Enantioselective Intramolecular Iodoetherification of γ-Hydroxyalkenes†

Sung Ho Kang,* Chul Min Park, and Sung Bae Lee

Center for Molecular Design and Synthesis, Department of Chemistry, School of Molecular Science (BK21), Korea Advanced Institute of Science and Technology, Daejeon 305-701, Korea
Received April 9, 2004

Key Words : Electrophile-promoted cyclizations, Enantioselective iodocyclization, Chiral iodonium cation

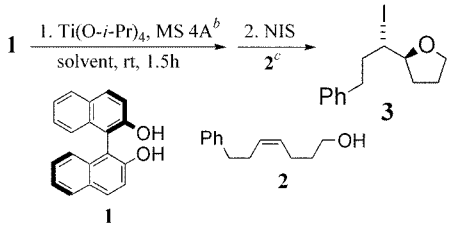
The prime issue in electrophile-promoted cyclizations is considered as the stereoselectivity involved in the formation of heterocycles.[1] Most of the stereoselective cyclizations have been implemented by substrate-controlled approach to exploit the preexisting stereogenic center(s) or the attached chiral auxiliary.[2] Alternative method has been attempted by reagent-controlled approach, which is mostly limited to phenylselenocyclization.[3] Since asymmetric catalysts can impose chiral environments around substrates or electrophiles, their development, though rarely explored, is conceived pivotal to achieve enantioselective cyclizations more efficiently. The related asymmetric cyclizations have been intended by oxymercuration with Hg(II) carboxylates[4] and with Hg(II)-bisoxazoline complexes,[5] iodolactonization with amine-iodonium ion complexes,[6] chlorohydroxylation with Pd(II)-BINAP complexes,[7] and iodocyclization with Ti(IV)-tartrate[8] and with Co(II)-salen complexes.[9] In this context, we herein report our results of iodocyclization using NIS (N-iodosuccinimide) in the presence of [(*R*)-Binol]$_2$-Ti(IV) complex.[10]

For the designed enantioselective iodocyclization, we planned to engender chiral iodonium cation by complexing I_2 or NIS with chiral Lewis acids. With a model substrate **2**, its iodocyclization was assayed using several kinds of chiral Lewis acids. [(*R*)-Binol]$_2$-Ti(IV) complex was found effective to relay its chirality to NIS. When the complex was generated in the presence of molecular sieve 4 Å (MS 4A), its catalytic activity was improved significantly, and the optimal amount of MS 4A was 10 mg per 3 mg of Ti(O-*i*-Pr)$_4$. Subsequently, asymmetric iodocyclization of **2** was carried out under various reaction conditions using NIS with 0.2 equiv of the aforementioned [(*R*)-Binol]$_2$-Ti(IV) complex. The experimental data in Table 1 reveal that in ethereal solvents the reaction rates decreased but higher enantioselectivity was secured presumably in part due to the slower background reaction. Although the highest % ee was reached in *t*-BuOMe at −20 °C (entry 6), the best results were obtained in the same solvent at 0 °C considering not only enantioselectivity but also chemical yield (entry 5). It is noted that the major product in toluene and CH_2Cl_2 was enantiomeric to that in ethereal solvents (entries 1 and 2).

Dependence of the iodocyclization on concentration was examined. The representative results are summarized in Table 2. The optimal concentration of substrate was observed to be 26.4 mM (entry 2). While the chemical conversion decreased greatly with the lower concentration, the stereoselectivity was affected a little by the concentration change (entries 1 and 3).

Enantioselective iodocyclization of various substrates **4**-**13** was performed under the established reaction conditions (Table 1, entry 5), and the outcomes are explained in Table 3. While all the chemical yields were good to excellent, the

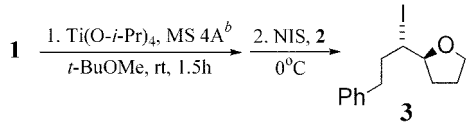
Table 1. Iodocyclization of **2** using [(*R*)-Binol]$_2$-Ti(IV) complex[a]



Entry	Solvent	Reaction Temp. (°C)	Reaction Time (h)	Yield (%)	Ee (%)[d]
1	PhMe	0	0.5	98	32[e]
2	CH_2Cl_2	−20	1.5	91	29[e]
3	Et_2O	0	2.5	93	60
4	*t*-BuOMe	rt	0.8	93	61
5	*t*-BuOMe	0	4	92	68
6	*t*-BuOMe	−20	4	51 (44)	72

[a]0.4 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. For determination of absolute configuration, see reference 5 and 9. [e]Major product was enantiomer of **3**.

Table 2. Concentration effect on iodocyclization of **2** using [(*R*)-Binol]$_2$-Ti(IV) complex[a]



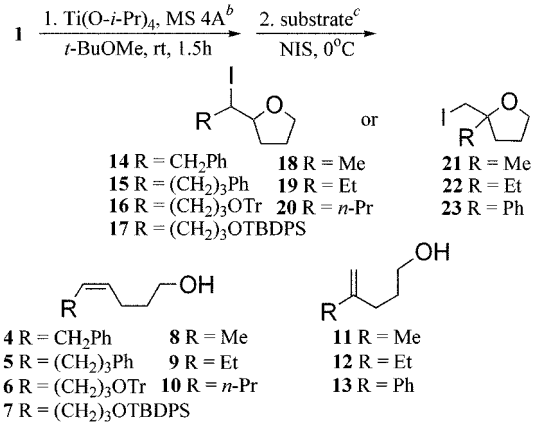
Entry	Concentration of **2** (mM)	Reaction Time (h)	Yield (%)	Ee (%)
1	13.2	4	31 (59)	60
2	26.4	4	92	68
3	52.8	1	90	65

[a]0.4 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.

†Dedicated to Prof. Yong Hae Kim in commemoration of his distinguished academic achievements.

*Corresponding Author. e-mail: shkang@kaist.ac.kr

Table 3. Iodocyclization of **4-13** using [(*R*)-Binol]$_2$-Ti(IV) complex[a]



Entry	Substrate	Reaction Time (h)	Product	Yield (%)	Ee (%)
1	**2**	4	**3**	92	68
2	**4**	18	**14**	77	31[d]
3	**5**	10	**15**	91	27[e]
4	**6**	6	**16**	81	14[f]
5	**7**	6	**17**	87	22[f]
6	**8**	4	**18**	87	10[g]
7	**9**	7	**19**	91	13[g]
8	**10**	10	**20**	96	28[g]
9	**11**	3	**21**	91	18[g]
10	**12**	3	**22**	98	21[g]
11	**13**	10	**23**	84	37[h]

[a]0.4 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-H. [e]Determined by HPLC analysis using Regis Welk-O1(*R*,*R*). [f]Determined by HPLC analysis of the corresponding benzoate using DAICEL OD. [g]Determined by GC analysis using CHIRALDEX B-DM. [h]Determined by HPLC analysis using DAICEL OD.

enantioselectivity ranged from 10 to 68% ee. The number of carbon between the olefinic double bond and the phenyl group caused the considerable % ee variation (entries 1-3). The stereselectivity was curiously influenced by the protecting group remote from the reaction site *i.e.* the olefinic double bond (entries 4 and 5). Comparing the structurally closely related substrates, the substrate with bulkier substituent gave rise to the corresponding iodotetrahydrofuran in higher enantioselectivity (entries 6-8 and entries 9-11).

In conclusion, we have demonstrated catalytic asymmetric iodocyclization of γ-hydroxyalkenes employing the unprecedented combination of NIS and [(*R*)-Binol]$_2$-Ti(IV) complex to produce tetrahydrofurans in 10 to 68% ee.

Acknowledgement. This work was supported by CMDS, KAIST and the Brain Korea 21 Project.

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