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Enantioselective iodocyclization and mercuriocyclization of γ-hydroxy-*cis*-alkenes*

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Abstract: Asymmetric iodocyclization and mercuriocyclization of γ-hydroxy-*cis*-alkenes have been established. The iodocyclization has been attained with 1.2 equiv of iodine in the presence of the catalyst system prepared from 0.3 equiv of (*R*,*R*)-salen–Co(II) complex and 0.75 equiv of NCS to produce 2-substituted tetrahydrofurans with up to 90 % ee. The mercuriocyclization has been achieved using 1.2 equiv of Hg(II) complexed with 4-(2-naphthyl)bisoxazoline (1:1 complex) in the presence of 5 equiv of K_2CO_3 and 10 equiv of MeOH to procure 2-substituted tetrahydrofurans with up to 95 % ee.

Keywords: Asymmetric iodocyclization; chiral Lewis acids; chiral Lewis bases; enantioselective mercuriocyclization; 4-(2-naphthyl)bisoxazoline.

One of the most concerned subjects in modern synthetic organic chemistry has involved the facial differentiation of olefinic double bonds. The superb facial selection has led to the advent of asymmetric epoxidation [1], dihydroxylation [2], aminohydroxylation [3], hydrogenation [4], and hydroboration [5]. Another versatile functionalization can be effected by electrophile-mediated additions [6], in which stereochemical and regiochemical issues are raised. Since the intramolecular additions (i.e., cyclizations) often control the latter issue by geometric constraint, it is rational to explore the asymmetric cyclizations in preference to the intermolecular additions. The asymmetric cyclizations can be carried out by substrate- or reagent-controlled approach. While most have employed the former, the latter has been rarely examined. In principle, the latter approach can be attained by using either chiral electrophile or achiral one in the presence of chiral catalyst. The related representatives comprise phenylselenocyclization with chiral selenium reagents [7], iodocyclization of bidentate substrates with iodine in the presence of chiral Ti(IV) tartrate [8], chlorohydroxylation with Pd(II)–BINAP complexes [9], iodolactonization with iodonium-dihydroquinine complexes [10], and oxymercuration of chiral Hg(II) carboxylates [11]. It is significant and intriguing to contrive chiral electrophiles to comprehend halonium and Hg(II) cation. In this paper, we describe enantioselective electrophile-promoted cyclizations of γ-hydroxy-*cis*-alkenes using iodonium ion with chiral Lewis acids and Hg(II) ion with chiral Lewis bases.

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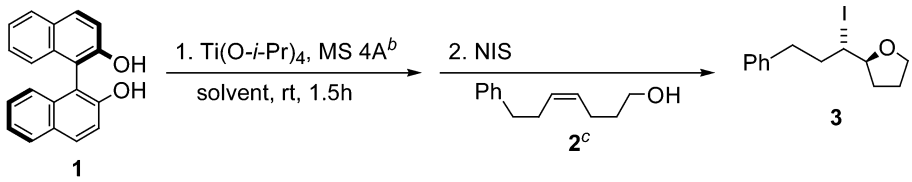
For our proposed asymmetric iodocyclization, we planned to engender chiral iodonium cation in situ by disposing chiral Lewis acid around the corresponding electrophile, which was conceived to relay the imposed chiral environment to substrate. In addition, the cyclization with the generated chiral iodonium reagent should exceed the background reaction to attain high enantioselectivity as well as a catalytic process. After assaying various chiral Lewis acids, (*R*)-BINOL–Ti(IV) complex was evaluated to show encouraging reactivity [12]. A model substrate **2** was cyclized with *N*-iodosuccinimide (NIS) in the presence of the complex, the optimal amount of which was determined as 0.2 equiv. The results in Table 1 indicated that ethereal solvents induced higher stereoselectivity probably in part due to the retarded background reaction. While the best cyclization in terms of stereoselectivity and reactivity was obtained in *t*-BuOMe at 0 °C, lowering the reaction temperature or using I_2 instead of NIS deteriorated the cyclization (entries 5–7).

Table 1 Iodocyclization of **2** in the presence of (*R*)-BINOL–Ti(IV) complex[a].



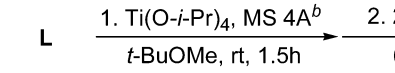
1 **2**[c] **3**

entry	solvent	reaction temp(°C)	reaction time(h)	% yield(sm)	% ee[d,e]
1	PhMe	0	1.5	94	31[f]
2	CH_2Cl_2	–20	2	87	31[f]
3	Et_2O	0	7	86	57
4	*t*-BuOMe	rt	2	90	59
5	*t*-BuOMe	0	9	94	65
6	*t*-BuOMe	–20	9	24(71)	47
7[g]	*t*-BuOMe	0	9	40(45)	9

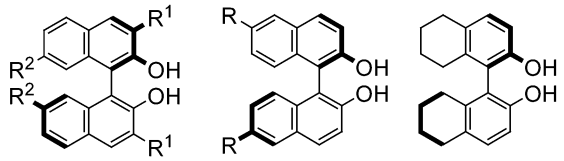
[a]0.2 Equiv of **1**, 0.2 equiv of Ti(O-*i*-Pr)$_4$ and 1.2 equiv of NIS were used. [b]10 Mg per 3 mg of Ti(O-*i*-Pr)$_4$ was added. [c][**2**] = 26.4 mM. [d]Determined by HPLC analysis using DAICEL OD. [e]For determination of absolute configuration, see reference 14. [f]Major product was enantiomer of **3**. [g]I_2 was used instead of NIS.

The catalytic activity of BINOL–Ti(IV) complex was perceived to depend on the amount of molecular sieve and its pore size greatly. 4 Å Molecular sieve (MS 4A) was superior to 3 Å and 5 Å species. Also, the cyclization was affected by concentrations of the reagents. Under the optimized reaction conditions to use 10 mg of MS 4A per 3 mg of Ti(O-*i*-Pr)$_4$ and 52.8 mM concentration of **2**, the cyclization was completed within 3 h to afford tetrahydrofuran **3** in 93 % yield and 65 % ee. In order to search for a better ligand, several Binol derivatives **4**–**8** were synthesized and applied to the reaction as chiral ligands. The experimental data in Table 2 disclose that the best was acquired with (*R*)-BINOL itself (entry 1). The aforementioned optimized iodocyclization conditions were employed for several γ-hydroxyalkenes **9**–**14** as depicted in Table 3. Their enantioselectivities were inferior to that from **2**, and the sterically least demanding ethylalkene **11** gave the lowest (entry 4). When (*R*)-BINOL–Ti(IV) complex was switched with [(*R*)-Binol]$_2$–Ti(IV) complex, the iodocyclization proceeded with the similar level of stereoselectivity and reactivity.

Table 2 Iodocyclization of **2** using Ti(IV) complexed with **4**–**8**[a].



entry	L	% yield(sm)	% ee
1	**1**	93	65
2	**4**	17(70)	12[d]
3	**5**	71(20)	17
4	**6**	90	53
5	**7**	86	26
6	**8**	43(39)	3[d]



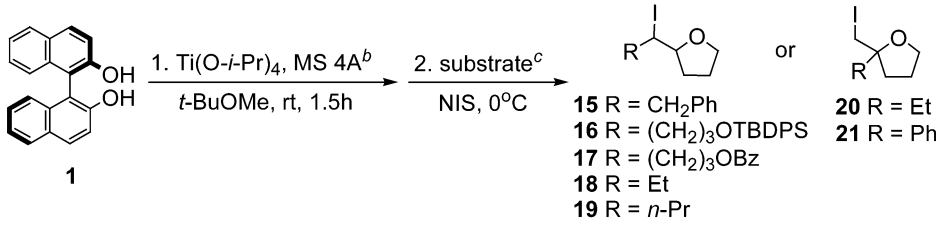
4 R^1 = Br R^2 = H
5 R^1 = H R^2 = OMe

6 R = Ph
7 R = Br

8

[a]0.2 Equiv of **2**, 0.2 equiv of Ti(O-*i*-Pr)$_4$ and 1.2 equiv of NIS were used. [b]10 mg per 3 mg of Ti(O-*i*-Pr)$_4$ was added. [c][**2**] = 52.8 mM. [d]Major product was enantiomer of **3**.

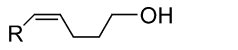
Table 3 Iodocyclization of **9**–**14** using (*R*)-BINOL–Ti(IV) complex[a].



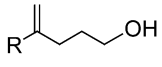
1

15 R = CH_2Ph
16 R = $(CH_2)_3OTBDPS$
17 R = $(CH_2)_3OBz$
18 R = Et
19 R = *n*-Pr

20 R = Et
21 R = Ph



9 R = CH_2Ph
10 R = $(CH_2)_3OTBDPS$
11 R = Et
12 R = *n*-Pr



13 R = Et
14 R = Ph

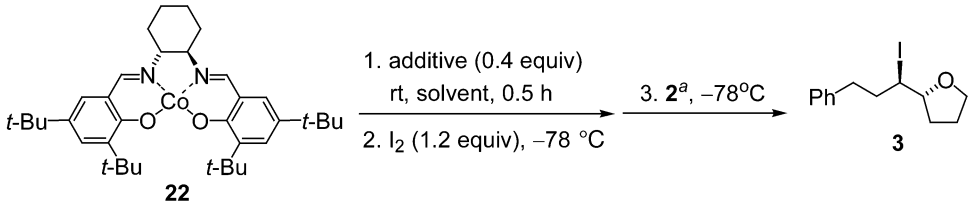
entry	substrate	reaction time(h)	product	% yield	% ee
1	**2**	3	**3**	93	65
2	**9**	18	**15**	89	31[d]
3	**10**	6	**16**	84	21[e]
4	**11**	3	**18**	90	13[f]
5	**12**	4	**19**	95	28[f]
6	**13**	2	**20**	89	20[f]
7	**14**	10	**21**	82	34[g]

[a]0.2 Equiv of **1**, 0.2 equiv of Ti(O-*i*-Pr)$_4$ and 1.2 equiv of NIS were used. [b]10 Mg per 3 mg of Ti(O-*i*-Pr)$_4$ was added. [c][substrate] = 52.8 mM. [d]Determined by HPLC analysis using DAICEL OD-H. [e]Determined by HPLC analysis of **17** using DAICEL OD. [f]Determined by GC analysis using CHIRALDEX B-DM. [g]Determined by HPLC analysis using DAICEL OD.

Another promising catalytic system could be derived from iodine and salen-metal complex couples [13]. After screening various salen complexes, (*R*,*R*)-salen–Co(II) complex **22** was estimated as the prospective Lewis acid. The asymmetric iodocyclization of **2** was performed using iodine in the presence of (*R*,*R*)-salen–Co(II) complex **22**. The outcomes are outlined in Table 4. The cyclization was completed with a catalytic amount of **22** rather than an equivalent quantity without any stereoinduction (entries 2, 3). Stereochemical amelioration was intended with several additives. While NCS enhanced the enantioselectivity considerably, NIS was not effective at all (entries 6–8). Even higher stereoselectivity was observed in toluene than in CH_2Cl_2, conceivably in part due to the slower background reaction in toluene (entries 1, 9). The most remarkable achievement was obtained with 1.2 equiv of I_2 in the presence of 0.3 equiv of **22** and 0.75 equiv of NCS in toluene (entry 10). Compromise between the maximum conversion and the minimal background reaction led to the optimized amount (1.2 equiv) of I_2.

Since the enantioselectivity was affected by concentration, the concentration effect was examined to get the highest % ee with 10.5 mM concentration of **2** (entry 11).

Table 4 Iodocyclization of **2** using (*R,R*)-salen–Co(II) complex **22** with additives.



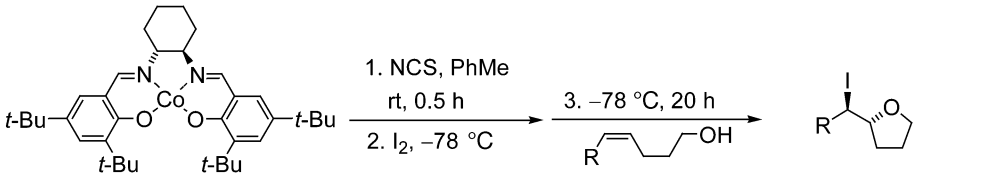
22

entry	equiv of **22**	additive	solvent	% yield (sm)	% ee
1	–	–	CH_2Cl_2	32 (63)	–
2[b]	1.0	–	CH_2Cl_2	13 (84)	0
3[b]	0.2	–	CH_2Cl_2	82	0
4	0.2	Ph_3PO	CH_2Cl_2	60 (21)	5
5	0.2	4-PPNO[c]	CH_2Cl_2	57 (26)	0
6	0.2	NCS	CH_2Cl_2	70 (16)	50
7	0.2	NCS	PhMe	73 (11)	76
8	0.2	NIS	PhMe	32 (47)	0
9	–	–	PhMe	16 (79)	–
10	0.3	NCS[d]	PhMe	89	83
11[e]	0.3	NCS[d]	PhMe	89	86

[a][**2**] = 15.8 mM. [b]1.5 Equiv of I_2 was used. [c]4-PPNO = 4-phenylpyridine N-oxide. [d]0.75 Equiv of NCS was used. [e][**2**] = 10.5 mM.

γ-Hydroxy-*cis*-alkenes **2**, **11**, **12**, and **23**–**26** were subjected to the iodocyclization under the developed conditions. When the reaction was scaled up from 0.1 to 0.4 mmol, the stereoselectivity was reduced by a few % ee with one portion addition of **2**, but the small discrepancy could be surmounted by syringe pump-driven addition of **2** over 8 h. All the substrates **2**, **11**, **12**, and **23**–**26** were cyclized by the slow addition method to reach good to excellent stereoinduction as summarized in Table 5. The relatively lower enantioselectivity was observed with the sterically least encumbered methylketone **24** and the branched isopropylketone **25** (entries 3, 6).

Table 5 Iodocyclization using (*R,R*)-salen–Co(II) **22** with NCS[a,b].



22

23 R = $(CH_2)_3Ph$
24 R = Me
11 R = Et
12 R = *n*-Pr
25 R = *i*-Pr
26 R = $(CH_2)_3OTr$

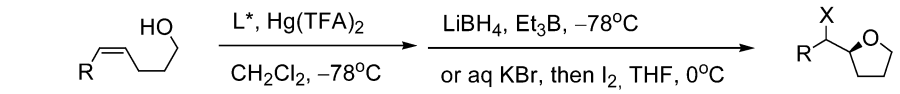
27 R = $(CH_2)_3Ph$
28 R = Me
18 R = Et
19 R = *n*-Pr
29 R = *i*-Pr
30 R = $(CH_2)_3OTr$
31 R = $(CH_2)_3OBz$

entry	substrate	product	% yield	% ee[c]
1	**2**	**3**	94	86
2	**23**	**27**	94	84[d]
3	**24**	**28**	96	67[e,f]
4	**11**	**18**	89	82[e,f]
5	**12**	**19**	85	85[e]
6	**25**	**29**	83	73[e]
7	**26**	**30**	89	90[g]

[a]0.3 Equiv of **22**, 0.75 equiv of NCS and 1.2 equiv of I_2 were used. [b]Substrate was added over 8 hours using a syringe pump. [c]For determination of absolute configuration, see reference 13. [d]Determined by HPLC analysis of reductively deiodinated product of **27** using Regis Welk-O1 (*R,R*). [e]Determined by GC analysis using CHIRALDEX B-DM. [f]The absolute configuration was not determined. [g]Determined by HPLC analysis of **31** using DAICEL OD.

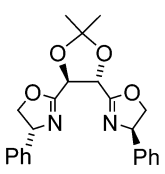
If chiral Hg(II) reagent can be devised, the electrophile also will be of great value and complementary in the asymmetric cyclization. The chiral reagent was designed by complexing Hg(II) ion with chiral Lewis base. For higher asymmetric induction, Hg(II) ion in the complex should be hold tightly for minimal racemic process and transferred to olefinic double bond readily for efficient cyclization. After testing several ligand–solvent systems, bisoxazolines and CH_2Cl_2 were determined adaptable [14]. Since tartrate-derived 4-phenylbisoxazolines among bisoxazolines were found more promising, substrates **2** and **10**–**12** were subjected to intramolecular mercurioetherification using the bisoxazolines **36**–**39**, and the produced organomercurials were reductively demercurated or iodinated. The outcomes in Table 6 suggest that (*R*)-3-phenylglycinol was matched with L-tartrate, but not with D-tartrate (entries 1, 2). L-Tartrate-derived bisoxazolines **37**–**39** provided the encouraging enantioselectivity. In addition, the stereoselectivity could be improved to some extent by varying the ketone-protecting group (entries 2, 3, 7). Inferior stereoinduction was observed with alkyl chain-containing substrates **11** and **12** (entries 5, 6).

Table 6 Mercuriocyclization using tartrate-derived bisoxazoline (L*)–Hg(II) complexes.

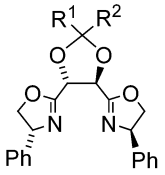


2 R = $(CH_2)_2$Ph
10 R = $(CH_2)_3$OTBDPS
11 R = Et **12** R = *n*-Pr

32 X = H, R = $(CH_2)_2$Ph
33 X = H, R = $(CH_2)_3$OTBDPS
34 X = I , R = Et **35** X = I , R = *n*-Pr



36



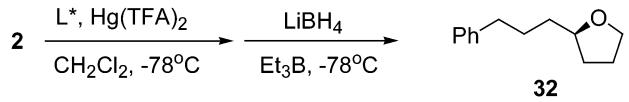
37 R^1, R^2 = Me
38 R^1, R^2 = *n*-Bu
39 R^1, R^2 = Me, Et

entry	substrate	L*	% yield[a]	% *ee*
1	**2**	**36**	73(**32**)	26[b]
2	**2**	**37**	75(**32**)	76[b]
3	**2**	**38**	77(**32**)	80[b]
4	**10**	**38**	75(**33**)	80[b]
5	**11**	**38**	84(**34**)	51[c,d]
6	**12**	**38**	80(**35**)	59[c,d]
7	**2**	**39**	77(**32**)	82[b]

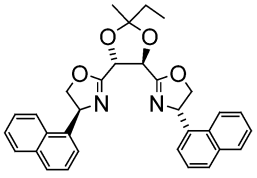
[a]Major product in parenthesis. [b]Determined by HPLC analysis using Regis Whelk-O1 (*R*,*R*) and DAICEL OD-H. [c]Determined by GC analysis using CHIRALDEX B-DM. [d]The absolute configuration was not determined.

To improve the enantioselective mercuriocyclization of **2** further, 4-naphthylbisoxazolines **40** and **41** having a methyl ethyl ketal-protecting group were prepared. The cyclization data in Table 7 indicate that 4-(2-naphthyl)bisoxazoline **41** was superior to 4-(1-naphthyl)bisoxazoline **40** (entries 1, 2). Addition of K_2CO_3 and MeOH enhanced the stereoselectivity even more. The mercuriocyclization of the substrates **11**, **12**, **24**–**26**, **42**, and **43** were implemented under the established reaction conditions to provide remarkable results presented in Table 8. Even alkyl chain-containing substrates **11**, **12**, **24**, **25**, and **43** were cyclized with excellent enantioselectivity.

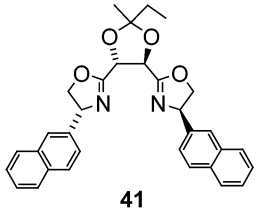
Table 7 Mercuriocyclization of **1** using 4-naphthylbisoxazoline (L*)–Hg (II) complexes.



32



40

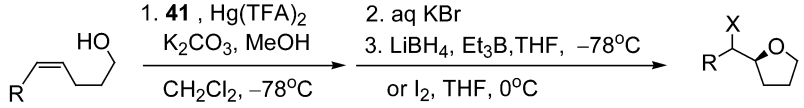


41

entry	L*	% yield	% *ee*
1	**40**	74	74
2	**41**	75	90
3[a]	**41**	75	95

[a]5.0 Equiv of K_2CO_3 and 10 equiv of MeOH were added.

Table 8 Mercuriocyclization using bisoxazoline **41**–Hg(II) complex (1.2 equiv) in the presence of K_2CO_3 (5 equiv) and MeOH (10 equiv).



26 R = $(CH_2)_3OTr$
42 R = $(CH_2)_2OTBDPS$
24 R = Me
25 R = *i*-Pr
43 R = *i*-Bu

44 X = H, R = $(CH_2)_3OTr$
45 X = H, R = $(CH_2)_2OTBDPS$
46 X = I, R = Me
47 X = I, R = *i*-Pr
48 X = I, R = *i*-Bu

entry	substrate	product	% yield[a]	% *ee*	entry	substrate	product	% yield[a]	% *ee*
1	**2**	**32**	75(9)	95	5	**11**	**34**	88(8)	90
2	**26**	**44**	72(13)	95	6	**12**	**35**	81(9)	92
3	**42**	**45**	68(20)	86	7	**25**	**47**	81(16)	89
4	**24**	**46**	76[b]	86	8	**43**	**48**	86(12)	91[c]

[a]Percentage of recovered sm in parentheses. [b]Due to its volatility, sm was not recovered. [c]The absolute configuration corresponds to the reductively deiodinated product of **48**.

In conclusion, we have developed highly enantioselective iodocyclization and mercuriocyclization of γ-hydroxy-*cis*-alkenes to form 2-substituted tetrahydrofurans with up to 90 and 95 % ee by the unprecedented catalyst system generated from (*R*,*R*)-salen–Co(II) complex and NCS, and the novel tartrate-derived 4-(2-naphthyl)bisoxazoline, respectively.

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