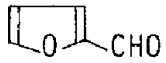
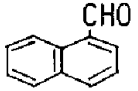
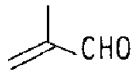
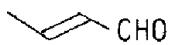
Pinacol Coupling



80 1

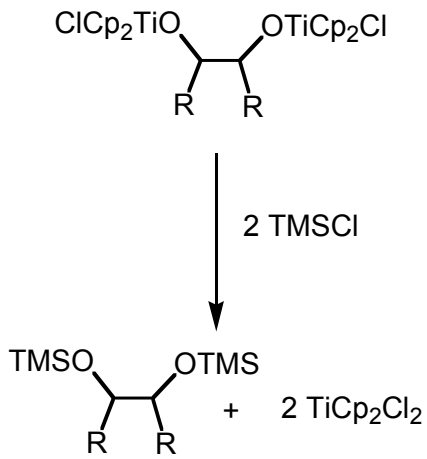


Proposed intermediate leading to high diastereoselectivity.

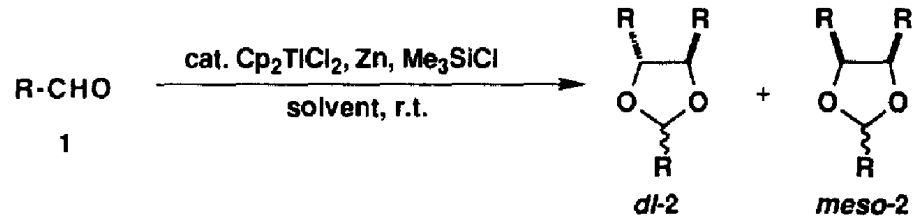
Aldehyde	Pinacol Yield(%)[b]	Ratio (T : E)[c]	Aldehyde	Pinacol Yield(%)[b]	Ratio (T : E)[c]
p-MeOPhCHO	96	100 : 1	p-PhPhCHO	80	18 : 1 [d]
p-MePhCHO	95	100 : 1	p-MeO_2CPhCHO	50	11 : 1 [d]
o-MePhCHO	89	58 : 1		84	40 : 1
	90	100 : 1 [d]		98	100 : 1 [d]
p-ClPhCHO	91	56 : 1		87	60 : 1 [d]

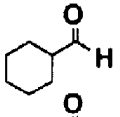
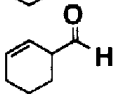
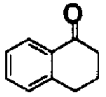
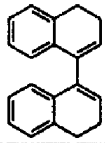
Y. Handa, J. Inanaga, *Tetrahedron Lett*. **1987**, *28*, 5717.

Development of Catalytic Pinacol Coupling



Product resting state before hydrolysis

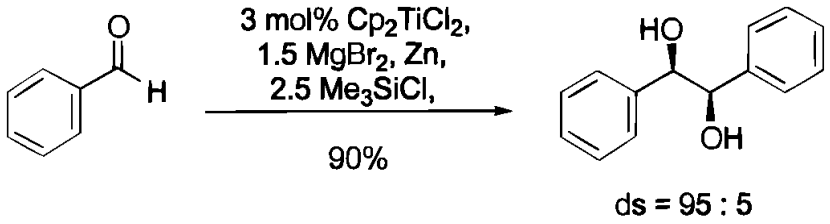


Run	Substrate	Product	Yield, %[b]	*dl* / *meso* [b]
1	$^{n}C_5H_{11}CHO$	2 (R = $^{n}C_5H_{11}$)	60	63 / 37
2	$PhCH_2CH_2CHO$	2 (R = $PhCH_2CH_2$)	88	67 / 33
3[c]		2 (R =)	87 (85)[d]	96 / 4
4[c]		2 (R =)	66 (53)[d]	81 / 19
5			65 (60)[d]	

[a] Reaction conditions: 1 (1.0 mmol), Zn (2.0 mmol ; activated by the treatment with HCl (1.5 M) and washed with diehtyl ether, purchased from Wako Pure Chemical Industries, Ltd.), Me_3SiCl (2.0 mmol), Cp_2TiCl_2 (3 mol%), DME (7 mL), r.t.,13 h unless otherwise stated. [b] Determined by ^1H NMR. [c] Reaction temperature, 0 °C. [d] Isolated yield.

T. Hirao, B. Hatano, M. Asahara, Y. Muguruma, A. Ogawa, *Tetrahedron Lett*. **1998**, *39*, 5247.

Development of Catalytic Pinacol Coupling



TMSCl and Zn can effect the pinacol coupling and proceeds with low diastereoselctivity.

Initial catalytic reactions gave worse diastereoselectivities than stoichiometric (86:14 to 50:50).

Silylation of Ti alkoxide determined to be the slow step in the reaction.

Low diastereoselectivies solved by slow addition of TMSCl, $MgBr_2$ and aldehyde to Ti(III) and Zn.

entry	Ar	yield/%	cis:trans
(3a)	4-Methyl-phenyl	82	92:8
(3b)	2-Furyl	88	92:8
(3c)	4-Cl-phenyl	78	93:7
(3d)	3-Cl-phenyl	87	93:7
(3e)	4-vinyl-phenyl	91	92:8
(3f)	4-crotonyloxy-phenyl	81	92:8

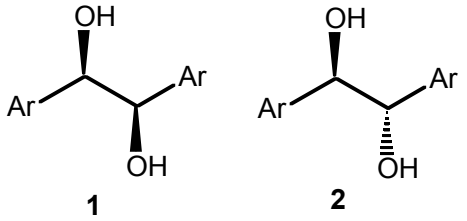
A. Gansäuer, *Synlett*. **1998**, 801.

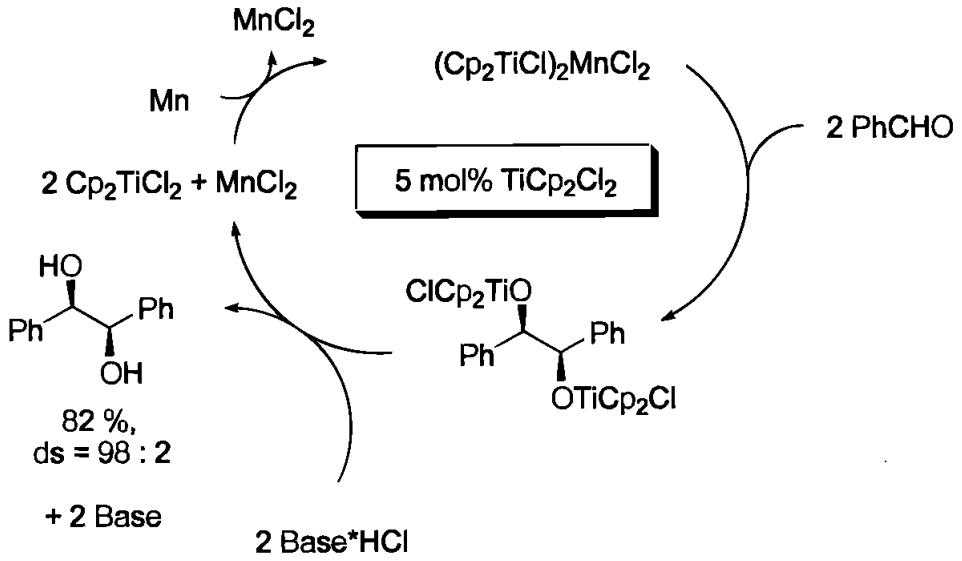
Modification of Catalytic Pinacol Coupling

Radicals are stable under protic conditions.

Selection of correct base important as to not oxidize the metal reductant or complex with the Titanium catalyst.

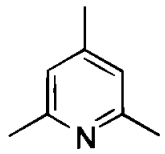
Addition of Amine HCl salt leads to increased diastereoselectivity, faster turnover compared to TMSCl catalyzed system.





entry	substrate	% yield	**1**:**2**[b]
1	2-MePhCHO	90	97:3
2	3-MePhCHO	85	97:3
3	4-MePhCHO	84	97:3
4	4-ClPhCHO	89	97:3
5	4-BrPhCHO	82	98:2
6	4-MeOPhCHO	91	99:1
7	4-AcOPhCHO	85	99:1
8	4-PhPhCHO	87	97:3
9	4-vinylPhCHO	85	96:4
10	2-thienylCHO	82	95:5

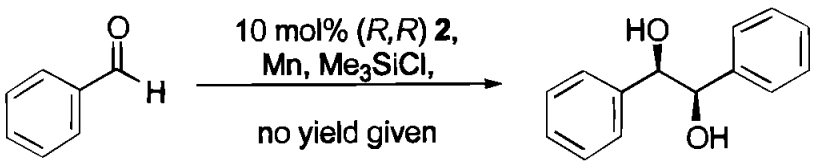
Base =



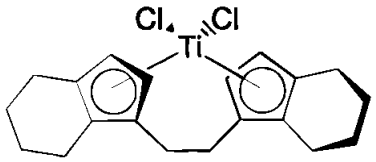
2,4,6-Collidine

A. Gansäuer, D. Bauer, *J. Org. Chem*. **1998**, *63*, 2070.

Enantioselective Pinacol Coupling

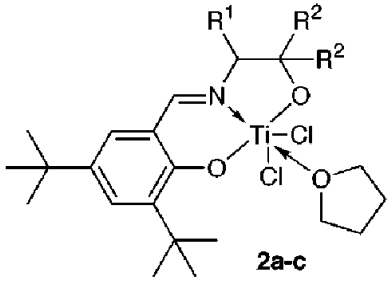


ds = 88 : 12,
60% ee



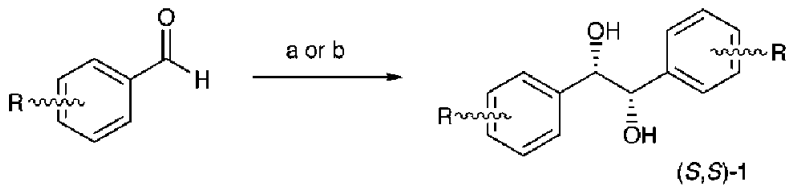
2

M. Dunlap, K. Nicholas, *Syn. Comm.* **1999**, *29*, 1097.



2a-c

(*S*)-**2a** R^1 = *i*-Pr; R^2 = H
(*S*)-**2b** R^1 = $PhCH_2$; R^2 = Ph
(*S,S*)-**2c** R^1, R^2 = indenyl



(*S,S*)-1

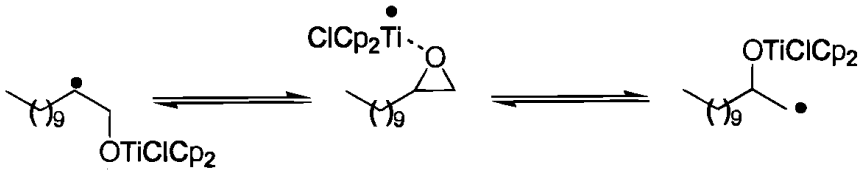
a. 1 equiv. **2b**, 3 equiv. Mn, CH_3CN (0.05 M in Ti), -10°C
b. 10 mol % **2b**, 3 equiv. Mn, 1.5 equiv. TMSCl, CH_3CN (0.01 M in Ti), 25°C

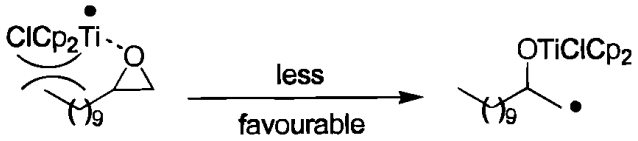
		stoichiometric[a]			catalytic		
entry	R	yield (%)[b]	*dl*:*meso*[c]	ee (%)[d]	yield (%)[b]	*dl*:*meso*[c]	ee (%)[d]
1	H	>95	98:2	77	94	96:4	63
2	H[e]				80	91:9	60
3	*o*-CH_3	>95	95:5	**85**	>95	86:14	64
4	*p*-CH_3	>95	97:3	**86**	>95	95:5	52
5	*p*-OCH_3	>95	98:2	**91**	84	95:5	58
6	*p*-OCH_3[f]	73	99:1	**88**			
7	*p*-Br	>95	95:5	48	81	83:17	16
8	*p*-CF_3	>95	81:19	7	90	63:17	5

[a] For the conditions used, see above. [b] Yield of isolated product after flash column chromatography on silica. [c] Measured by HPLC. [d] Enantiomeric excesses were measured by HPLC analysis on a Pirkle (*S,S*)-Whelk column (entries1 and 2) or a Chiralcel AD column (entries 3−8). [e] Two mole percent of **2b** was used. [f] Cerium Mishmetall was used instead of Mn, and the reaction was carried out at room temperature.

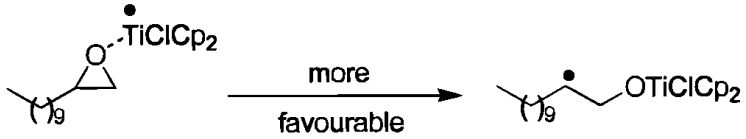
A. Bensari, J. Renaud, O. Riant, *Org. Lett.* **2001**, 3, 3863.

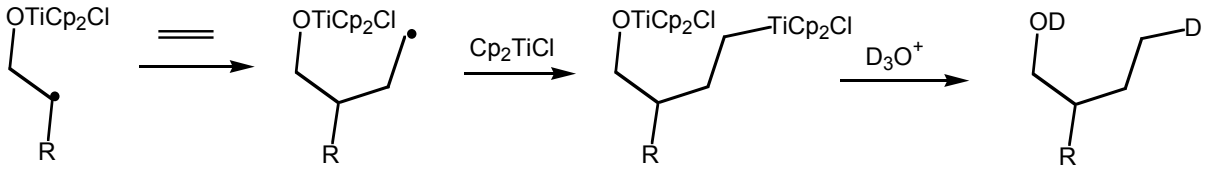
Mechanism of Epoxide Opening

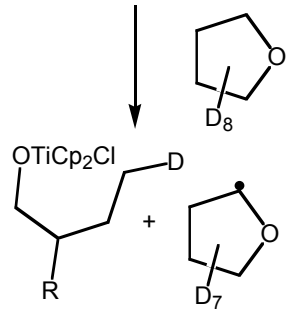




Product ratios show higher substituted radical formed. Titanium attached to radical it created--reagent control.





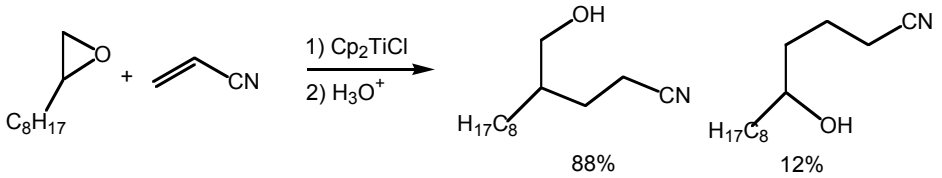


Reductive termination pathway depends on reactivity of intermediate radical.

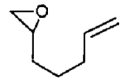
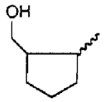
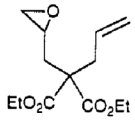
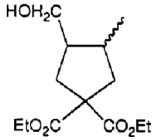
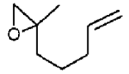
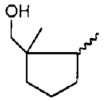
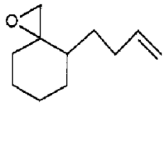
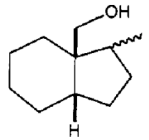
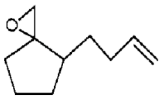
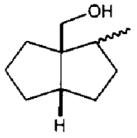
T. RajanBabu, W. Nugent, *J. Am. Chem. Soc*. 1994, 116, 986.

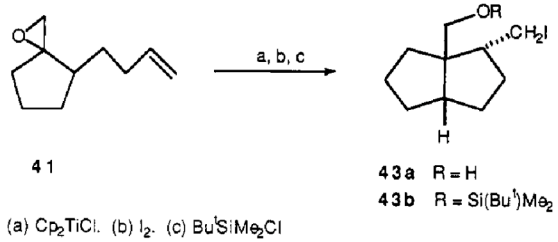
A. Gansäuer, H. Bluhm, *Chem. Rev*. **2000**, *100*, 2771.

Epoxide Opening and Trapping

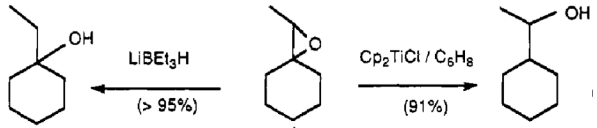


Radical formation at the higher substituted carbon.

entry	epoxide	product (% yield)	isomer ratio
1	 29	 31a (70)	cis/trans 2:1
2	 35	 36 (68)	cis/trans 85:15
3	 37	 38 (94)	cis/trans 1:1
4	 39	 40 (82)	endo/exo 55:45
5	 41	 42 (88)	endo/exo 90:10



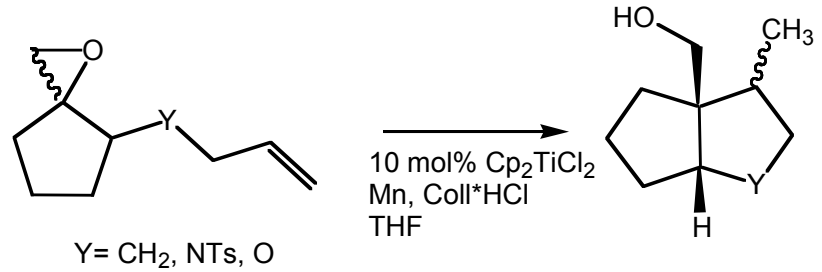
Electrophilic workup

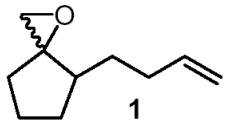
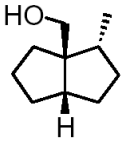
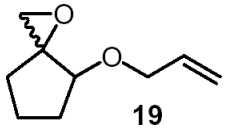
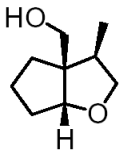
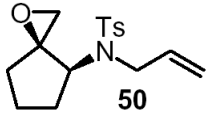
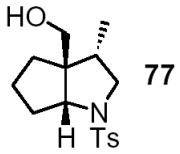


Complementary to nucleophilic epoxide opening

T. RajanBabu, W. Nugent, *J. Am. Chem. Soc*. **1994**, *116*, 986.

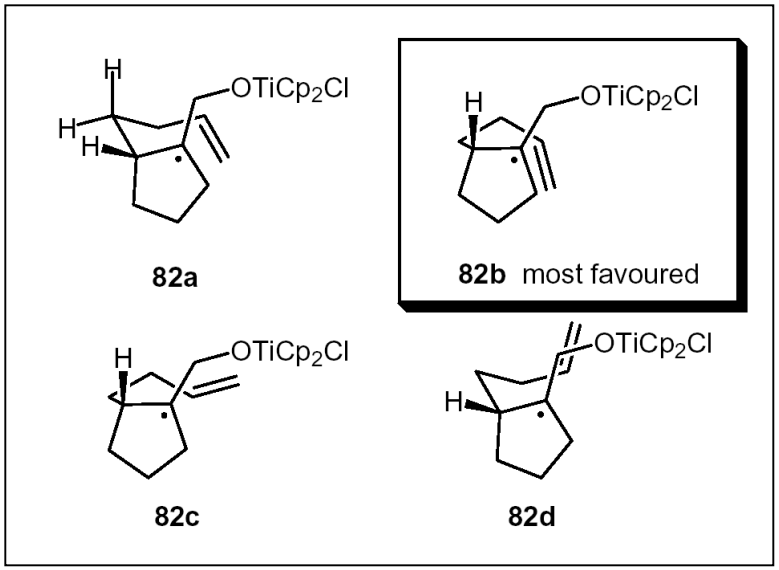
Diastereoselectivity in 5-member ring formation

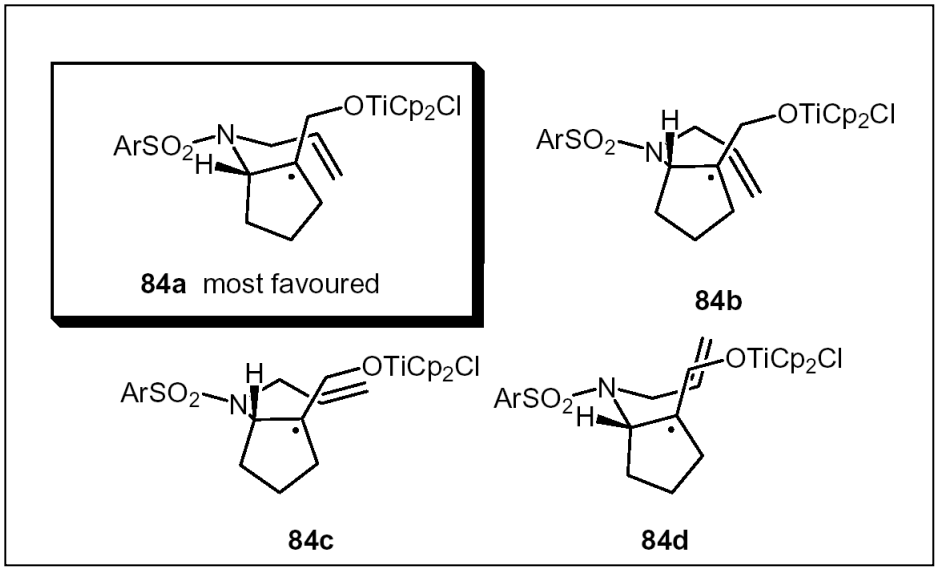


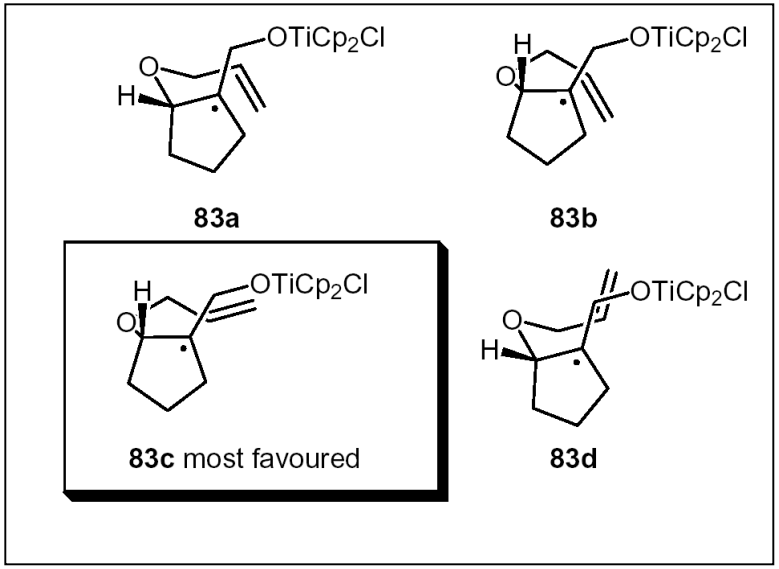
Substrate	Product	Yield/ [%]	dr
 **1** dr 75:25	 **56**	66[b]	>98:2
 **19** dr >97:3	 **65**	68	58:42
 **50**	 **77**	62[b]	86:14

A. Gansäuer, M. Pierobon, H. Bluhm, *Synthesis* **2001**, 2500

Diastereoselectivity in 5-member ring formation

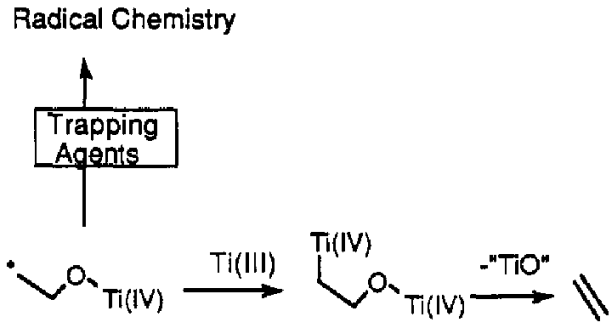






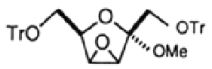
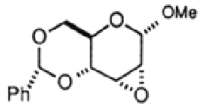
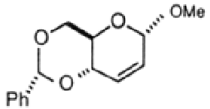
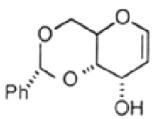
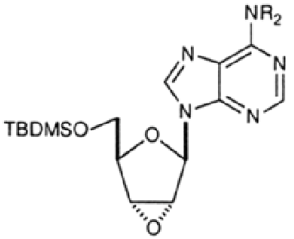
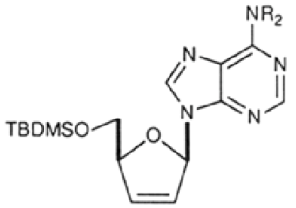
A. Gansäuer, M. Pierobon, H. Bluhm, *Synthesis* **2001**, 2500.

Deoxygenation of Epoxides



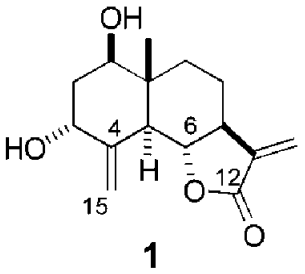
Deoxygenation discouraged in the presence of trapping agents with inverse addition of Cp_2TiCl to minimize the concentration of Ti(III).

Effective for sensitive functional groups, especially acid sensitive.

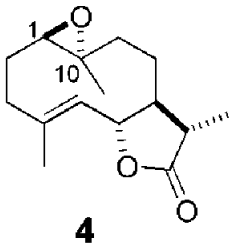
entry	epoxide	product (yield)
1	 **2**	**3** (66)
2	 **4**	 **5** (78)  **6** (16)
3	 **7a** R = H **7b** R = C(O)Ph	 **8a** R = H (69) **8b** R = C(O)Ph

T. RajanBabu, W. Nugent, *J. Am. Chem. Soc*. **1994**, *116*, 986

Effects of Solvent and Water



(+)-3-hydroxyreynosin



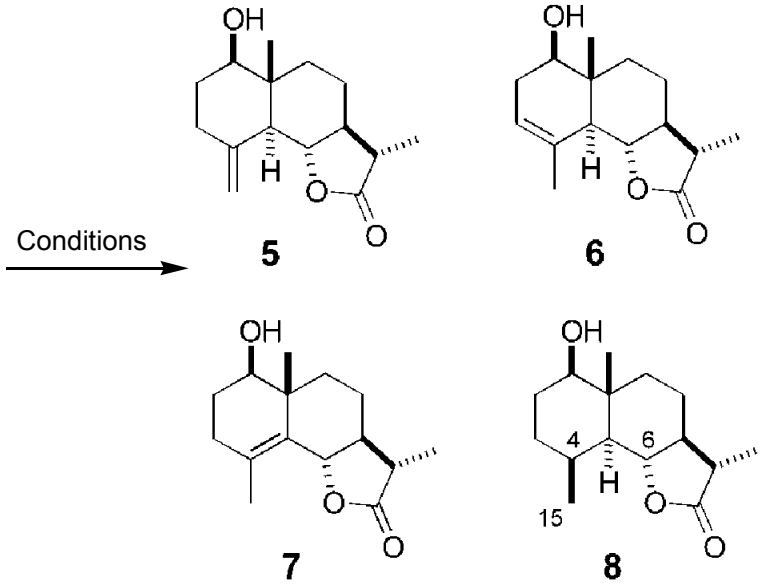


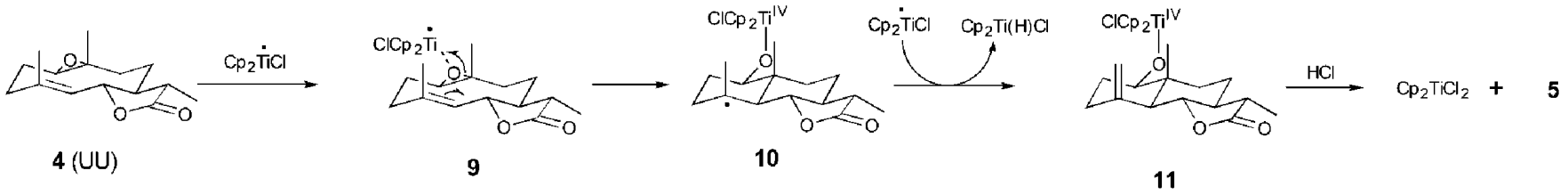
Table 1. Relative Proportions[a] (%) of Compounds 4–8 Obtained after Acid-Induced and Cp_2TiCl-Promoted Transannular Cyclizations of 4 in Different Solvents

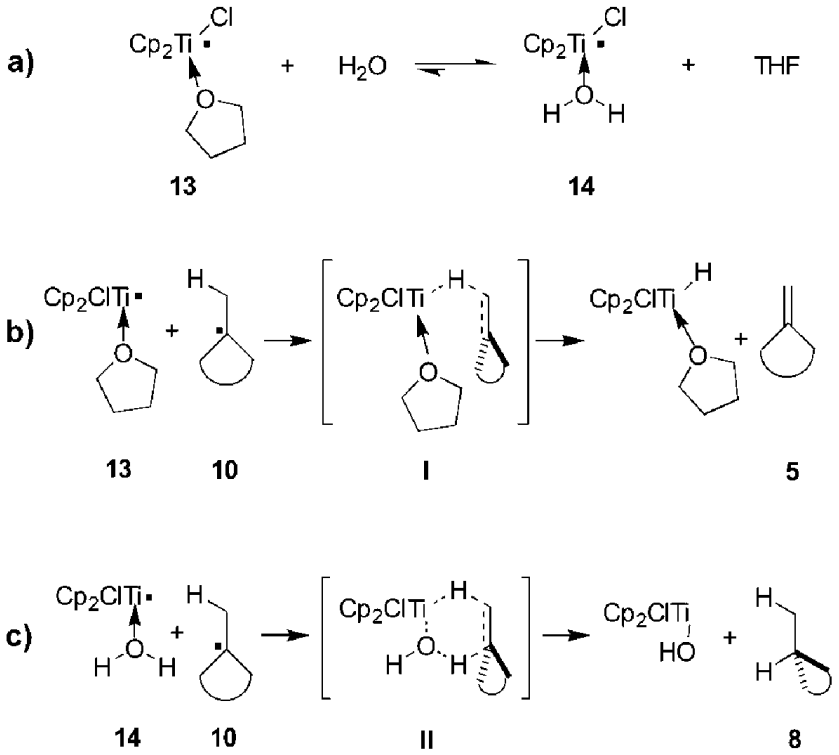
entry	reagent (equiv)	solvent	additive (equiv)	4	5	6	7	8
1	TsOH (0.5)	CH_2Cl_2			8	82	10	
2	BF_3 (0.6)	CH_2Cl_2			40	57	3	
3	$MnCl_2$ (1.5)	THF			19	63	18	
4	Cp_2TiCl (3.3)	THF			91	6		3
5	Cp_2TiCl (3.3)	PhH			84	12		4
6	Cp_2TiCl (3.3)	$PhCH_3$			86	4		10
7	Cp_2TiCl (3.0)	PhH	1,4-C_6H_8[b] (30.0)		86	8		6
8	Cp_2TiCl (1.1)	PhH		12	36	29	8	15
9	Cp_2TiCl (3.3)	CH_2Cl_2			40	49	8	3
10	Cp_2TiCl (3.3)	CCl_4			40	55	5	
11	Cp_2TiCl (3.3)	THF	H_2O (28.0)		13	8	8	71

[a] Relative proportions were determined on the basis of the ^1H NMR spectra of the mixtures formed in every experiment. [b] 1,4-C_6H_8 = 1,4-cyclohexadiene.

A. Barrero, J. Oltra, J. Cuerva, A. Rosales, *J. Org. Chem*. **2002**, *67*, 2566.

Effects of Solvent and Water





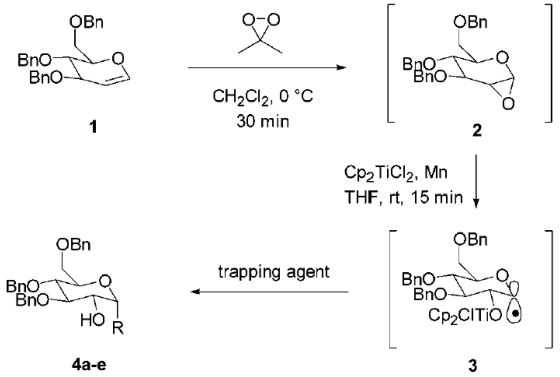
Proposed concerted transition state leads only to 6-endo cyclization with no 5-exo product.

Tertiary radical hindered--it is not trapped by Ti(III) or reduced by 1,4-cyclohexadiene.

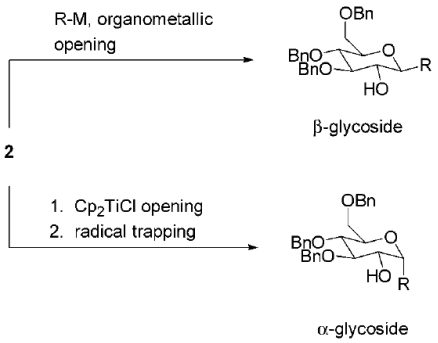
Deuterium incorporation is observed at C4 when D_2O is used.

A. Barrero, J. Oltra, J. Cuerva, A. Rosales, *J. Org. Chem.* **2002**, *67*, 2566.

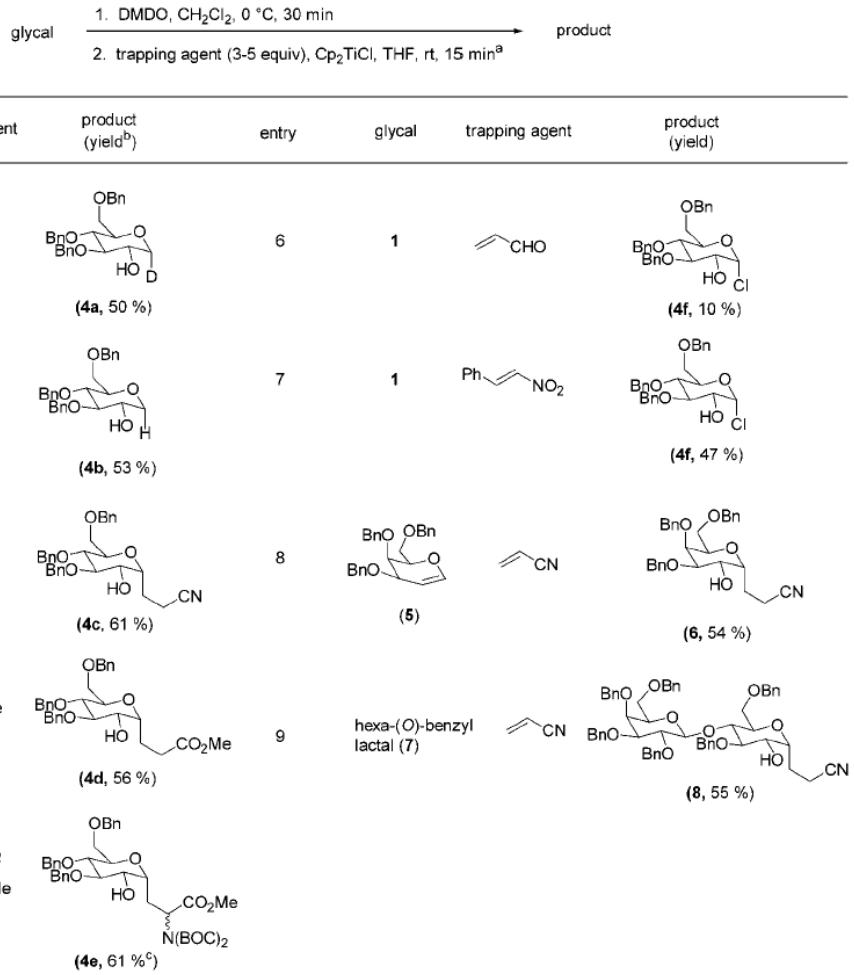
Formation of β-glycosides



Reaction Scheme



Complementary to Nucleophile

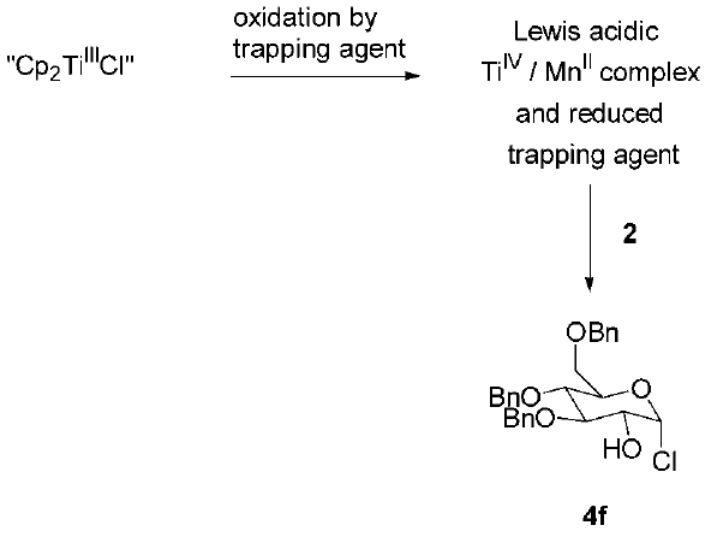


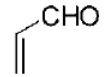
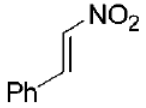
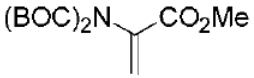
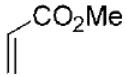
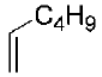
Reaction Scope

J. Parrish, R. Little, *Org. Lett.* **2002**, *4*, 1439

Formation of β-glycosides

Reduction



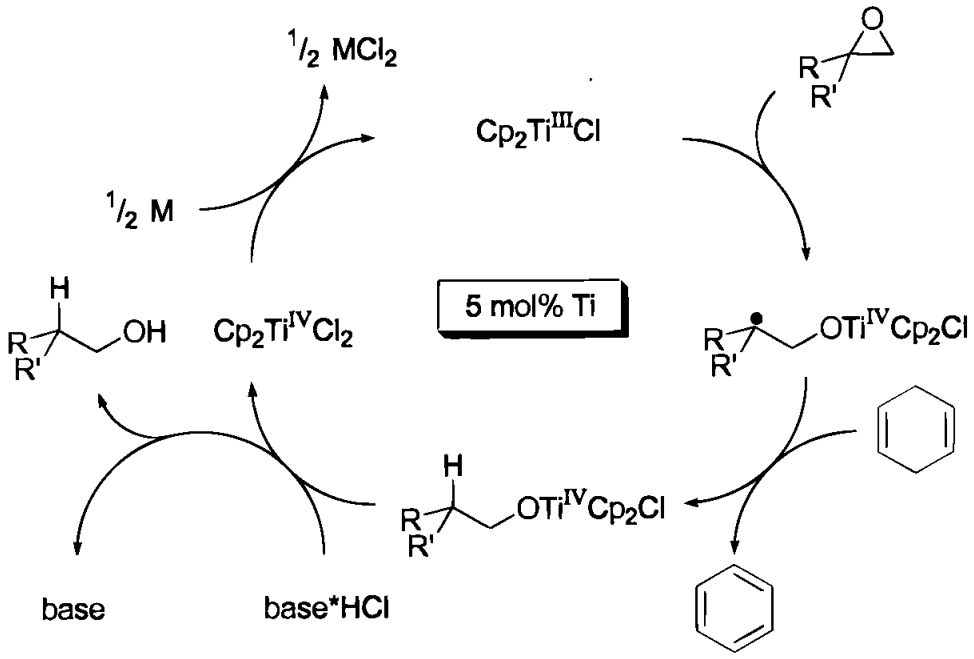
trapping agent	E_{pc} (V)	reactivity
	-1.8	quenches
	-2.55	quenches
	-2.73	traps
	-2.83	traps
	-2.93	traps
	> -3.3	unreactive
	> -3.3	unreactive

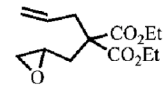
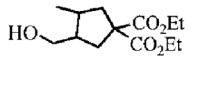
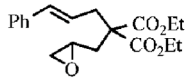
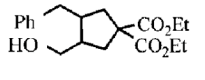
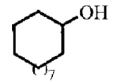
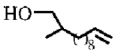
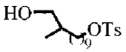
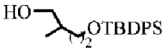
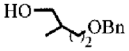
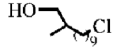
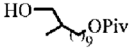
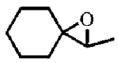
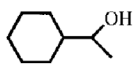
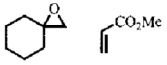
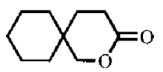
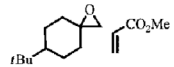
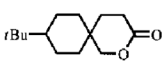
Lewis acidic epoxide opening yields the undesired product.

Trapping agent must be of the correct electronic nature.

J. Parrish, R. Little, *Org. Lett.* **2002**, *4*, 1439

Catalytic Epoxide Opening



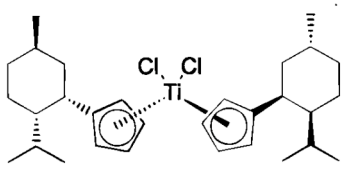
Entry	Substrate	t [h]	Yield [%]	Product
1		30	78[b]	
2		30	55[c]	
3		30	83[d]	
4		16	72	
5		18	58	
6		18	86	
7		12	67	
8		18	74	
9		18	69	
10	**1** 4-phenyl-2-butanone	60	70 95	**2** 4-phenyl-2-butanone
11		30	76[e]	
12		40	77[e]	
13		40	82[e,f]	

[a] See Experimental Section. [b] *cis*:*trans* = 88:12. [c] *cis*:*trans* = 85:15. [d] Substrate was a mixture of *cis* und *trans* isomers. [e] Zn was used as reductant. [f] *cis*:*trans* = 14:86.

A. Gansäuer, H. Bluhm, *Chem. Rev.* **2000**, *100*, 2771

A. Gansäuer, M. Pierobon, H. Bluhm, *Angew. Chem, Int. Ed.* **1998**, *37*, 101

Catalytic Asymmetric Epoxide Opening



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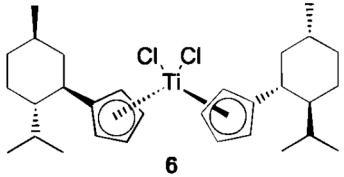

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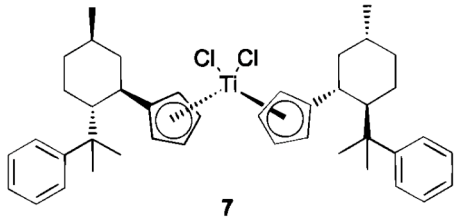

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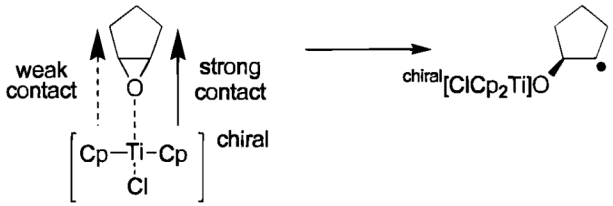

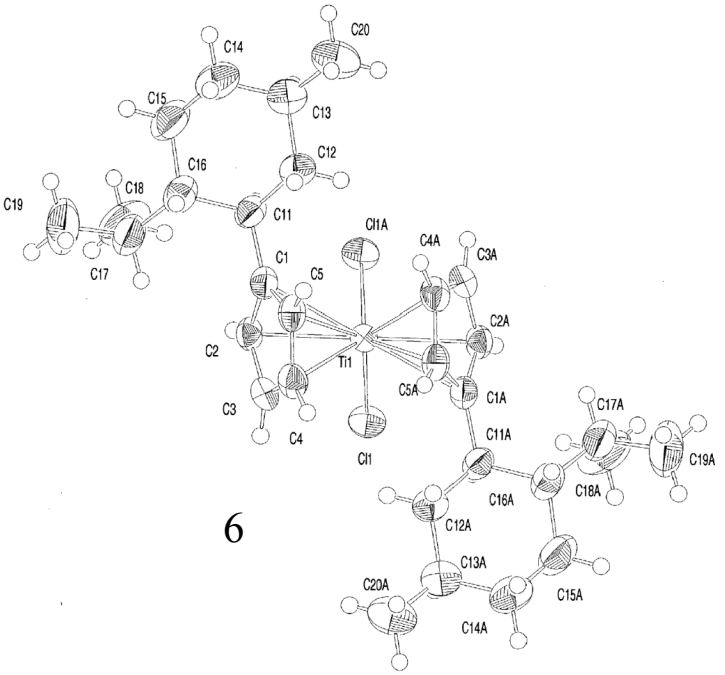

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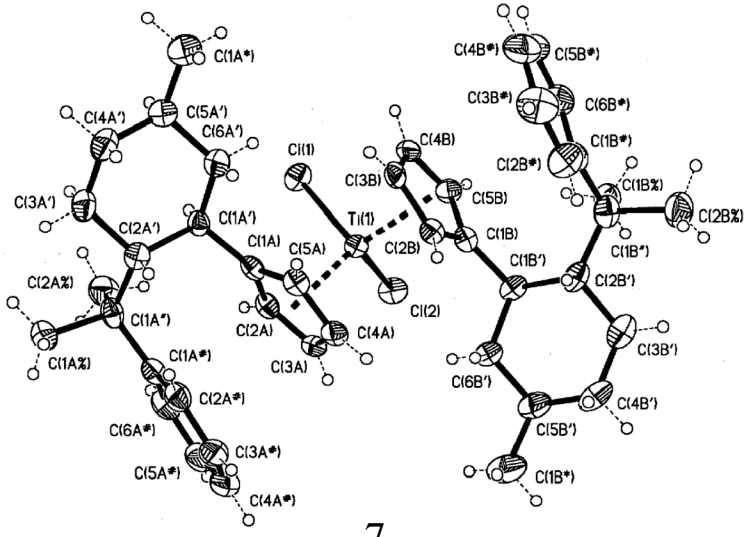

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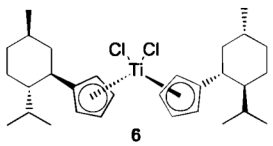
A. Gansäuer, H. Bluhm, *Chem. Rev*. **2000**, *100*, 2771.

A. Gansäuer, H. Bluhm, M. Pierobon, M. Keller, *Organometallics*, **2001**, *20*, 914.

Catalytic Asymmetric Epoxide Opening



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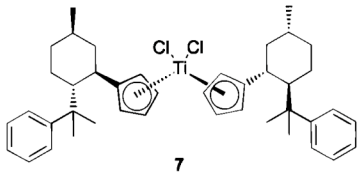

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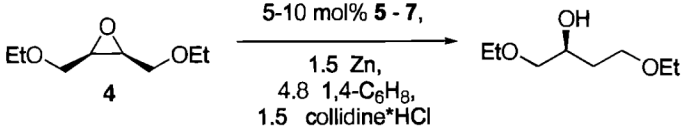
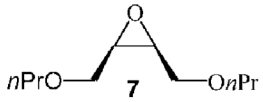
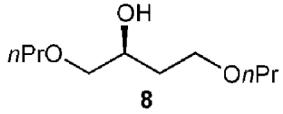
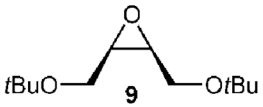
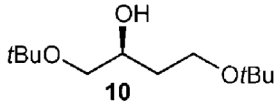
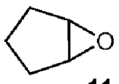
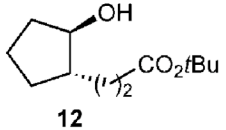
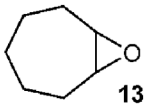
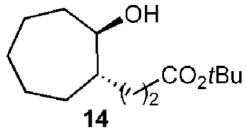


cat, mol % cat	yield [%]	(*R*):(*S*)
5, 10	51	76:24
6, 10	74	3:97
7, 5	65	3.5:96.5

Catalyst	Substrate	Product	Yield [%], ee [%]
7 [5a]	 **7**	 **8**	60, 92[b]
7	 **9**	 **10**	68, 74[c]
7 [5a]	 **11**	 **12**	69, 73[b], [e]
7 [5a]	 **13**	 **14**	60, 82[c], [f]
6	**7**	**8**	70, 91[c]
6	**9**	**10**	66, 86[b]
6	**11**	**12**	72, 81[b],[e]
6	**13**	**14**	78, 80[d], [f]

[a] 5 mol % catalyst.
[b] By GC on an Ivadex 7/OV 1701; G/294 column.
[c] By GC on a heptakis(2,6-di-*O*-methyl-*O*-pentyl)-*β*-cyclodextrin/OV 1701 (1/4) column.
[d] By GC of the corresponding trifluoroacetate on a heptakis(2,6-di-*O*-methyl-*O*-pentyl)-*β*-cyclodextrin/OV 1701 (1/4) column.
[e] ds > 96:4.
[f] ds = 87:13 for both catalysts.

A. Gansäuer, H. Bluhm, T. Lauterbach, *Adv. Synth. Catal.* **2001**, *343*, 785

Conclusion

Cp_2TiCl is a mild reducing agent for pinacol and epoxide opening reactions.

Opposite chemoselectivity to nucleophilic epoxide opening.

Reagent controlled enantioselective modifications to the Ti(III) reagent now emerging.

A wide range of functional groups are tolerated.

The oxidation/reduction of reagents and substrates can have significant effect on success of reaction.

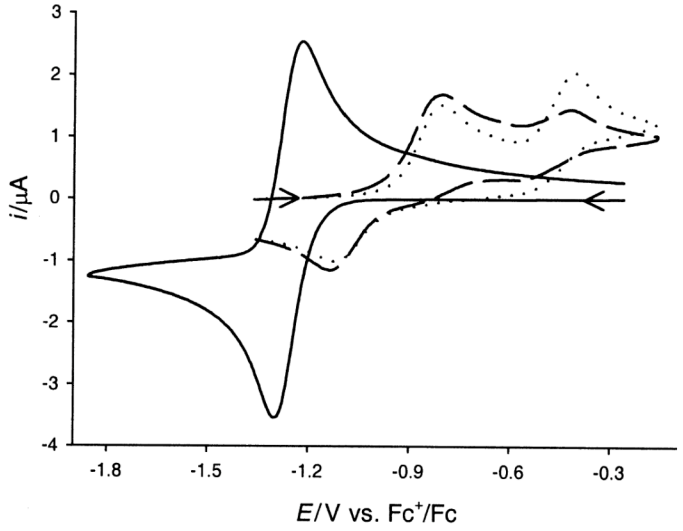


Figure 2. Cyclic voltammograms of three different titanocene chlorides (2 mM) recorded in 0.2 M Bu_4NPF_6/THF at a glassy carbon electrode (∅ = 1 mm) at a sweep rate of 0.1 $V \cdot s^{-1}$: Cp_2TiCl_2 (—), Cp_2TiCl_2/Zn (·····), Cp_2TiCl_2/Mn (– –). The arrows indicate the starting point and direction of the sweeps.

T. Skrydstrup, *Chemistry*, **2001**, 435

Entry	Equivalents of HMPA vs. SmI_2[a]	Oxidation Potential, V[b]	ΔE, V (kcal)
1	0	-1.33	0
2	1	-1.43	0.10 (2.3)
3	2	-1.46	0.13 (3.0)
4	3	-1.95	0.62 (14.0)
5	4	-2.05	0.72 (16.6)
6	5	-2.05	0.72 (16.6)
7	6	-2.05	0.72 (16.6)

a) concentration of SmI_2 = 0.5 mM. b) vs. $Ag/AgNO_3$ reference electrode in THF.

R. Flowers, *Tetrahedron Lett.* **1997**, 1137

	E° reduction potential	
Li--Li^+ + e	3.05	Ti(IV) --> Ti(II)
Na--Na^+ + e	2.71	
Mg --> Mg^{2+} + 2e	2.37	
Al --> Al^{3+} + 3e	1.66	Ti(IV) --> Ti(III)
Mn --> Mn^{2+} + 2e	1.18	
Zn --> Zn^{2+} + 2e	0.76	
Fe --> Fe^{2+} + 2e	0.44	Ti(III) + MCl_x --> Ti(IV) + M
Ni --> Ni^{3+} + 3e	0.25	

D. Sekutowski, Low Valent Organometallic Titanium Compounds, Dissertation, UIUC, 1975