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Enantioselective Mercuriocyclization of γ-Hydroxy-*cis*-alkenes

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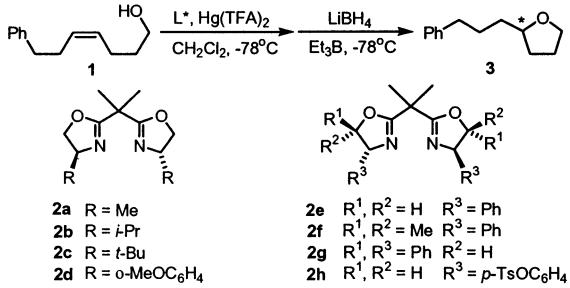
Asymmetric functionalization of olefinic double bonds is considered as the prime challenging subject in modern synthetic organic chemistry. The most reverend achievements in this area have been procured by asymmetric epoxidation,[1] dihydroxylation,[2] aminohydroxylation,[3] hydrogenation,[4] and hydroboration.[5] Another efficient installation of versatile functional groups at olefinic double bonds has been consummated by intra- and intermolecular electrophile-promoted addition reactions.[6] Most of the stereoselective addition reactions have been effected through substrate-controlled diastereoselectivity. Since reagent-controlled asymmetric addition reactions can be more efficacious and complementary, development of the corresponding version is of great value and has been arduously pursued. The reagent-controlled reactions have been mostly executed by organoselenylation using chiral selenium reagents prepared from binaphthalene,[7] ortho-substituted benzene,[8] ferrocene,[9] and camphor derivatives.[10] Other rarely explored asymmetric addition reactions comprise iodolactonization with iodonium ion−dihydroquinine complexes,[11] oxymercuration with chiral Hg(II) carboxylates,[12] chlorohydroxylation with Pd(II)−BINAP complexes,[13] and iodocyclization with iodine in the presence of chiral Ti(IV) alkoxides.[14] Among them, the last may belong to substrate-controlled version due to the probable formation of substrate−chiral Ti(IV) alkoxide complexes. Herein we describe unprecedented asymmetric mercuriocyclization using chiral bisoxazolines as ligands to form 2-substituted tetrahydrofurans with high enantioselectivity.

It was thought that a chiral environment around Hg(II) would be imposed by its complexation with chiral ligands. To achieve a high degree of enantioselectivity with the chiral complex in mercuriocyclization, its coordination bond should be not only tight enough to hold Hg(II) for minimal racemic process but also loose enough to share Hg(II) with the olefinic double bond for efficient cyclization. After screening several kinds of ligands and solvents, bisoxazolines and CH_2Cl_2 were found conformable. A model substrate **1** was subjected to 1.2 equiv of Hg(II) complexed with bisoxazolines **2a**−**h** (1:1 complexes), followed by in situ reductive demercuration[15] to give tetrahydrofuran **3**. The results are summarized in Table 1. Although the cyclization barely proceeded with 4-*tert*-butylbisoxazoline **2c** (entry 3), comparable chemical yields were obtained with others. While 4-alkylbisoxazolines **2a**−**c** resulted in lower % ee (entries 1−3), the highest % ee was attained with 4-phenylbisoxazoline **2e** (entry 4).[16] Introduction of substituent(s) into the 4-phenyl group or the 5-position of oxazoline deteriorated the enantioselectivity (entries 5−8).

Keeping the phenyl groups in bisoxazoline, its framework was switched from dimethylmalonate to tartrate. Intramolecular mercurioetherification of substrates **1** and **4**−**6** were performed using tartrate-derived bisoxazolines **2i**−**l**,[17] and the generated organomercurials were reductively demercurated or iodinated. The outcomes reported in Table 2 reveal that D-tartrate was mismatched with (*R*)-3-phenylglycinol (entry 1). L-Tartrate-derived bisoxazolines **2j**−**l** improved the enantioselectivity conspicuously. In addition, variation of the ketal protecting group affected it to some extent

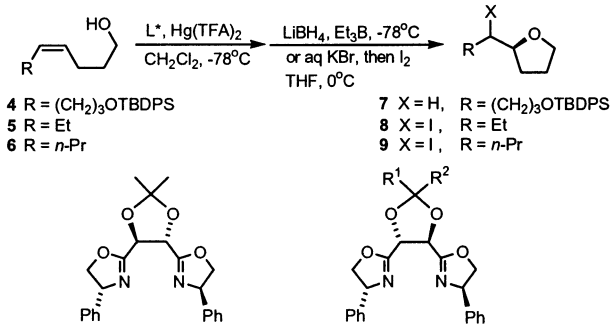
Table 1. Mercuriocyclization of **1** Using Dimethylmalonate-Derived Bisoxazoline (L*)−Hg(II) Complexes



entry	L*	% yield	% ee[b,c]
1	**2a**	76	27 (S)
2	**2b**	75	<5
3	**2c**	8[a]	<5
4	**2e**	74	65 (R)
5	**2f**	74	49 (R)
6	**2g**	76	54 (R)
7	**2h**	72	26 (R)
8	**2d**	73	18 (S)

[a] After 12 h, **1** was recovered in 88%. [b] Determined by HPLC analysis using Regis Whelk-O1 (R,R). [c] For determination of absolute configuration, see Supporting Information.

Table 2. Mercuriocyclization Using Tartrate-Derived Bisoxazoline (L*)−Hg(II) Complexes



entry	substrate	L*	% yield[a]	% ee[b]
1	**1**	**2i**	73 (**3**)	26 (*R*)[c]
2	**1**	**2j**	75 (**3**)	76 (*R*)[c]
3	**1**	**2k**	77 (**3**)	80 (*R*)[c]
4	**4**	**2k**	75 (**7**)	80 (*R*)[c]
5	**5**	**2k**	84 (**8**)	51[d,e]
6	**6**	**2k**	80 (**9**)	59[d,e]
7	**1**	**2l**	77 (**3**)	82 (*R*)[c]

[a] Major product in parentheses. [b] For determination of absolute configuration, see Supporting Information. [c] Determined by HPLC analysis using Regis Whelk-O1 (R,R) and DAICEL OD-H. [d] Determined by GC analysis using CHIRALDEX B-DM. [e] The absolute configuration was not determined.

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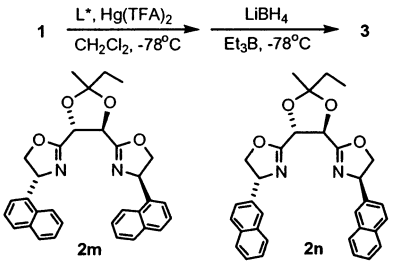
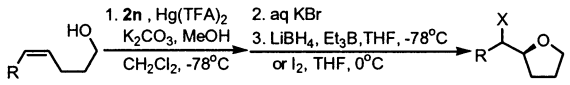
Table 3. Mercuriocyclization of **1** Using 4-Naphthylbisoxazoline (L*)−Hg(II) Complexes



entry	L*	% yield	% ee
1	**2m**	74	74 (*R*)
2	**2n**	75	90 (*R*)
3[a]	**2n**	75	95 (*R*)

[a] 5 equiv of K_2CO_3 and 10 equiv of MeOH were added.

Table 4. Mercuriocyclization Using Bisoxazoline **2n**−Hg(II) Complex (1.2 equiv) in the Presence of K_2CO_3 (5 equiv) and MeOH (10 equiv)



10 R = $(CH_2)_3OTr$
11 R = $(CH_2)_2OTBDPS$
12 R = Me
13 R = *i*-Pr
14 R = *i*-Bu

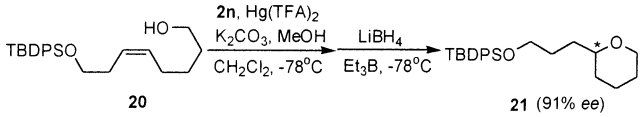
15 X = H, R = $(CH_2)_3OTr$
16 X = H, R = $(CH_2)_2OTBDPS$
17 X = I , R = Me
18 X = I , R = *i*-Pr
19 X = I , R = *i*-Bu

entry	substrate	product	% yield[a]	% ee[c]
1	**1**	**3**	75 (9)	95 (*R*)
2	**10**	**15**	72 (13)	95 (*R*)[d]
3	**11**	**16**	68 (20)	86 (*S*)[d]
4	**12**	**17**	76[b]	86[e,f]
5	**5**	**8**	88 (8)	90[e,f]
6	**6**	**9**	81 (9)	92[e,f]
7	**13**	**18**	91 (16)	89[e,f]
8	**14**	**19**	86 (12)	91 (*R*)[e,g]

[a] Percentage of recovered sm in parentheses. [b] Due to its volatility, sm was not recovered. [c] For determination of absolute configuration, see Supporting Information. [d] Determined by HPLC analysis using DAICEL OD-H. [e] Determined by GC analysis using CHIRALDEX B-DM. [f] The absolute configuration was not determined. [g] The absolute configuration corresponds to the reductively deiodinated product of **19**.

(entries 2, 3, and 7). Alkyl chain-containing substrates **5** and **6** showed inferior stereoselectivity (entries 5 and 6).

Since **2l** seemed to be a little better than **2k** in terms of enantioselectivity and stability, 4-naphthylbisoxazolines **2m** and **2n**[3b,18] having a methyl ethyl ketal protecting group were designed to improve the asymmetric mercuriocyclization of **1** further. The experimental data in Table 3 manifest that 4-(2-naphthyl)bisoxazoline **2n** was superior to 4-(1-naphthyl)bisoxazoline **2m** (entries 1 and 2). When the cyclization was implemented in the presence of K_2CO_3 and MeOH, even more enhanced enantioselectivity was accomplished (entry 3). The established cyclization conditions were applied to various (*Z*)-olefinic γ-hydroxy alkenes **1**, **5**, **6**, and **10**−**14** to provide excellent results presented in Table 4. Remarkable enantioselectivity was attained even with alkyl chain-containing substrates **5**, **6**, and **12**−**14** (entries 4−8). Besides, the ligand was recovered quantitatively as bisoxazoline (40−50%), and a mixture of mono- and diamide, which could be recycled. Finally, δ-hydroxyalkene **20** was cyclized under the identical conditions to furnish tetrahydropyran **21** in 91% ee and 48% yield along with 41% of recovered **20**.



In conclusion, we have developed highly enantioselective mercuriocyclization of γ-hydroxy-*cis*-alkenes employing novel tartrate-derived 4-(2-naphthyl)bisoxazoline **2n** to produce 2-monosubstituted tetrahydrofurans up to 95% ee.

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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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