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# Enantioselective Iodolactonization Catalyzed by Chiral Quaternary Ammonium Salts Derived from Cinchonidine

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**Abstract:** Chiral quaternary ammonium salts derived from cinchonidine have been applied to catalyze the stereoselective iodolactonizations of *trans*-5-aryl-4-pentenoic acids leading to a mixture of two regioselectively iodolactonized products with fair to excellent yield (37−98%) and moderate enantioselectivity (exo = 42.0% ee, endo = 31.0% ee) under mild conditions. This work is the first example of asymmetric iodolactonization reaction in the presence of less than a stoichiometric amount of chiral reagent.

Halolactonizations are useful chemical transformations for the construction of lactones from olefinic carboxylic acids, carboxylic esters, and amides.[1] In extensive studies on the stereoselectivity of these reactions, it has been proved that the stereochemistry of the halolactonized product can be controlled by substrates or reagents. While the substrate-controlled method has been studied in some detail[2] and applied in the synthesis of natural products,[3] there is a lack of understanding of how the stereochemistry of the lactones is influenced under reagent-controlled conditions.

To our knowledge, there are only four examples of the reagent-controlled stereoselective halolactonizations. Taguchi and co-workers[4] first demonstrated that the formation of chiral titanium complex with hydroxycarboxylic acid moiety gave rise to the highest enantioselectivity known so far (65% ee) in the iodolactonization of diallyl (hydroxy) acetic acid. In a different approach, Grossman and Trupp[5] used chiral $I^+$ complex to promote the iodolactonization of *cis*-4-heptenic acid only leading to less than 15% ee. An improved work[6] was reported by Wirth's group: up to 48% ee was achieved in the iodolactonizations of 4-aryl-4-pentenoic acids by the complex ICl on chiral primary amines. Also, only 4.8% ee was obtained in an attempted stereoselective bromolactonization of 4-pentenoic acid with the complex from chiral pyridine derivatives and $Br^+$.[7] It is true that the catalytic enantioselective halolactonization is the epitome of the reagent-controlled asymmetric halolactonizations, however, there is no report on such examples to date. Recently, the catalytic asymmetric iodocyclization by unprecedented use of chiral salen−Co(II) complex and NCS has also been developed independently.[8]

Prior to the work reported herein, we used carboxylate ion pairs combined with stoichiometric cinchona alkaloids as chiral sources leading to moderate enantioselectivity (35% ee) in the iodolactonizations of *trans*-5-aryl-4-pentenoic acids.[9] Then, quaternary ammonium salts derived from cinchonidine were tried as chiral phase-transfer catalysts[10] to catalyze the iodolactonizations of these substrates and the enantioselectivity of the reaction was also observed. This is a novel protocol for reagent-controlled asymmetric iodolactonization. Although the enantioselectivities are not high (exo = 42.0% ee, endo = 31.0% ee), this method, as far as we know, is the first example of asymmetric iodolactonization reaction in the presence of less than a stoichiometric amount of chiral reagent. Here, the new experimental results are reported.

*trans*-5-Phenyl-4-pentenoic acid **1a** was initially treated with iodine and saturated aqueous sodium hydrogen carbonate in $CH_2Cl_2$ (Scheme 1). As expected, the competition between exo and endo adducts[1a,d] resulted in the formation of a mixture of $\gamma$- and $\delta$-lactones in a ratio of 20:80. As the major regioisomeric product, the formation of **3a** should account for the electronic factors from the phenyl group at the 5-position of **1a**. Interestingly, when a catalytic amount of *N*-benzyl cinchonidinium chloride **4a** (30 mol %) was added to the reaction as a chiral phase-transfer catalyst (CPTC), the ratio of the reaction products **2a**:**3a** was reversed and gave detectable enantioselectivity. In this case, the endo product **3a** is the minor regioisomeric product, perhaps due to the steric repulsion between the phenyl group of acid **1a** and the larger carboxylate ion pair combined with **4a** in the asymmetric transition state. This initial result prompted us to pursue

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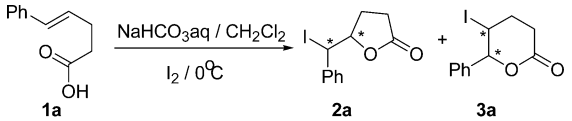
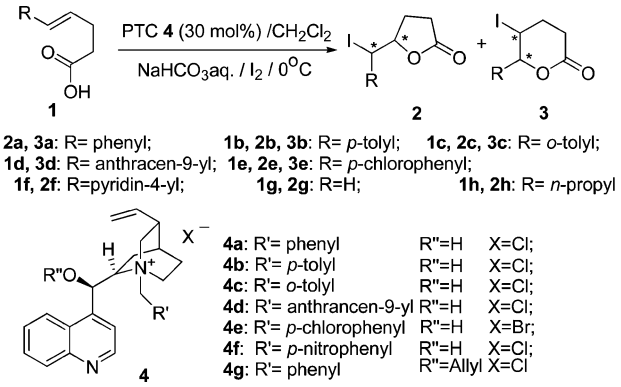
**SCHEME 1. Iodolactonization of 1a**




**SCHEME 2. Enantioselective Iodolactonizations of Acids 1 in the Presence of CPTCs**




the enantioselective iodolactonization catalyzed by such kinds of CPTCs.

The solvent effect on the selectivity of the heterogeneous reaction was first investigated. It has been proved that the solvent had a significant effect on the reaction yield but only limited influence on the enantioselectivity. Both ether−water and benzene−water systems gave fair reaction yields (63 and 80%) without any enantioselectivity but suffered longer reaction process. Whereas, methylene chloride−water and chloroform−water systems increased the reaction yield to 95% with similar detectable enantioselectivity. The observation may be attributed to the increased solvent polarity of the reaction system.

Then the substrate influence of this iodolactonization was examined using a number of *trans*-5-substituted 4-pentenoic acids[11] prepared according to the known procedures and treated under the preferred $CH_2Cl_2-H_2O$/**4a** condition (Scheme 2). As the results revealed in Table 1, an aromatic substituent at the 5-position of acids **1** (entries 1−6) is necessary for the detectable enantioselectivity. It may be due to the effect of $\pi-\pi$ interaction between the aromatic substituent of the acids **1** and the *N*-benzyl group of **4a** when the iodonium intermediate is attacked by the chiral carboxylate ion pair formed with **4a**. Unsaturated carboxylic acids (entries 7, 8) with hydrogen or an aliphatic substituent at the 5-position only lead to racemic $\gamma$-lactones. From the results shown in Table 1, it is also clear that the electrostatic interaction from aromatic group at the 5-position of acids **1** is crucial

**TABLE 1. Asymmetric Iodolactonizations of Acids 1 Catalyzed by 4a[a]**

| entry | acid | % yield of **2** + **3**[12a] | **2**:**3**[12b] | % ee of **2**[12c] | % ee of **3**[12c] |
|---|---|---|---|---|---|
| 1 | **1a** | 93 | 70:30 | 7.0 (1′*R*, 5*S*)[12d] | 6.0 (5*S*, 6*S*)[12d] |
| 2 | **1b** | 92 | 17:83 | 12.0 | 6.0 |
| 3 | **1c** | 86 | 55:45 | 16.0 | 9.0 |
| 4 | **1d** | 37 | 0:100 | | 10.0 |
| 5 | **1e** | 98 | 75:25 | 12.0 | 6.0 |
| 6 | **1f** | 56 | 100:0 | 17.0 | |
| 7 | **1g** | 90 | 100:0 | 0 | |
| 8 | **1h** | 80 | 100:0 | 0 | |

[a] Performed with **1** (1 mmol), **4a** (30 mol %), $CH_2Cl_2$ (10 mL), aq $NaHCO_3$ (5 mL), $I_2$ (1.5 mmol), 0 °C, in the dark.

**TABLE 2. Results of the Stereoselective Iodolactonization of 1e Using Various 4 as Catalysts[a]**

| entry | CPTC | **2e**:**3e**[12b] | % ee **2e**[12c] | % ee **3e**[12c] |
|---|---|---|---|---|
| 1 | **4a** | 75:25 | 12.0 | 6.0 |
| 2 | **4b** | 78:22 | 10.0 | 7.0 |
| 3 | **4c** | 79:21 | 17.5 | 12.0 |
| 4 | **4d** | 56:44 | 17.5 | 28.0 |
| 5 | **4e** | 77:23 | 10.0 | 8.0 |
| 6 | **4f** | 58:42 | 6.0 | 14.0 |
| 7 | **4g** | 55:45 | 0 | 0 |

[a] Performed with **1e** (1 mmol), **4** (30 mol %), $CH_2Cl_2$ (10 mL), aq $NaHCO_3$ (5 mL), $I_2$ (1.5 mmol), 0 °C, in the dark.

for the regioselectivities of these iodolactonizations. The substrate with an electron-donating aryl group (entries 2, 4) leads to an increase in the ratio of the endo product to the exo product during cyclization. In contrast, an electron-withdrawing substituent at the aromatic moiety of **1** (entries 5, 6) is disadvantageous to the formation of the endo product. The substrate with an ortho substituent at its aryl group gives poor regioselectivity (entry 3).

An interesting discovery of the heterogeneous iodolactonizations of *trans*-5-aryl-4-pentenoic acids was that varying the stoichiometric ratio of the phase-transfer catalyst to the substrate also causes the regioselectivity of the reaction to radically change. When the acid **1e** is treated using different molar ratios of the catalyst **4a** (10, 20, 30, and 100 mol %), respectively, the product ratio of $\gamma$- and $\delta$-lactone varies from 50:50 to a remarkable 94:6. On the other hand, increasing the ratio between the catalyst and the reaction substrate has only limited influence on the enantioselectivity of the reaction.

Consideration of the structural impact of the CPTCs to the iodolactonization of **1e** was examined using catalysts **4b**−**g** in a 30% molar ratio, and the results are shown in Table 2. The result suggests that a major improvement in the enantioselectivity of the reaction is observed when a bulky substituent such as an anthracen-9-yl-methyl group is introduced to form the quaternary ammonium salts **4d** (entry 4). The only O-substituted CPTC, **4g**, completely destroyed the stereoselectivity of the catalyst (entry 7).

The combination of the optimized reaction solvent system and the catalyst **4d** was then used to catalyze a set of asymmetric iodolactonizations of acids **1**. The regioselectivities and enantiomeric excess values are summarized in Table 3.

In conclusion, we have demonstrated that the heterogeneous enantioselective iodolactonizations of *trans*-5-aryl-4-pentenoic acids can be achieved with moderate

(11) *trans*-5-Substituted 4-pentenoic acids **1a**−**f** and **1h** were prepared stereoselectively from 1-substituted propylen-1-ol and triethyl orthoacetate via a Claisen rearrangement followed by basic cleavage of the ethyl ester. For general procedure of Claisen rearrangement involved in this paper, see: Richard, K. H.; Raghovan, S.; Seiji, S. *J. Org. Chem*. **1972**, *37*, 3737−3740.

(12) (a) Isolated yield. (b) Determined by $^1$H NMR. (c) Determined by $^1$H NMR with (*R*)-(−)-2,2,2-trifluoro-1-(9-anthryl) ethanol. The absolute configuration of the major enantiomer of **2** and **3** was not determined. (d) For determination of absolute configuration, see Supporting Information.

**TABLE 3. Enantioselective Iodolactonizations of Acids 1 Using 4d as a Catalyst**[a]

| acid | % yield **2** + **3**[12a] | **2**:**3**[12b] | % ee **2**[12c] | % ee **3**[12c] |
|---|---|---|---|---|
| **1a** | 80 | 47:53 | 16.0 (1'*R*, 5*S*)[12d] | 30.5 (5*S*, 6*S*)[12d] |
| **1b** | 80 | 15:85 | 31.0 | 12.0 |
| **1c** | 89 | 22:78 | 42.0 | 10.0 |
| **1d** | 38 | 0:100 | | 31.0 |
| **1e** | 90 | 56:44 | 17.5 | 28.0 |
| **1f** | 40 | 100:0 | 22.0 | |

[a] Performed with **1** (1 mmol), **4d** (30 mol %), $CH_2Cl_2$ (10 mL), aq $NaHCO_3$ (5 mL), $I_2$ (1.5 mmol), 0 °C, in the dark.

enantiomeric excess using a catalytic amount of the readily available chiral quaternary ammonium salts as chiral phase-transfer catalysts. Although the enantioselectivity of the reaction has not been high for practical asymmetric synthesis, this research provided a possibility for development of its catalytic asymmetric version. Further studies to optimize this reaction are in progress.

## Experimental Section

**General Procedure for Iodolactonizations of Acids 1.** To a solution of acid **1a** (176 mg, 1 mmol) and CPTC **4d** (150 mg, 0.3 mmol) in $CH_2Cl_2$ (10 mL) was added saturated aqueous $NaHCO_3$ (5 mL). After the mixture was stirred for 10 min, iodine (380 mg, 1.5 mmol) was added to this rapidly stirred two-phase reaction mixture at 0 °C. The flask was protected from light and stirred for 10 h at 0 °C. The reaction mixture was diluted with $CH_2Cl_2$ (100 mL) and then quenched with saturated aqueous $Na_2S_2O_3$. The organic layer was separated and washed with saturated aqueous $NaHCO_3$ (2 × 60 mL) and brine (1 × 60 mL) and dried over $MgSO_4$. After removal of solvent in vacuo, the resulting crude iodolactones were purified by chromatography (silica, ether−petroleum ether) to give a mixture of two regioisomeric products **2a** and **3a** (242 mg, 80%; **2a**, 16.0% ee; **3a**, 30.5% ee). Products were stored at −20 °C protected from light. The two structural isomers **2a** and **3a**, **2b** and **3b**, **2c** and **3c**, and **2e** and **3e** could not be separated by chromatography in our experiment. The ratios of them were determined by $^1$H NMR. The enantiomeric excess values of products **2** and **3** were also confirmed by $^1$H NMR (600 MHz) with (*R*)-(−)-2,2,2-trifluoro-1-(9-anthryl)ethanol.

**5-(Iodo-phenyl-methyl)-dihydrofuran-2-one (2a):** white solid; IR (KBr) 3029, 2940, 1760, 1188 cm$^{-1}$; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 2.12−2.20 (m, 1H), 2.53−2.65 (m, 3H), 4.86−4.92 (m, 1H,), 5.12 (d, $J$ = 8.0 Hz, 1H), 7.27−7.34 (m, 3H), 7.41 (d, $J$ = 7.6 Hz, 2H); MS (EI, 30 eV) $m/z$ (%) 302 (4) [M$^+$], 175 (100). Anal. Calcd for $C_{11}H_{11}IO_2$: C, 43.73; H, 3.67. Found: C, 43.47; H, 3.56. Elemental analysis was obtained with a mixture of two structural isomers **2a** and **3a**.

**5-Iodo-6-phenyl-tetrahydro-pyran-2-one (3a):** white solid; IR (KBr) 3036, 2950, 1723, 1205 cm$^{-1}$; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 2.30−2.49 (m, 2H), 2.68−2.76 (m, 1H), 2.82−2.90 (m, 1H), 4.40−4.45 (m, 1H), 5.60 (d, $J$ = 8.0 Hz, 1H), 7.32−7.34 (m, 2H), 7.39−7.41 (m, 3H); MS (EI, 30 eV) $m/z$ (%) 302 (6) [M$^+$], 175 (100). Anal. Calcd for $C_{11}H_{11}IO_2$: C, 43.73; H, 3.67. Found: C, 43.47; H, 3.56. Elemental analysis was obtained with a mixture of two structural isomers **2a** and **3a**.

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**Supporting Information Available:** Experimental procedures for the preparation and characterization data of products **1b**−**f**, **1h**, **2a**−**c**, **2e**, **2f**, **2h**, **3a**−**e**, **4b**, **4c**, and **4e**−**g** and determination of absolute configurations of **2a** and **3a**. This material is available free of charge via the Internet at http://pubs.acs.org.

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