Enantioselective Iodolactonizations of 4-Pentenoic Acid Derivatives Mediated by Chiral Salen–Co(II) Complex

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Abstract: This work presents the salen–Co(II) complex catalyzed enantioselective iodolactonizations of various 4-pentenoic acid derivatives with good enantioselectivities (up to 83% ee).

Key words: asymmetric catalysis, salen complex, synthesis, lactones, iodolactonization

Enantioselective halolactonization of olefinic carboxylic acids has recently evoked growing interest since this transformation is a key reaction in a rich variety of organic syntheses, particularly for some biologically important compounds.[1,2] Subsequent functional transformations through the lactone moiety or halo group reinforce this protocol. Two strategies by means of chiral substrate- and reagent-controlled transformations were investigated so far. While the substrate-controlled approach has been shown to be efficient in obtaining good enantioselectivity,[3] its general application is restricted due to the limited availability of chiral precursors. Recent interest is shifted to the reagent-induced asymmetric halolactonization, where several systems such as chiral titanium complex,[4] chiral pyridine derivatives,[5] chiral amines,[6] and cinchona derivatives[7] were investigated. However, in most cases, only poor to moderate enantioselectivities were obtained. Therefore, development of an effective protocol with high enantioselectivity is strongly desirable. Herein, we describe a novel salen–Co(II) complex, which effected the iodolactonization catalytically and afforded the highest enantioselectivity among the reagent-controlled iodolactonization protocols known so far.[4–7] Salen–metal complexes have been successfully used in a broad range of asymmetric transformations such as Diels–Alder reactions,[8a] Michael additions,[8b] alkylations,[8c] epoxidations,[8d] epoxide ring-opening reactions,[8e] and iodocyclic etherifications.[9]

Initially, several salen–metal complexes of Co(II), Mn(III), Cr(III), and Al(III)[10] (Figure 1, **1a**–**d**) were examined employing 4-phenyl-4-pentenoic acid (**2**) as substrate with I_2 as I^+ source since the asymmetric halolactonization of this compound has been extensively studied,[6,11] and thereby, facilitating a rapid evaluation of our Lewis acid complexes. The preliminary results revealed that in the respective presence of the four complexes, iodolactonization of **2** afforded γ-lactone **3** as a single product in moderate yield associated with the recovery of starting material (Table 1, entries 2–9). Moreover, the use of the complexes substoichiometrically (30%) was more efficient than in a stoichiometric amount. Concerning the enantioselectivity, only **1a** gave rise to an enantiomeric excess (16%) among the four catalysts **1a**–**d**. Therefore **1a** was chosen as the catalyst to further optimize the reaction conditions.

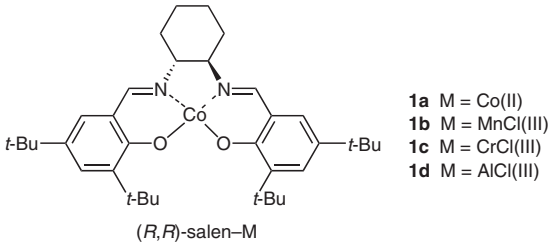

Figure 1 Chiral salen–metal complexes evaluated in this study

We first investigated the effect of various additives on the iodolactonization outcome, such as NCS, NBS, Ph_3PO, cinchonidine, *N*-benzyl cinchonidinium chloride, Bu_4NBr, Bu_4NI, pyridine, *tert*-butyl alcohol, *n*-butylamine, and molecular sieves.[12] Unfortunately, in most cases, addition of various additives gave only a small influence on the enantioselectivity and yield except for NCS,[9a] whose presence led to an increased ee value from 16% to 27% as well as yield from 48% to 58% (Table 1, entry 10). Thus, salen–Co(II) coupled with a combination of NCS was employed to search a suitable solvent and temperature system.

Table 2 lists the results of the solvent and temperature effect on iodolactonization. We observed a strong solvent dependence of the yield and enantioselectivity, and found that utilization of toluene led to a large increase of enantioselectivity with an ee value of up to 50% (entry 5), although the yield was somewhat lowered (ca. 25%). Using toluene as solvent, we examined the temperature effect by elevating the temperature from –78 °C via –48 °C to –18 °C, and found that the yield increased dramatically from 25% to 93% without affecting significantly the enantioselectivity (entries 5–7).

With the optimized salen complex, solvent, additive, and reaction temperature in hand, our next attention was shift-

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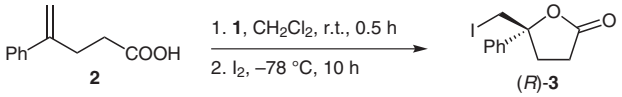
ed to the further optimization of the molar equivalent of salen complex **1a** and NCS additives by setting the reaction temperature at –18 °C in toluene. The results are summarized in Table 3. The data show that by varying the molar amount of **1a** from 0.1 to 1.0 equivalent (entries 1–6), the best enantioselectivity (56% ee) was afforded in the presence of 0.4 or 0.5 equivalent of **1a** (entries 3 and 4). Further increase of **1a** led to a slightly decreased ee (%) as well as yield, and decrease of **1a** gave rise to a largely reduced ee (%) although the yield was somewhat increased.

Investigation into the effect of NCS on the behavior of lactonization revealed that utilization of 0.25 equivalent of NCS afforded the best selectivity (66% ee) coupled with a moderate yield (67%) as a comparison of the results in entry 9 and others from entries 7–13. Finally, after an extensive experimental exploration of other reaction conditions, such as the elongation of reaction time, tuning the amount of I_2, and addition of base, K_2CO_3, Na_2CO_3 and $NaHCO_3$, we eventually found that lactone **3** could be obtained with good selectivity (67% ee) as well as high yield (87%) by employing 1.4 equivalent of I_2 (entry 16).

Now, the optimized conditions for the iodolactonization of 4-phenyl-4-pentenoic acid (**2**) are 0.4 equivalent of salen–Co(II) **1a** as Lewis acid, toluene as solvent, 0.25 equivalent of NCS as additive, and 1.4 equivalent of I_2 as

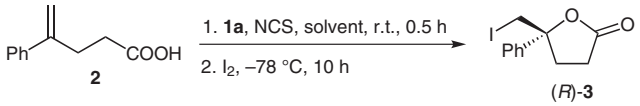
Table 1 Iodolactonization of **2** Using (*R*,*R*)-Salen–M Complexes with Additives[a]



Entry	(*R*,*R*)-Salen–M (equiv)	Yield (%)[b]	ee (%)[c]
1	–	12	0
2	**1a** (0.3)	48	16
3	**1a** (1.0)	21	3
4	**1b** (0.3)	54	0
5	**1b** (1.0)	30	4
6	**1c** (0.3)	44	0
7	**1c** (1.0)	27	0
8	**1d** (0.3)	31	3
9	**1d** (1.0)	11	1
10[d]	**1a** (0.3)	58	27

[a] Reactions were carried out using salen–M complexes (0.051–0.170 mmol), I_2 (0.170 mmol), additive (0.127 mmol), and **2** (0.170 mmol) in CH_2Cl_2 (8 mL).
[b] Isolated yield.
[c] Determined by HPLC analysis using DAICEL OD-H.
[d] The reaction was performed in the presence of 0.75 equiv of NCS.

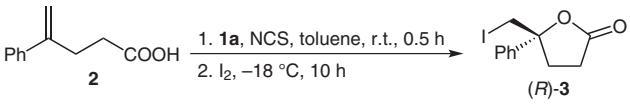
Table 2 Solvent and Temperature Effect on the Stereoselective Iodolactonization to **3**[a]



Entry	Solvent	Temp (°C)	Yield (%)[b]	ee (%)[c]
1	CH_2Cl_2	–78	58	27
2	Et_2O	–78	77	14
3	THF	–78	49	3
4	MeCN	–15	91	0
5	PhMe	–78	25	50
6	PhMe	–48	64	52
7	PhMe	–18	93	50

[a] Reactions were carried out using **1a** (0.051 mmol), NCS (0.127 mmol), I_2 (0.170 mmol), and **2** (0.170 mmol) in solvent (8 mL).
[b] Isolated yield.
[c] Determined by HPLC analysis using DAICEL OD-H.

Table 3 Effect of the Amount of **1a**, NCS, and I_2 on the Asymmetric Iodolactonization of **2**[a]

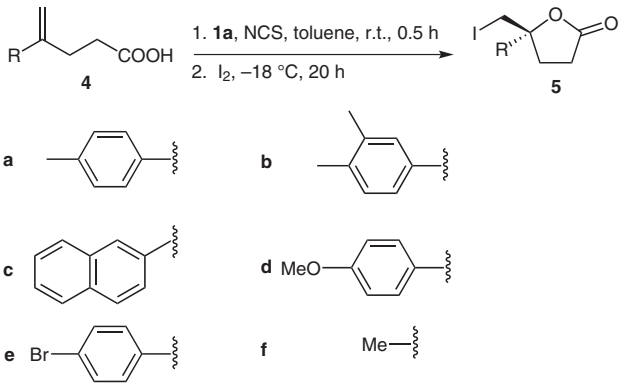


Entry	**1a** (equiv)	NCS (equiv)	I_2 (equiv)	Yield (%)[b]	ee (%)[c]
1	0.3	0.75	1.0	93	50
2	0.1	0.75	1.0	90	30
3	0.4	0.75	1.0	88	56
4	0.5	0.75	1.0	84	56
5	0.7	0.75	1.0	84	55
6	1.0	0.75	1.0	74	55
7	0.4	0.1	1.0	53	62
8	0.4	0.2	1.0	63	65
9	0.4	0.25	1.0	67	66
10	0.4	0.3	1.0	71	64
11	0.4	0.4	1.0	75	63
12	0.4	0.5	1.0	78	58
13	0.4	1.0	1.0	86	55
14[d]	0.4	0.25	1.0	75	66
15[d]	0.4	0.25	1.2	83	67
16[d]	0.4	0.25	1.4	87	67

[a] Reactions were carried out using **1a** (0.017–0.170 mmol), NCS (0.017–0.170 mmol), I_2 (0.170–0.238 mmol), and **2** (0.170 mmol) in toluene (8 mL).
[b] Isolated yield.
[c] Determined by HPLC analysis using DAICEL OD-H.
[d] Reaction was stirred for 20 h.

I^+ source at –18 °C. Under these conditions, a range of substrates having various substituents such as sterically bulky, electron-rich and electron-deficient, and aromatic and aliphatic groups[13] (**4a–f**) were investigated. As shown in Table 4, in most cases, good enantioselectivities paired with high yield were obtained for a diverse class of substrates, indicating that this protocol is amenable to a broad range of substances.[14] Of particularly interest is that the substrate **4f**, whose structure is substituted by a small aliphatic methyl group, also exhibited a fairly good selectivity with an ee value of 55% (entry 7). This result is in sharp contrast to the other reagent-controlled asymmetric iodolactonizations where substitution of the substrates by an aliphatic group such as methyl and isopropyl substituents virtually produced lactones in racemic form.[6a,7] Finally, it should be mentioned that the electronic nature of the substituent affects notably the outcome of the lactonization reactions. For instance, by introducing an electron-rich OMe group into the phenyl ring (**4d**), the selectivity of the cyclization was markedly decreased (entry 5). However, an electron-deficient Br instead of OMe tends to increase the ee value (entry 6). In fact, similar influence has also been noted for some analogous 4-substituted 4-pentenoic acids, and is attributed probably to the different stability of the intermediate iodonium ion as affected by the electronic property of the substituents.[6a]

Table 4 Iodolactonizations of Substituted 4-Pentenoic Acid Using the Optimized Conditions[a]



Entry	Substrate	Product	Yield (%)[b]	ee (%)[c]
1	**2**	**3**[15]	87	67
2	**4a**	**5a**	93	70
3	**4b**	**5b**	92	71
4	**4c**	**5c**	86	83
5	**4d**	**5d**	89	22
6	**4e**	**5e**	72	73
7	**4f**	**5f**	73	55[d]

[a] Reactions were carried out using **1a** (0.068 mmol), NCS (0.043 mmol), I_2 (0.238 mmol), and substrate (0.170 mmol) in toluene (8 mL).
[b] Isolated yield.
[c] Determined by HPLC analysis using DAICEL OD-H.
[d] Determined by GC analysis using CHIRASIL-DEX CB.

In conclusion, we have developed a new reagent-controlled protocol for stereoselective iodolactonization by using catalytical amount of chiral salen–Co(II) complex as Lewis acid. This protocol is shown to be efficient and applicable to a range of substrates, providing iodolactones with high yield as well as good selectivity. The ee values of the obtained lactones are at least 20% higher when compared to the reported data for substrates **2** and **4a**.[6a] Most interestingly, the salen–Co(II) complex exhibited also fairly good selectivity to the 4-methyl-4-pentenoic acid **4f** (ee = 55%), in sharp contrast to the racemic form as appeared in previous reports.[6a,7] Consequently, the method presented in this work is believed to be highly potential for the stereoselective construction of halolactone derivatives. Further work towards the development of a more effective salen–Co system by modifying the salen ligands, for instance, introducing electronic and steric effects, and the application of the system to a broader range of substrates is currently under way.

Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synlett.

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(10) Compounds **1a–d** were purchased from Aldrich.

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(13) Compounds **2** and **4a–f** were prepared from the corresponding 4-substituted-4-oxo-butanoic acid ethyl ester via Witting methylenation followed by basic cleavage of the ethyl ester.

(14) (a) The absolute configuration of **3**, **5a**, and **5d** was established to be *R* by comparing the retention time with that of the ref. 6a in this paper. (b) The absolute configuration of **5b**, **5c**, and **5e** was assigned as *R* on the basis of the measurement and comparison of their specific rotations with that of **3**, assuming that the presence of a substituent on the benzene ring does not reverse between the direction of specific rotation and configuration. (c) The absolute configuration of **5f** was not determined.

(15) **General Procedure for Iodolactonization of Substituted 4-Pentenoic Acid**

Salen complex **1a** (41.1 mg, 0.068 mmol) and NCS (5.7 mg, 0.043 mmol) was dissolved in toluene (8.0 mL), and stirred at r.t. for 30 min. After cooling down the resulting solution to –18 °C with ice salt bath, I_2 (60.5 mg, 0.238 mmol) was added as solid to the solution, and stirred at –18 °C for 5 min. Compound **2** (30.0 mg, 0.170 mmol) was added to the mixture and cyclized for an additional 20 h at –18 °C. The reaction mixture was quenched with 10% aq $Na_2S_2O_3$ (20 mL) and extracted with CH_2Cl_2 (3 × 20 mL). The organic layer was separated and washed with sat. aq Na_2CO_3. After removal of solvent in vacuo, the resulting crude product was purified by chromatography on silica gel (elution with EtOAc–PE = 1:5) to give lactone **3** (44.6 mg, 87%). The ee was determined by HPLC analysis [hexane–2-PrOH = 9:1; Chiralcel OD-H; 1.0 mL/min; 254 nm; t_R (*S**) = 18.7 min; t_R (*R**) = 21.4 min].