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Catalytic Enantioselective Iodocyclization of γ-Hydroxy-*cis*-alkenes

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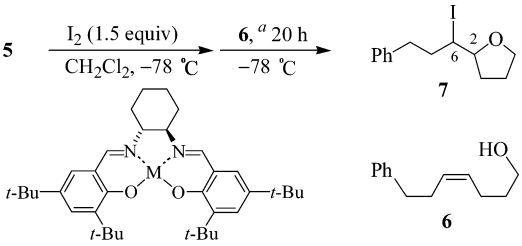
Electrophile-promoted cyclizations belong to one of the most frequently practiced organic transformations in heterocyclic chemistry, which can be extended to the useful functionalization of olefinic double bonds.[1] Although extensive efforts have been made to explore these cycloadditions under a variety of conditions, their enantioselective version has been rarely investigated. The stereoselective electrophile-mediated cyclizations have been mostly limited to the substrate-controlled intramolecular cyclization.[2] In recent years, chiral selenium reagents have been designed to consummate the asymmetric reagent-controlled intramolecular selenocyclization, albeit relatively impractically.[3] Other reported asymmetric cycloadditions have been implemented through iodolactonization with iodonium ion−chiral amine complexes,[4] iodocyclization of bidentate substrates with iodine in the presence of chiral Ti(IV) alkoxide,[5] chlorohydroxylation with Pd(II)−BINAP complex,[6] and oxymercuration with chiral Hg(II) carboxylates[7] or Hg(II)−bisoxazoline complexes.[8] It is challenging to devise chiral electrophiles comprising especially halonium and Hg(II) cations. Furthermore, the reagents are usually required in excess amounts to complete corresponding iodocyclizations. Therefore, it is of great value and significance to develop catalytic asymmetric iodocyclization. In this communication, we report our interim results of catalytic enantioselective intramolecular iodoetherification of γ-hydroxy-*cis*-alkenes using chiral salen−Co complexes to form 2-substituted tetrahydrofurans.

To effect our proposed asymmetric iodocyclization, it is imperative to impose a chiral environment around the iodonium cation, which should be transmitted to substrate ultimately. Besides, the generated chiral iodonium reagent should be more activated to secure higher enantioselectivity by suppressing background cyclization in a relative sense. After screening various combination of iodonium reagents, and Lewis acids or bases as activators as well as chirality providers, iodine and salen−metal complex couples were found promising. Representative examples are described in Table 1. In the absence of the complexes, iodocyclization of **6** progressed to some extent (entry 1). While the highest enantioselectivity was acquired with 1.0 equiv of (*R*,*R*)-salen−CrCl complex **4**,[9] no stereoselectivity was observed with (*R*,*R*)-salen−Co complex **1**[10] (entries 2, 3, and 8). It is noted that the major product with (*R*,*R*)-salen−FeCl complex **2**[11] is enantiomeric to those with the remaining complexes (entries 4 and 5).[10,12] Since the cyclization was driven to completion using only **1** catalytically rather than in a stoichiometric amount (entries 2 and 3), (*R*,*R*)-salen−Co complex **1** was chosen as the seeking Lewis acid.

Amelioration of the stereochemical reactivity of **1** was pursued with several additives.[13] The results are displayed in Table 2, where it can be seen that there is considerable enhancement of enantioselectivity with NCS but no effect with NIS (entries 3−5). Toluene turned out to be an even better solvent than CH_2Cl_2, probably in part due to the reduced background reaction in the former (entry 6). Optimization of the iodocyclization was elaborated by adjusting the relative amounts of the involved reagents. The most salient iodoetherification was achieved with 1.2 equiv of I_2 in the presence of 0.3 equiv of **1** and 0.75 equiv of NCS in toluene (entry 7). It was found that the longer mixing time of **1** and NCS degenerated the stereoselectivity. The amount of iodine needed was determined by the optimal compromise between the minimal background reaction and the maximum conversion. Further improvement of the stereoselectivity was explored by examining concentration effect. Among the examined concentrations (31.6, 15.8, 10.5, 7.9, 5.3 mM),

Table 1. Iodocyclization of **6** Using (*R*,*R*)-Salen−M Complexes **1**−**5**

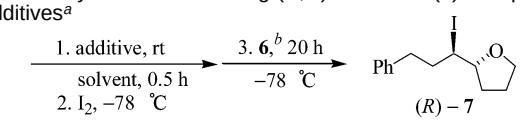


1 : M = Co **3** : M = MnCl **5** : M = $TiCl_2$
2 : M = FeCl **4** : M = CrCl

entry	(*R*,*R*)-salen–M (equiv)	% yield[c]	% ee[d,e]
1[b]	−	32 (63)	−
2	**1** (1.0)	13 (84)	0
3	**1** (0.2)	82	0
4	**2** (1.0)	57 (37)	20 (2*S*,6*S*)
5	**2** (0.2)	19 (58)	7 (2*S*,6*S*)
6	**3** (1.0)	44 (47)	42 (2*R*,6*R*)
7	**3** (0.2)	43 (37)	21 (2*R*,6*R*)
8	**4** (1.0)	57 (42)	60 (2*R*,6*R*)
9	**4** (0.2)	25 (74)	29 (2*R*,6*R*)
10	**5** (1.0)	44 (47)	20 (2*R*,6*R*)
11	**5** (0.2)	41 (53)	4 (2*R*,6*R*)

[a] [**6**] = 15.8 mM. [b] The iodocyclization was carried out with 1.2 equiv of I_2. [c] Percentage of recovered sm in parentheses. [d] Determined by HPLC analysis using DAICEL OD-H. [e] For determination of absolute configuration, see Supporting Information.

Table 2. Iodocyclization of **6** Using (*R*,*R*)-Salen−Co(II) Complex **1** with Additives[a]



entry	additive	solvent	% yield[d]	% ee
1	Ph_3PO	CH_2Cl_2	60 (21)	5
2	4-PPNO[c]	CH_2Cl_2	57 (26)	0
3	NCS	CH_2Cl_2	70 (16)	50
4	NCS	PhMe	73 (11)	76
5	NIS	PhMe	32 (47)	0
6[e]	−	PhMe	16 (79)	−
7[f]	NCS	PhMe	89	83

[a] 0.2 equiv of **1**, 0.4 equiv of additive and 1.2 equiv of I_2 were used. [b] [**6**] = 15.8 mM. [c] 4-PPNO = 4-phenylpyridine *N*-oxide. [d] Percentage of recovered sm in parentheses. [e] Iodocyclization was carried out without **1**. [f] 0.3 equiv of **1**, 0.75 equiv of NCS and 1.2 equiv of I_2 were used.

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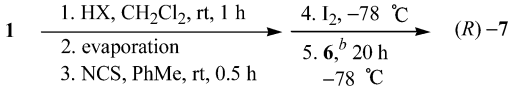
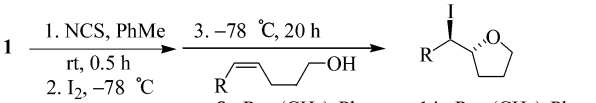
Table 3. Iodocyclization of **6** Using (*R,R*)-Salen−Co(III) Complexes[a]



entry	HX	% yield	% ee
1	−	89	86
2	$PhCO_2H$	86	40
3	$2,4,6\text{-}Me_3C_6H_2CO_2H$	89	71
4	C_6F_5OH	79	76
5	$(CF_3)_3COH$	82	84

[a] 0.3 equiv of **1**, 0.3 equiv of HX, 0.75 equiv of NCS and 1.2 equiv of I_2 were used. [b] [**6**] = 10.5 mM.

Table 4. Iodocyclization Using (*R,R*)-Salen-Co(II) **1** with NCS[a,b]



8 : R = $(CH_2)_3Ph$ **14** : R = $(CH_2)_3Ph$
9 : R = Me **15** : R = Me
10 : R = Et **16** : R = Et
11 : R = *n*-Pr **17** : R = *n*-Pr
12 : R = *i*-Pr **18** : R = *i*-Pr
13 : R = $(CH_2)_3OTr$ **19** : R = $(CH_2)_3OTr$
20 : R = $(CH_2)_3OBz$

entry	substrate	product	% yield	% ee[c]
1	**6**	(*R*)-**7**	94	86
2	**8**	**14**	94	84[d]
3	**9**	**15**	96	67[e,f]
4	**10**	**16**	89	82[e,f]
5	**11**	**17**	85	85[e]
6	**12**	**18**	83	73[e]
7	**13**	**19**	89	90[g]

[a] 0.3 equiv of **1**, 0.75 equiv of NCS and 1.2 equiv of I_2 were used. [b] Substrate was added over 8 h using a syringe pump. [c] For determination of absolute configuration, see Supporting Information. [d] Determined by HPLC analysis of reductively deiodinated product of **14** 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 **20** using DAICEL OD.

the highest enantioselectivity was attained with 10.5 mM concentration of **6**.[14]

More acidic (*R,R*)-salen−Co(III) complexes, which are speculatively formed from (*R,R*)-salen−Co(II) complex and NCS, were generated in situ from **1** with protic oxidants to explore their effectiveness on the asymmetric iodocyclization.[15] The cyclization was carried out using the complexes under the optimized reaction conditions, and the outcomes are reported in Table 3. Although the complexes prepared with 2,4,6-trimethylbenzoic acid, pentafluorophenol, and perfluoro-*tert*-butyl alcohol delivered good asymmetric induction, none of them was superior to **1** (entries 1 and 3−5).[16] Since (*R*)-**7** was produced in 11% yield and 35% ee using perfluoro-*tert*-butyl alcohol without NCS, NCS proved to be the essential additive. In a related experiment using (*R,R*)-salen−Co(III)Cl,[17] (*R*)-**7** was afforded in 79% ee but only 35% yield. In addition, the salen structure was varied by switching the two C_5- and $C_{5'}$-*tert*-butyl groups with chloro, *tert*-butoxy, phenyl, methyl, and 2,4,6-trimethylbenzyloxy groups.[18] Among the corresponding (*R,R*)-salen−Co(II) complexes, the etherification was completed with only methylsalen−Co(II) complex to give (*R*)-**7** in 83% yield and 47% ee. While little stereoselectivity was elicited with chlorosalen−Co(II) complex, the highest 57% ee was engendered with 2,4,6-trimethylbenzyloxysalen−Co(II) complex.

Iodocyclization of various γ-hydroxy-*cis*-alkenes **6**−**13** was conducted under the optimized conditions. When the reaction scale increased from 0.1 to 0.4 mmol, addition of the model substrate **6** in one portion reduced the enantioselectivity by a few percent ee. Since a little discrepancy could be surmounted by dropwise addition of **6** over 8 h, the method was also applied to the others. The experimental data shown in Table 4 reveal that remarkable enantioselectivity was realized with most of the substrates, although somewhat lower asymmetric induction was observed with the sterically least demanding methylalkene **9** and the branched isopropylalkene **12** (entries 3 and 6).[19]

In conclusion, we have developed a highly enantioselective iodocyclization of γ-hydroxy-*cis*-alkenes by unprecedented use of the catalyst system derived from (*R,R*)-salen−Co(II) complex and NCS to procure 2-substituted tetrahydrofurans up to 90% ee, which, to the best of our knowledge, is the highest reported value in the related iodocyclizations.

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Supporting Information Available: Experimental details (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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(16) To investigate the possible involvement of HCl in the cyclization, which might be generated in situ, iodocyclization of **6** was carried out using 0.15 equiv of NCS and 0.6 equiv of HCl instead of 0.75 equiv of NCS to provide (*R*)-**7** in 81% ee and 39% yield.
(17) The preparation method of (*R,R*)-salen−Co(III)Cl was gratefully provided by Mr. Sang Kyun Kim from Prof. Jacobsen's group at Harvard University. Hong, J. Ph.D. Thesis, Harvard University, Cambridge, Massachusetts, 2001.
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(19) Iodocyclization of **6** was scaled up to 2.6 mmol with comparable enantioselectivity and chemical yield (85% ee and 89% yield).

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