Oxygen Heterocycles

Catalytic Asymmetric Mercuriocyclization of γ-Hydroxy-*cis*-Alkenes**

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Conversion of prochiral olefinic double bonds into the corresponding chiral functional groups is one of the most influential fields of study in modern synthetic organic chemistry, which has been realized preeminently through asymmetric epoxidation,[1] dihydroxylation,[2] aminohydroxylation,[3] hydrogenation,[4] and hydroboration.[5] Another versatile process can be evolved from electrophile-promoted additions.[6] Whereas few studies into intermolecular asymmetric additions have been carried out, the intramolecular version has been explored to some extent. The latter asymmetric cyclizations have been achieved by substrate-controlled means, but rarely through reagent-controlled methods. Although the reagent-controlled approach has been recognized as more challenging and beneficial, progress has lagged behind owing to lack of lucid strategic clues. Examples include organoselenylation with chiral selenium reagents,[7] iodocyclization with iodonium ion/dihydriquinine complexes,[8] iodocyclization with Co^{II}–salen complexes,[9] and mercuriocyclization with Hg^{II}–bisoxazoline complexes.[10] Most of the aforementioned methods have some limitations such as poor enantioselectivity, multistep synthesis of the involved reagent, and excessive use of the expensive reagent. Since our reported intramolecular mercurioetherification also requires 1.2 equivalents of chiral Hg^{II} complexes, even though the reaction itself is highly enantioselective,[10] development of the corresponding catalytic version would no doubt have a significant impact. Herein we describe asymmetric mercuriocyclization by using catalytic amounts of chiral bisoxazoline to prepare highly enantiopure 2-substituted tetrahydrofurans.

To develop a catalytic version of asymmetric mercuriocyclization, we proposed the use of catalytic amounts of a chiral bisoxazoline together with excess amounts of readily available achiral ligand, which can hold all the existing Hg^{II} ions tightly enough to transfer preferentially not to the olefinic substrate but to the chiral ligand. After assaying several kinds of additives, amine bases were found to retard the cyclization significantly. Based on the observation, structural tuning led us to choose oxazoline as the prospective achiral ligand. Since our proposed relaying process was shown experimentally to work with a complex between Hg^{II} and oxazoline **2** (1:2), mercuriocyclization of the model substrate **1** was implemented with this complex composition in the

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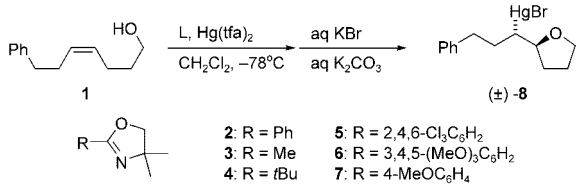
presence of various oxazolines to evaluate which one would be effective. Some of the results are presented in Table 1. Although **4** and **5** promoted the cyclization to a greater extent (Table 1, entries 3 and 4), the use of **2**, **3**, **6**, and **7** seemed to induce more-encouraging progress (Table 1, entries 1, 2, 5, and 6).

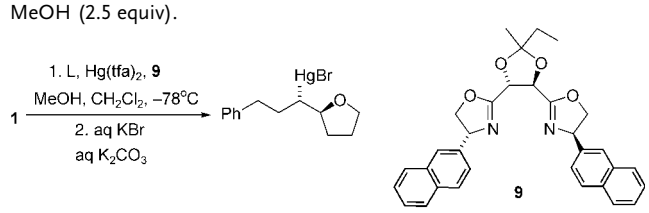
Table 1: Mecuriocyclization of **1** in the presence of oxazoline–Hg^{II} complexes (L_2Hg^{II}; 1.2 equiv).



Entry	L	Yield [%]	Recovered starting material [%]
1	**2**	22	74
2	**3**	23	72
3	**4**	44	48
4	**5**	55	41
5	**6**	8	90
6	**7**	11	83

With the promising relay ligands in hand, catalytic asymmetric mercuriocyclization of **1** was attempted with the corresponding Hg^{II} complexes in the presence of bisoxazoline **9**. The outcomes are summarized in Table 2. As reported

Table 2: Mecuriocyclization of **1** by using oxazoline L–Hg^{II} complexes (L_2Hg^{II}; 1.2 equiv) in the presence of bisoxazoline **9** (0.3 equiv) and MeOH (2.5 equiv).

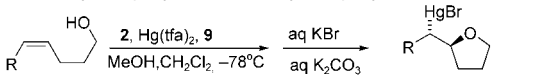


Entry	L	Yield (sm)[a] [%]	*ee* [%][b,c,d]
1[e]	**2**	70 (26)	89
2	**2**	72 (24)	90
3	**3**	47 (52)	89
4	**6**	72 (26)	91
5	**7**	39 (54)	72

[a] Values in parentheses refer to the recovery of starting material. [b] Measured for the reductively demercurated product ($LiBH_4$ and Et_3B in THF at −78 °C). [c] Determined by HPLC analysis using Regis Welk-O1 (*R*,*R*). [d] For the determination of the absolute configuration, see reference [10]. [e] MeOH (10 equiv) and K_2CO_3 (5 equiv) were added.

before, MeOH (10 equiv) and K_2CO_3 (5 equiv) were employed as additives and resulted in good chemical conversion and remarkable stereoselectivity (Table 2, entry 1). Later, it was found that the addition of 2.5 equivalents of MeOH was sufficient to give comparable results (Table 2, entry 2). The best cyclization was attained with oxazolines **2** and **6** (Table 2, entries 2 and 4). The reaction conditions in Table 2, entry 2 were applied to substrates **10**–**12**. The experimental data in Table 3 reveal that the enantioselectivity

Table 3: Mecuriocyclization with **2**–Hg^{II} (1.2 equiv) in the presence of bisoxazoline **9** (0.3 equiv) and MeOH (2.5 equiv).



10 R = $(CH_2)_2$OTBDPS
11 R = $(CH_2)_3$OTBDPS
12 R = *i*Pr
13 R = $(CH_2)_2$OTBDPS
14 R = $(CH_2)_3$OTBDPS
15 R = *i*Pr

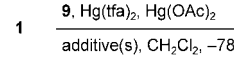
Entry	Substrate	Product	Yield (sm) [%]	*ee* [%][a]
1	**1**	**8**	72 (24)	90
2	**10**	**13**	51 (46)	82[b,c]
3	**11**	**14**	63 (35)	91[b,c]
4	**12**	**15**	42 (56)	75[d,e]

[a] For the determination of the absolute configuration, see reference [10]. [b] Measured for the reductively demercurated product ($LiBH_4$ and Et_3B in THF at −78 °C). [c] Determined by HPLC analysis using DAICEL OD-H. [d] Measured for the iodinated product (I_2 in THF at 0 °C). [e] Determined by GC analysis using CHIRALDEX B-DM. The absolute configuration was not determined.

reached a more satisfactory level than the chemical conversion. When the cyclization proceeded further, it became slower, probably as a result of the gradually increasing oxazoline concentration. All attempts to suppress the ligating power of the generated excess oxazoline with acidic additives proved futile.

To ameliorate the incomplete conversion, a different protocol was elicited. In the second approach, **1** was treated with the complex between **9** and Hg^{II} (1:1; 0.2 equiv) in the presence of $Hg(OAc)_2$ (1.0 equiv) and additive(s). The use of MeOH (10 equiv) with or without K_2CO_3 resulted in moderate enantioselectivity (Table 4, entries 1 and 2). The use of allyl alcohol instead of MeOH led to improved stereoselectivity, notably with poorer chemical yield (Table 4, entry 3). The best cyclization resulted when the amount of MeOH was adjusted to 1.5 equivalents (Table 4, entry 5).

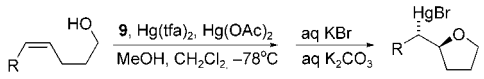
Table 4: Mecuriocyclization of **1** with **9**–Hg^{II} (0.2 equiv) in the presence of $Hg(OAc)_2$ (1.0 equiv) and additive(s).



Entry	Additive (equiv)	Yield (sm) [%]	*ee* [%]
1	MeOH (10), K_2CO_3 (5)	84 (10)	54
2	MeOH (10)	92 (5)	43
3	allyl alcohol (10)	61 (25)	74
4	*i*PrOH	77 (19)	37
5	MeOH (1.5)	87 (11)	91

A variety of *Z* olefinic hydroxyalkenes **10**–**12** and **16**–**22** were subjected to the developed cyclization conditions. Under conditions A (Table 5), most of the substrates delivered good to excellent stereoselectivity; however, **10** and **12**

Table 5: Mecuriocyclization with **9**–Hg^{II} in the presence of $Hg(OAc)_2$ and MeOH.



16 R = Me
17 R = Et
18 R = *n*Pr
19 R = $CH_2CH{=}CH_2$
20 R = $(CH_2)_2CH{=}CMe_2$
21 R = $(CH_2)_2CO_2Bn$
22 R = $(CH_2)_2CO_2tBu$

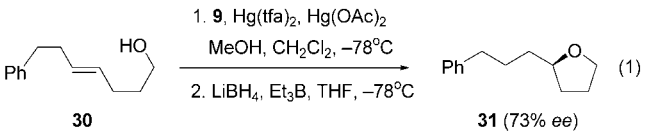
23 R = Me
24 R = Et
25 R = *n*Pr
26 R = $CH_2CH{=}CH_2$
27 R = $(CH_2)_2CH{=}CMe_2$
28 R = $(CH_2)_2CO_2Bn$
29 R = $(CH_2)_2CO_2tBu$

Entry	Substrate	Product	Conditions A[a] Yield (sm) [%]	*ee* [%]	Conditions B[b] Yield (sm) [%]	*ee* [%][b,c]
1	**1**	**8**	87 (11)	91	93 (6)	94
2	**10**	**13**	71 (25)	48	80 (17)	84
3	**11**	**14**	81 (17)	91	87 (11)	95
4	**16**	**23**	79 (15)	78	72 (15)	82[d,e]
5	**17**	**24**	84 (9)	79	83 (10)	87[d,e]
6	**18**	**25**	72 (13)	88	68 (20)	90[d,e]
7	**12**	**15**	83 (10)	22	70 (13)	73
8	**19**	**26**	83 (11)	75	80 (12)	84[d,e]
9	**20**	**27**	83 (10)	88	79 (11)	93[e,f9
10	**21**	**28**	87 (11)	71	80 (15)	82[g]
11	**22**	**29**	75 (14)	83	72 (19)	92[g]

[a] Conditions A: 0.2 equiv of **9**, 0.2 equiv of $Hg(tfa)_2$, 1.5 equiv of MeOH and 1.0 equiv of $Hg(OAc)_2$ were used. Conditions B: 0.3 equiv of **9**, 0.2 equiv of $Hg(tfa)_2$, 2.0 equiv of MeOH and 1.0 equiv of $Hg(OAc)_2$ were used. [b] For the determination of the absolute configuration, see reference [10]. [c] Determined by GC analysis using CHIRALDEX B-DM. [d] Measured for the iodinated product (I_2 in THF at 0°C). [e] The absolute configuration was not detetermined. [f] Measured for the reductively demercurated product ($LiBH_4$ and Et_3B in THF at −78°C). [g] Measured for the reductively demercurated alcohol, which was produced by concomitant reductive demercuration and ester reduction using $LiBH_4$ and Et_3B in THF at −78°C.

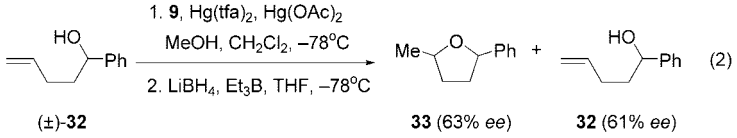
resulted in poor enantioselectivity (Table 5, entries 2 and 7). To overcome the inferior asymmetric induction, it was necessary to maintain the concentration of the free Hg^{II} ion as low as possible. As a consequence, the cyclization conditions were optimized by increasing the amount of **9** to 0.3 equivalents with 2.0 equivalents of MeOH (Table 5, conditions B). The enantioselectivity under the established conditions was improved considerably from 48 to 84% *ee* for **13** and from 22 to 73% *ee* for **15** (Table 5, entries 2 and 7). Most of the remaining substrates also underwent cyclization with significant enantiomeric enhancement.[11] Scrutiny of the data suggests that not only the steric bulk of the substituent but also the distance of the bulky region from the olefinic double bond seem to be greatly influential. It is possible that the two factors are involved in forming the tight coordination bond between the substrate and **9**–Hg^{II} complex, which is thought to be crucial for high facial selectivity.

Finally, the newly developed cyclization conditions were employed for the asymmetric mercurioetherification of the *trans* alkene **30** (isomeric to **1**) and the racemic terminal alkene (±)-**32** as a kinetic resolution experiment. The former proceeded somewhat more sluggishly to afford the expected tetrahydrofuran **31** in 74% yield with 73% *ee* (15% of recovered **30**) [Eq. (1), tfa = trifluoroacetate].



30 **31** (73% *ee*)

On the other hand, the latter produced 43% of the *trans*-2,5-disubstituted tetrahydrofuran **33** with 63% *ee*, and 47% of starting alcohol **32** with 61% *ee* [Eq. (2)].



(±)-**32** **33** (63% *ee*) **32** (61% *ee*)

In conclusion, we have established a highly enantioselective catalytic mercuriocyclization of γ-hydroxy-*cis*-alkenes employing $Hg(OAc)_2$ in the presence of catalytic amounts of the 4-(2-naphthyl)bisoxazoline–Hg^{II} (**9**–Hg^{II}) complex to obtain 2-monosubstituted tetrahydrofurans with up to 95% *ee*.

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[11] When the cyclization of **1** was scaled up from 0.2 to 2.0 mmol, the enantioselectivity decreased to 90% *ee*. However, the addition of **1** by a syringe pump over 8 h instead of in one portion restored it to the initial level (93% *ee*).

