Literature presentation

By Hu, Gang

Feb. 3, 2006

Application of Titanium BINOLate In Asymmetric 1,3-Dipolar Cycloaddition

Asymmetric 1,3-Dipolar Cycloaddition Reaction of Nitrones and Acrolein with a Bis-Titanium Catalyst as Chiral Lewis Acid

Taichi Kano, Takuya Hashimoto, and Keiji Maruoka*

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Enantioselective 1,3-Dipolar Cycloaddition Reaction between Diazoacetates and r**-Substituted Acroleins: Total Synthesis of Manzacidin A**

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J. Am. Chem. Soc. **ASAP**

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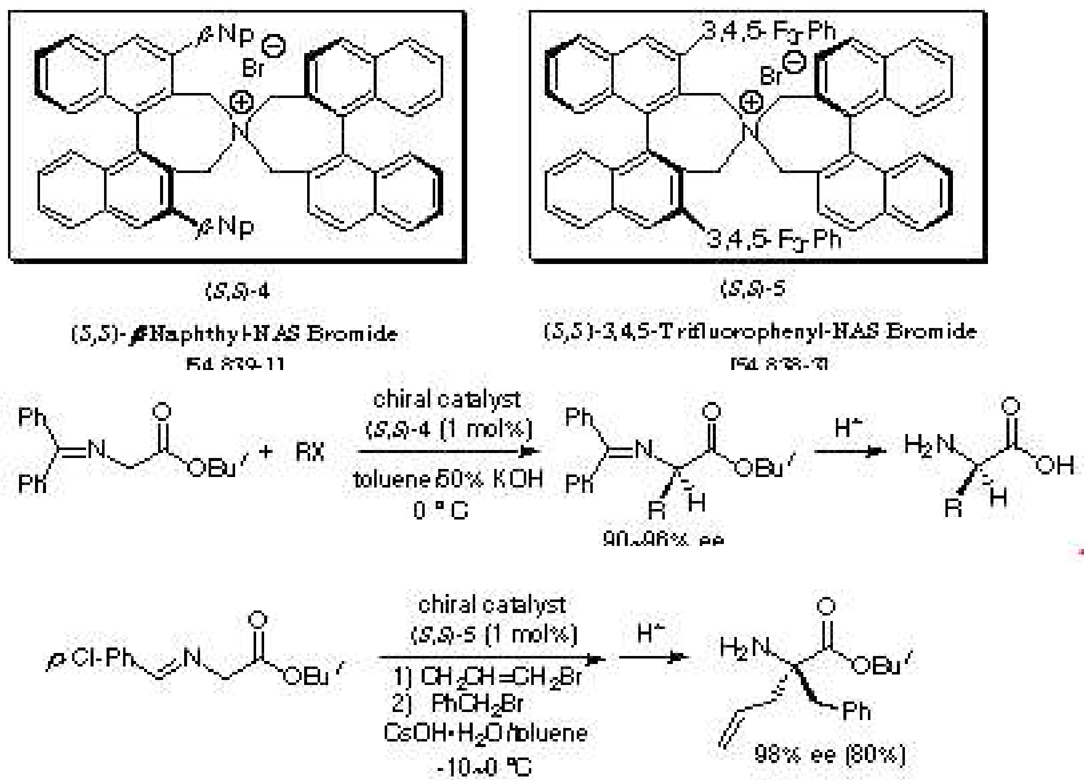
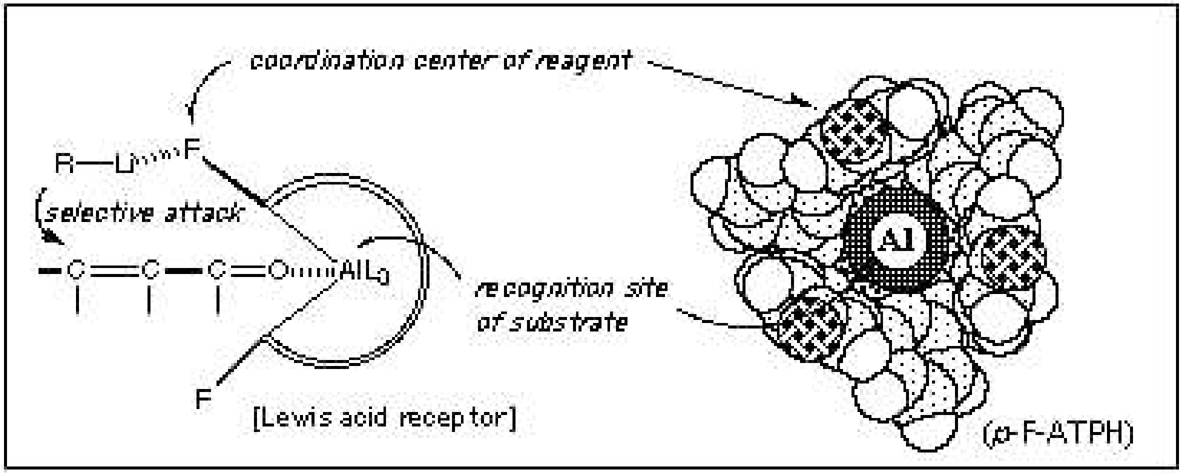
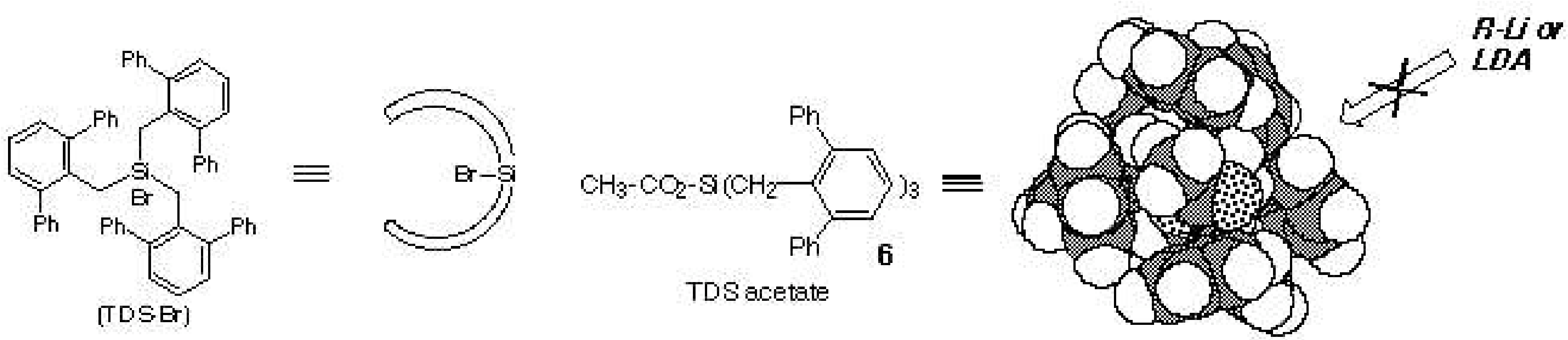
Environmentally-Benign Organic Syntheisis



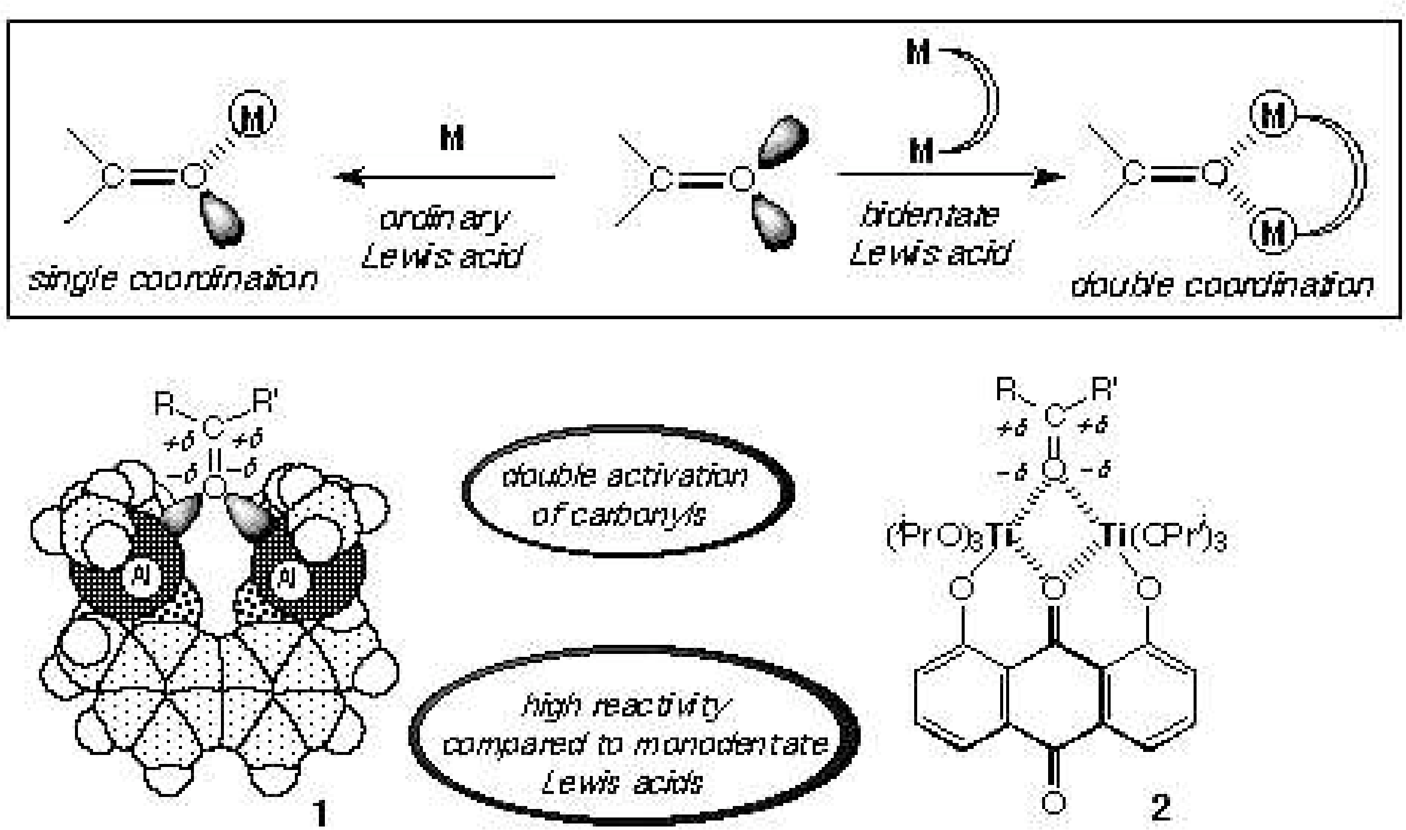
http://kuchem.kyoto-u.ac.jp/yugo/maruoka-hp/maruoka/maruoka.html

Bowl-Shaped Artificial Enzymes and their Synthetic Utility





Bidentate Lewis Acid Chemistry



Asymmetric 1,3-Dipolar Cycloaddition Reaction of Nitrones and Acrolein

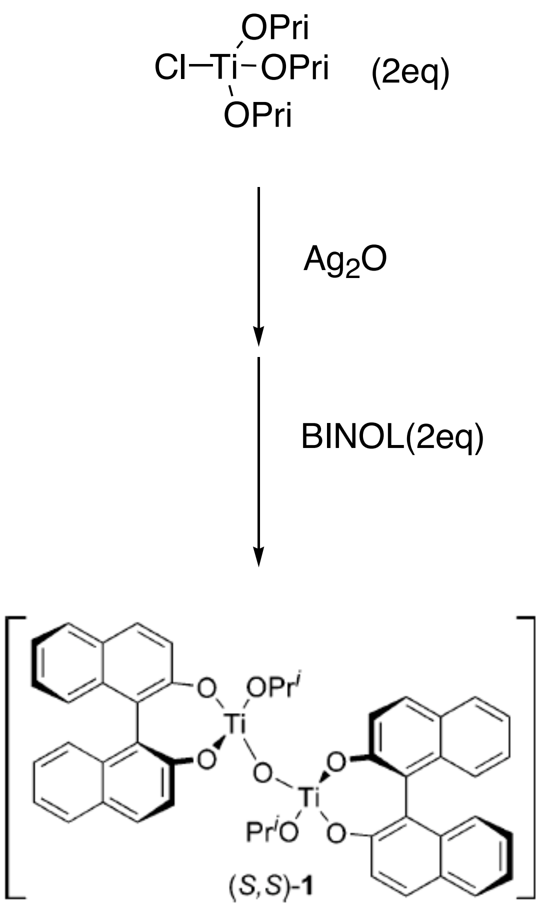
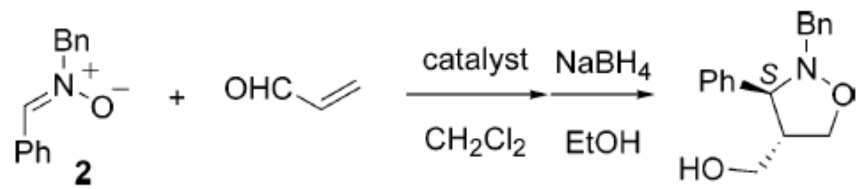


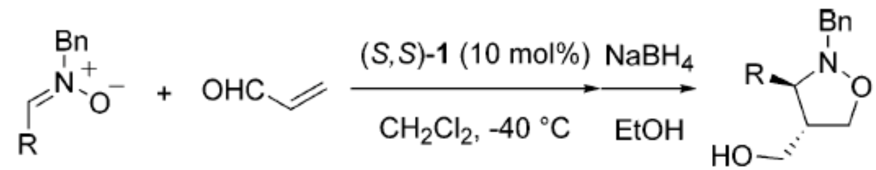
Table 1. Asymmetric 1,3-Dipolar Cycloaddition between Nitrone **2** and Acrolein[a]

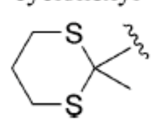


entry	catalyst	(mol %)	conditions (°C, h)	yield (%)[b,c]	ee (%)[d] [config][e]
1	(*S*,*S*)-**1**	10	0, 2	78	89 [*S*]
2	$Ti(Oi\text{-}Pr)_4$ (*S*)-BINOL	20	0, 2	40	60 [*S*]
3	$ClTi(Oi\text{-}Pr)_3$ (*S*)-BINOL	20	0, 2	36	60 [*S*]
4	(*S*,*S*)-**1**	10	−20, 17	90	91 [*S*]
5	(*S*,*S*)-**1**	10	−40, 24	94	93 [*S*]

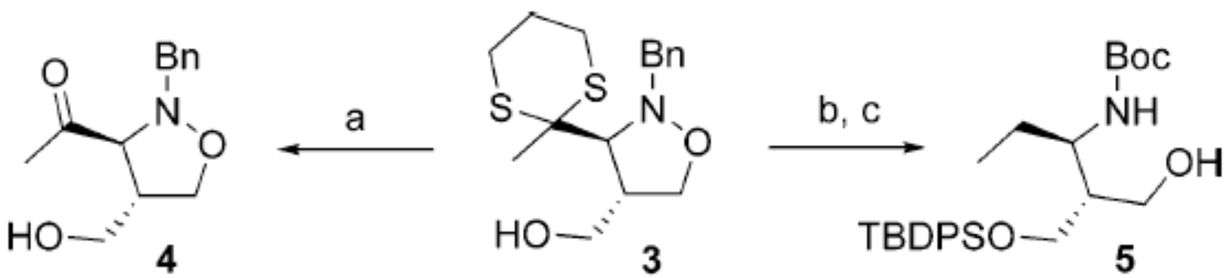
[a] The reaction of nitrone **2** and acrolein (1.5 equiv) was carried out in the presence of chiral bis-Ti(IV) oxide (*S*,*S*)-**1** or chiral mono-Ti(IV) in CH_2Cl_2. [b] Isolated yield. [c] Only the endo isomer was detected by ^{1}H NMR spectroscopy. [d] Determined by HPLC analysis using chiral column (Chiralpak OD-H, Daicel Chemical Industries, Ltd.). [e] Determined by comparison of the sign of optical rotation with the reported value.[5a]

Table 2. Asymmetric 1,3-Dipolar Cycloadditions between Nitrones and Acrolein[a]

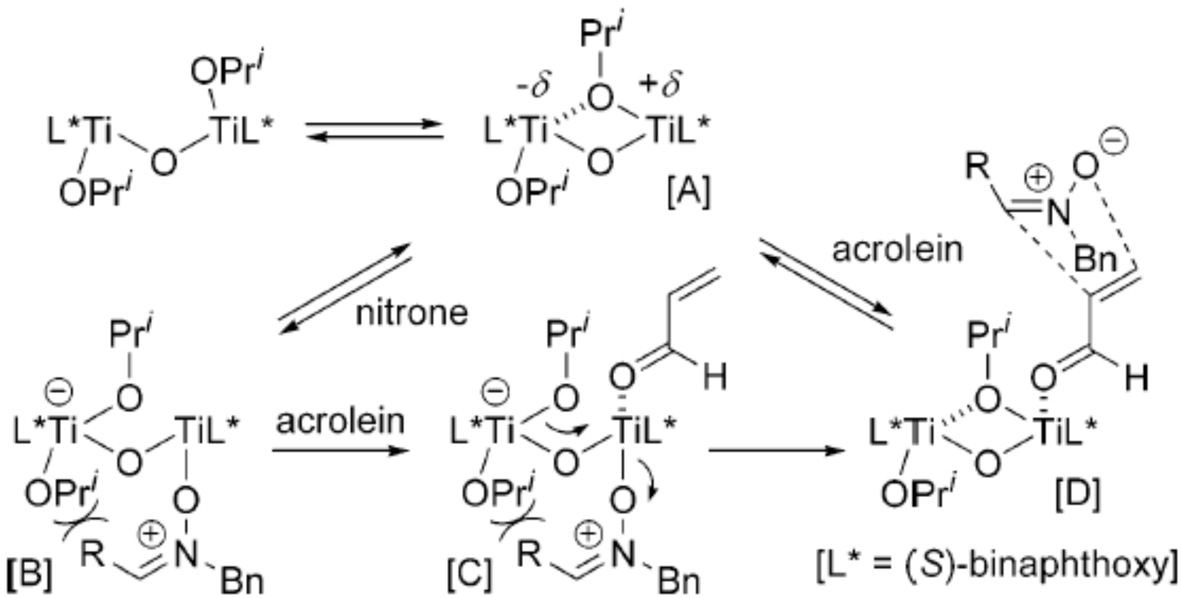


entry	R	time (h)	yield (%)[b,c]	ee (%)[d]
1	Ph	24	94	93
2	4-MePh	24	81	94
3	4-MeOPh	40	76	88
4	4-ClPh	39	85	88
5	2-naphthyl	24	92	93
6	*t*-Bu	14	90	97
7	cyclohexyl	24	62	70
8		24	86	97

Scheme 1



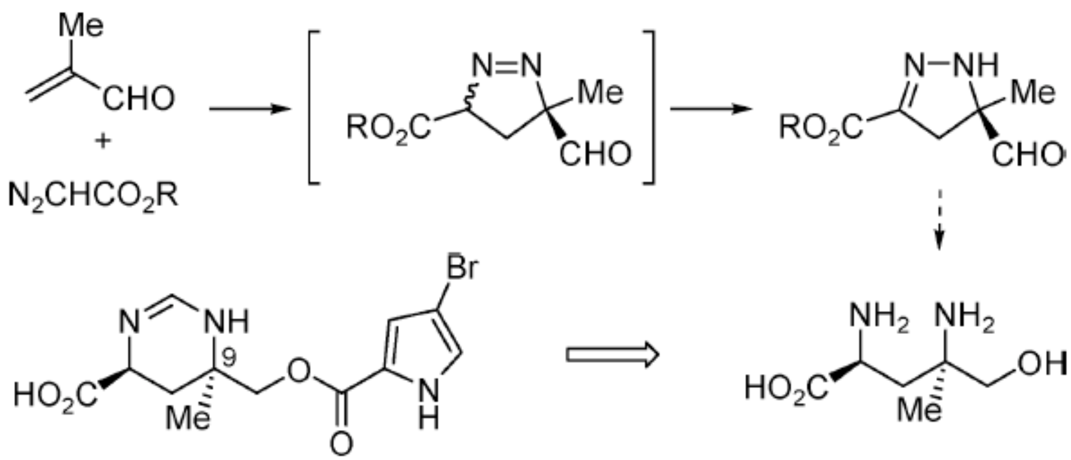
(a) HgO, $HgCl_2$, CH_3CN, 75%; (b) TBDPSCl, Et_3N, DMAP, CH_2Cl_2;
(c) Raney Ni, $(Boc)_2O$, *i*-PrOH, H_2, 46% (2 steps).



L*Ti
OPr^i
TiL*
O
Pr^i
-δ
+δ
[A]
R
O
N
Bn
acrolein
nitrone
H
[B]
[C]
[D]
[L* = (S)-binaphthoxy]

Enantioselective 1,3-Dipolar Cycloaddition Reaction between Diazoacetates and r-Substituted Acroleins

Scheme 1

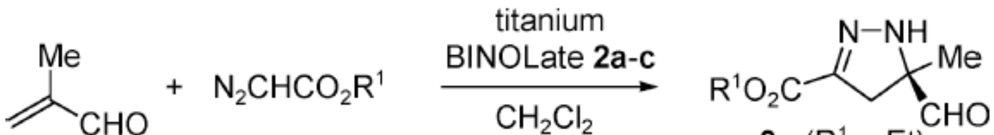


1a manzacidin A
1b manzacidin C (C9 epimer)

Isolated from Okinawan sponge:

Hymeniacidonsp

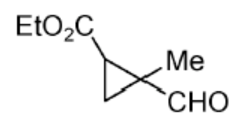
Table 1. Enantioselective 1,3-Dipolar Cycloaddition between Alkyl Diazoacetates and Methacrolein[a]



3a (R[1] = Et)
3b (R[1] = *t*-Bu)

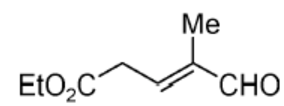
entry	R[1]	catalyst (mol %)	conditions (°C, h)	yield (%)[b]	ee (%)[c]
1	Et	–	rt, 40	16	
2	Et	**2a** (10)	0, 1	–	
3	Et	**2a** (10)	−40, 4	42	88
4	Et	**2b** (10)	−40, 2	54	90
5	Et	**2c** (5)	−40, 3	52	95
6	*t*-Bu	**2b** (10)	−40, 1	52	91
7	*t*-Bu	**2c** (5)	−40, 1	43	94

[a] Reactions were performed with methacrolein (1.0 mmol) and alkyl diazoacetates (1.5 mmol) in the presence of a chiral titanium catalyst in CH_2Cl_2. [b] Isolated yield. [c] Determined by chiral HPLC analysis after reduction of the aldehyde.



4

37%



5

11%

2a: (S)-BINOL/Ti(OPr^i)$_4$ (1:1)

2b: (S)-BINOL/Ti(OPr^i)$_4$ (2:1)

2c:

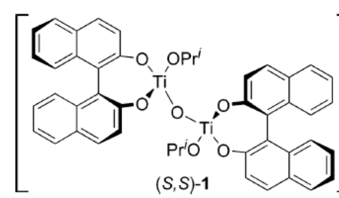
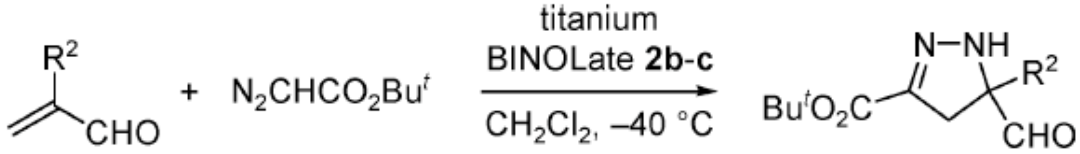


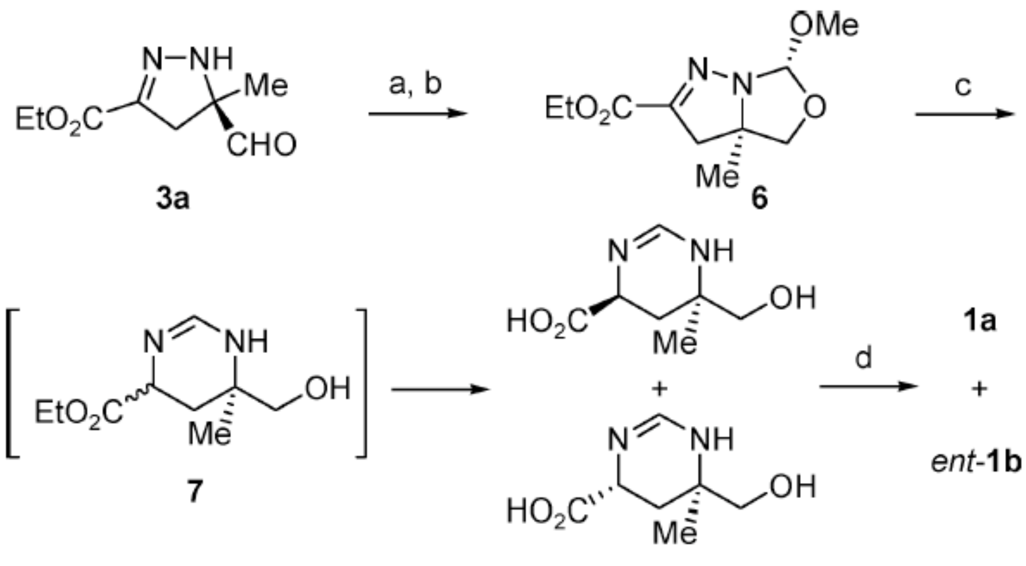
Table 2. Enantioselective 1,3-Dipolar Cycloaddition between *tert*-Butyl Diazoacetate and α-Substituted Acroleins[a]



entry	R^2	catalyst (mol %)	time (h)	yield (%)[b]	ee (%)[c]
1	Me	**2b** (10)	1	52	91[d]
2	Me	**2c** (5)	1	43	94[d]
3	Et	**2b** (10)	3	63	83
4	Et	**2c** (5)	3	48	84
5	$BnOCH_2CH_2$	**2b** (10)	1	81	80
6	$PhCH_2CH_2$	**2b** (10)	4	63	82
7	*i*-Pr	**2b** (10)	3	82	92
8	Cy	**2b** (10)	5	77	94
9	Cy	**2c** (5)	5	75	94

[a] Reactions were performed with α-substituted acroleins (1.0 mmol) and *tert*-butyl diazoacetate (1.5 mmol) in the presence of a chiral titanium catalyst in CH_2Cl_2. [b] Isolated yield. [c] Determined by chiral HPLC analysis. [d] Determined by chiral HPLC analysis after reduction of the aldehyde.

Scheme 2. Total Synthesis of Manzacidin A[a]



[a] Conditions: (a) $NaBH_4$, EtOAc, 73%; (b) PPTS, $HC(OMe)_3$, 89%; (c) Raney-Ni, H_2, $^{i}PrOH/H_2O$; (d) 4-bromo-2-trichloroacetylpyrrole, NaH, DMF, 50% (two steps).