Enantioselective Electrochemical Lactonization Using Chiral Iodoarenes as Mediators

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Abstract The enantioselective electrochemical lactonization of diketo acid derivatives using chiral iodoarenes as redox mediators is reported for the first time. Good to high stereoselectivities are observed in the lactonization and also in intermolecular α-alkoxylations of diketo ester derivatives. This enantioselective process was then adapted to an electrochemical flow microreactor where only small amounts of supporting electrolyte were necessary.

Key words electrolysis, flow microreactors, hypervalent iodine, lactonization, stereoselective synthesis

The utility of chiral hypervalent iodine compounds for enantioselective oxidative reactions represents an important and interesting area in organic chemistry. Specifically, as a versatile and general oxidation system, the combination of mCPBA as the stoichiometric oxidant and chiral iodoarenes as catalysts has been successfully applied to various transformations, including the asymmetric difunctionalization of alkenes, the stereoselective dearomatization of phenol or naphthol derivatives, enantioselective oxidative rearrangement and the enantioselective synthesis of spirooxindole derivatives. Nevertheless, although enantioselective oxidative lactonization has been well developed via the dearomatization of phenol or naphthol derivatives using chiral iodoarenes in combination with mCPBA, direct lactone synthesis through oxidative cyclization of keto acids is underdeveloped, and only moderate enantioselectivities (<51% ee) were achieved (Scheme 1, eq. 1).

As an efficient and environmentally friendly protocol for organic synthesis, electrochemical conversions have recently gained more attention as often an excess amount of conventional chemical oxidants and reducing reagents can be avoided. Although the electrochemical oxidative α-lactonization of γ-keto acids has been reported using n-Bu4NI as the mediator (Scheme 1, eq. 2), the enantioselective electrolysiss of lactones is still unexplored. In organic electrochemistry, iodoarenes represent a versatile class of redox mediators, which can generate hypervalent iodine(III) reagents via anodic oxidation to accomplish various transformations without use of a stoichiometric oxidant such as mCPBA. The first electrolysis of iodoarenes described the synthesis of (difluoroiodo)benzene, by Schmidt and Meinert in 1960, and subsequently Fuchigami has contributed to the development of different fluorination reactions in electrochemistry. Recently, the anodic oxidation of iodoarenes in trifluoroethanol and hexafluoroisopropanol (HFIP) has been reported by Nishiyama and Francke and their co-workers, who accomplished C–N and C–O bond formations. Some reviews in this area have recently been published.
The anodic oxidation of chiral iodoarenes and subsequent enantioselective synthesis has never been reported, although there are many reported works on stereoselective oxidative functionalizations using hypervalent iodine reagents. Herein, we report the enantioselective electrochemical α-lactonization and α-alkoxylation of diketo acid derivatives with chiral iodoarenes as electron-transfer mediators. These asymmetric reactions have been performed in batch chemistry but can also proceed using an electrochemical flow reactor with lower amounts of electrolyte (Scheme 1, eq. 3).

Initial reactions were performed using diketo acid 1a as a model substrate for the enantioselective lactonization with chiral iodoarene 2b as redox mediator, and platinum as anode and cathode material, under galvanostatic conditions at 7 mA (Scheme 2). Since fluorinated solvents are known to stabilize iodine(III) reagents by the anodic oxidation, TFE was initially chosen as the solvent.

Several commonly used electrolytes were investigated in the electrochemical reaction shown in Scheme 2 (Table 1, entries 1–3); the use of n-Bu4NBF4 as the electrolyte gave lactone 3a in good yield (70%) and enantioselectivity (71% ee) (entry 3). Although the reaction does proceed in the absence of trifluoroacetic acid (TFA), both the efficiency and enantioselectivity were decreased (Table 1, entry 4). For this electrochemical process, the solvent HFIP is not a good choice and only results in moderate yield and lower enantioselectivity (Table 1, entry 5); no product was detected using acetonitrile as the solvent. There is also no product formed in the absence of either electrolyte or chiral iodoarene, and with catalytic amounts of 2b only traces of the product were observed (Table 1, entries 6–8). A decrease in the reaction temperature to –10 °C did not improve the enantioselectivity, but only resulted in a lower yield of 3a (Table 1, entry 9).

The absolute configuration of the major isomer of 3a was shown to be (S) via X-ray crystallographic analysis (Scheme 2). Other lactate-based 2-iodoresorcinol derivatives were also employed as potential electron-transfer mediators, including iodoarenes that have previously found applications in the enantioselective oxidative dearomatization of naphthols. Neither 2a nor 2c gave better results than 2b (Table 1, entries 10 and 11) while the chiral iodoarenes 2d and 2e containing benzyl ester and amide functionalities decomposed after several minutes under the electrochemical reaction conditions.

To explore the generality and the substrate scope of this electrochemical reaction, some diketo acid derivatives 1 were subjected to the electrolysis conditions (Scheme 3). The electrolysis of substrates bearing electron-rich or -poor groups on the indanone moiety gave the corresponding lactones 3b–3d in moderate yields with reasonable enantioselectivities. For the naphthyl-substituted substrate 1e, the reaction proceeded in high yield leading to the product 3e in 63% ee. Also, tetralone derivatives such as 1f led to the cyclized product 3f in 58% yield and 47% ee, while lactone 3g without an aryl moiety was only formed in 36% yield as a racemate.

When the carbonyl group and carboxylic acid were both fixed to an aromatic ring as 3h, the reaction proceeded well with good selectivity. Unfortunately, the attempted cyclization of the monobenzyl substrate 5-oxo-5-phenylpentanoic acid (11) failed to give any desired product 3i, which was previously reported in high yield under electrochemical conditions with n-Bu4NI as the mediator.

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**Table 1** Enantioselective Electrochemical Lactonization of 1a to 3a Using Chiral Iodoarenes

<table>
<thead>
<tr>
<th>Entry</th>
<th>Electrolyte</th>
<th>Yield (%)</th>
<th>ee (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2b (1.2 eq), LiClO4</td>
<td>30</td>
<td>67</td>
</tr>
<tr>
<td>2</td>
<td>2b (1.2 eq), 0.05 M n-Bu4NClO4</td>
<td>61</td>
<td>65</td>
</tr>
<tr>
<td>3</td>
<td>2b (1.2 eq), 0.05 M n-Bu4NBF4</td>
<td>70</td>
<td>71</td>
</tr>
<tr>
<td>4</td>
<td>2b (1.2 eq), 0.05 M n-Bu4NBF4, no TFA added</td>
<td>51</td>
<td>61</td>
</tr>
<tr>
<td>5</td>
<td>2b (1.2 eq), 0.05 M n-Bu4NBF4, HFIP instead of TFE</td>
<td>50</td>
<td>29</td>
</tr>
<tr>
<td>6</td>
<td>2b (1.2 eq)</td>
<td>0</td>
<td>–</td>
</tr>
<tr>
<td>7</td>
<td>no iodoarene, 0.05 M LiClO4</td>
<td>0</td>
<td>–</td>
</tr>
<tr>
<td>8</td>
<td>2b (0.2 eq), 0.05 M n-Bu4NBF4</td>
<td>&lt;5</td>
<td>–</td>
</tr>
<tr>
<td>9</td>
<td>2b (1.2 eq), 0.05 M n-Bu4NBF4</td>
<td>41</td>
<td>70</td>
</tr>
<tr>
<td>10</td>
<td>2a (1.2 eq), 0.05 M n-Bu4NBF4</td>
<td>54</td>
<td>67</td>
</tr>
<tr>
<td>11</td>
<td>2c (1.2 eq), 0.05 M n-Bu4NBF4</td>
<td>15</td>
<td>68</td>
</tr>
</tbody>
</table>

* a Reaction conditions: Pt cathode, Pt anode, 1a (0.025 M), 2 (0.03 M), electrolyte (0.05 M), TFA (0.075 M), solvent (4 mL), undivided cell (charge passed: 2.6 F).
  b Determined by HPLC.
  c The reaction was performed at –10 °C.
It has been reported that oxidative lactonization can be achieved with a combination of chiral iodoarenes and mCPBA as stoichiometric oxidant. Therefore, the combination of 2b and mCPBA was compared to the electrochemical reaction conditions, leading to products 3a, 3g and 3i. Compounds 3a and 3g were obtained with similar yields and selectivities, while 3i could be isolated in moderate yield and low enantioselectivity only using the combination of 2b and mCPBA (Scheme 3).

With chiral iodoarene 2b, intermolecular C–O bond functionalization was also investigated using ester 4 as a substrate under the standard electrochemical conditions (Scheme 4). Protonic solvents such as water, alcohols and acetic acid were chosen, together with TFE, due to their conductivity and nucelophilicity.

Pleasingly, the electrochemical reaction of ester 4 in a mixture of TFE/H2O (3:1) with 2b as the chiral mediator gave the desired α-hydroxy product 5a in moderate yield with 31% ee. Although the reaction efficiency was reduced in solvent mixtures of TFE with methanol or ethanol, high enantioselectivities (up to 79% ee) were observed (5b and 5c). However, when the electrolysis was attempted in the solvent TFE/AcOH (3:1), the desired α-acetoxy product 5d was not detected. The absolute configuration of compounds 5 was assigned by analogy to compound 3a.

Compared with batch processes for electrochemical reactions, continuous flow reactors can reduce the amount or avoid the use of electrolytes because of the close distance of the electrodes. We have reported electrochemical flow microreactors for several oxidative transformations. Pleasingly, the present enantioselective lactonization could also be successfully accomplished using an electrochemical flow microreactor with a lower concentration of n-Bu4NBF4 (5 mM) (Scheme 5), despite a slight decrease in the efficiency and enantioselectivity. There is no conversion without catalytic amounts of electrolyte and the conversion decreases when the platinum cathode is replaced by graphite. To the best of our knowledge, this is the first enantioselective reaction with iodine(III) reagents generated in an electrochemical flow microreactor.

Additional experiments were carried out to further explore the mechanism of this enantioselective electrolytic lactonization. Initially, a stepwise batch process was performed. After the anodic oxidation of mediator 2b, substrate 1a was added to the reaction mixture. However, this stepwise protocol only led to the desired product 3a in 9% yield (65% ee) (Scheme 6). In the 1H NMR spectra of the electrolyzed 2b in TFE, a downfield peak at around 7.24 ppm was observed indicating the formation of an iodine(III) species, but this peak disappeared after several hours or after removal of the solvent (see the Supporting Information). This indicates the formation of an unstable iodine(III) species Ar−IL2 by electrolysis of iodoarene 2b. In addition, cy-
In summary, we have developed an electrochemical method for enantioselective lactonization using chiral lactate-based iodoarenes as redox mediators. This protocol was also applied to the intermolecular α-alkylation of diketo esters with good enantioselectivities. Furthermore, it was demonstrated that this enantioselective transformation could be adapted to an electrochemical flow microreactor with lower supporting electrolyte concentration. Further studies on stereoselective electrosynthesis using chiral iodoarenes are currently in progress.

All reactions were carried out in oven-dried glassware under an atmosphere of nitrogen/argon using anhydrous solvents. All commercial reagents were used as received. 1H NMR spectra were recorded at 400 or 500 MHz on Bruker DPX 400 or DPX 500 spectrometers. Chemical shifts are reported in parts per million (ppm, δ) relative to TMS (δ 0.00). 1H NMR splitting patterns are designated as singlet (s), doublet (d), doublet of doublet (dd), triplet (t), quartet (q), multiplet (m). 13C NMR spectra were recorded at 100 or 125 MHz. Mass spectra were obtained using a Waters Xevo G2-S ESI mass spectrometers. IR spectra were recorded as neat on a Shimadzu FTIR Affinity-1S spectrophotometer. Melting points were determined using a Gallenkamp hot-stage apparatus and are uncorrected. Optical rotations were measured using a 10.0 mL cell with a 1.0 dm path length on a SCHMIDT + HAENSCH UniPol L polarimeter apparatus and are reported as [α]c in g per 100 mL, solvent at 20 °C.

Methyl 4-Oxo-4-(1-oxo-2,3-dihydro-1H-inden-2-yl)butanoate (4)
To a solution of diisopropylamine (1.6 g, 15.8 mmol) in THF (40 mL) was added 2.5 M n-Buli in hexane (6.9 mL, 17.4 mmol) at –78 °C. The resulting solution was stirred at –78 °C and then at room temperature for an additional 30 min. The solution was cooled to –78 °C, and to this solution was added dropwise a solution of 1-iodoarene (1 g, 5 mmol) in THF (10 mL). After 1 h at –78 °C, to the solution was added dropwise methyl-4-chloro-4-oxobutyrate (1.36 mL, 11 mmol) in THF (5 mL). The resulting solution was warmed to room temperature over 2 h, and then quenched with saturated NH4Cl solution. The organic phase was separated, and the water phase was extracted with Et2O (3 × 20 mL). The combined organic layers were dried, concentrated and purified by chromatography (petroleum ether/EtOAc, 5:1) to give 4 as a colorless solid; yield: 1.01 g (51%); mp 57–59 °C.

IR (neat): 3025, 1734, 1628, 1545, 1221, 1167, 1038, 779, 731 cm–1.

1H NMR (500 MHz, CDCl3): δ = 7.78 (d, J = 8.0 Hz, 1 H), 7.55–7.48 (m, 2 H), 7.41 (t, J = 7.5 Hz, 1 H), 7.30 (s, 3 H), 3.64 (s, 2 H), 2.82 (t, J = 6.0 Hz, 2 H), 2.75 (t, J = 6.0 Hz, 2 H).

13C NMR (125 MHz, CDCl3): δ = 187.5, 182.4, 173.0, 146.8, 137.7, 132.4, 127.3, 125.6, 122.8, 110.6, 51.9, 30.5, 30.4, 28.9.


4-Oxo-4-(1-oxo-2,3-dihydro-1H-inden-2-yl)butanoic Acid (1a)
Compound 4 (1.2 g, 5 mmol) was dissolved in THF/MeOH/water (3:1:1 v/v/v, 20 mL). To this mixture 1 M LiOH in water (10 mL) was added and the resulting solution stirred overnight. After removal of organic solvent in vacuo, the aqueous phase was acidified with HCl until pH 3. The mixture was extracted with EtOAc (3 × 20 mL). The combined organic fractions were dried with sodium sulfate and cont-
centrated in vacuo to give the crude acid 1a, which was recrystallized from EtoAc to give 1a as a white solid; yield: 1.03 g (89%); mp 119–121 °C.

IR (neat): 3025, 1699, 1624, 1549, 1404, 1067, 972, 775 cm⁻¹.

1H NMR (500 MHz, CD₃OD): δ (two isomers) = 7.70 (d, J = 7.5 Hz, 0.77 H) (major), 7.68–7.60 (m, 1 H), 7.57–7.52 (m, 2 H), 7.44–7.35 (m, 1.23 H), 3.66 (s, 1.54 H) (major), 3.60 (d, J = 16.5 Hz, 0.46 H), 3.28–3.25 (m, 0.23 H), 3.19 (d, J = 16.5 Hz, 0.46 H), 2.98–2.90 (m, 0.46 H), 2.83 (t, J = 6.5 Hz, 1.54 H) (major), 2.70 (t, J = 6.5 Hz, 1.63 H) (major), 2.63–2.50 (m, 0.77 H).

13C NMR (125 MHz, CD₃OD): δ = 204.4, 202.1, 176.3, 156.2, 148.7, 139.1, 136.8, 136.5, 133.7, 128.9, 128.5, 128.0, 127.0, 125.3, 123.6, 111.2, 38.6, 31.6, 31.5, 29.9, 29.3, 28.8.


4-Oxo-4-(1-oxo-1H-inden-2-yl)-butanoic Acid (1e)

Yield: 1.01 g (71%); white solid; mp 164–166 °C.

IR (neat): 3010, 1710, 1591, 1541, 1340, 1219, 1062, 870, 783 cm⁻¹.

1H NMR (500 MHz, DMSO-d₆): δ (two isomers) = 12.2 (br s, 1 H), 8.97 (d, J = 8.5 Hz, 0.45 H), 8.92 (d, J = 8.5 Hz, 0.55 H) (major), 8.27 (d, J = 7.0 Hz, 0.55 H) (major), 8.20 (d, J = 7.5 Hz, 0.45 H), 8.08 (d, J = 8.0 Hz, 1 H), 7.77–7.67 (m, 2 H), 7.63 (t, J = 7.5 Hz, 1 H), 4.34 (tt, J = 7.5, 2.5 Hz, 0.45 H), 3.59–3.52 (m, 0.55 H) (major), 3.35–3.16 (m, 1.45 H), 3.00–2.90 (m, 0.55 H) (major), 2.78 (t, J = 7.5 Hz, 1 H), 2.48–2.44 (m, 2 H).

13C NMR (125 MHz, DMSO-d₆): δ = 203.1, 200.4, 190.0, 176.3, 173.5, 173.4, 158.4, 149.7, 136.5, 133.8, 132.3, 131.2, 128.7, 128.2, 126.5, 124.3, 123.8, 122.7, 111.0, 61.1, 37.1, 30.3, 29.6, 28.0, 27.6, 27.6.


4-Oxo-4-(1-oxo-2,3-dihydro-1H-inden-2-yl)-4-oxobutoanoic Acid (1b)

Yield: 406 mg (31%); white solid; mp 132–134 °C.

IR (neat): 3003, 1718, 1647, 1576, 1492, 1375, 1024, 877, 786 cm⁻¹.

1H NMR (400 MHz, DMSO-d₆): δ (two isomers) = 12.2 (br s, 1 H), 7.52 (d, J = 8.4 Hz, 0.40 H), 7.40 (d, J = 8.4 Hz, 0.60 H) (major), 7.29 (dd, J = 8.4, 2.8 Hz, 0.40 H), 7.25–7.20 (m, 0.60 H) (major), 7.15 (dd, J = 8.4, 2.8 Hz, 0.60 H) (major), 7.00 (dd, J = 2.8 Hz, 0.40 H), 4.25 (dd, J = 8.0, 2.8 Hz, 0.60 H) (major), 3.81 (s, 2 H), 3.79 (s, 1 H), 3.56 (br s, 1.40 H), 3.37 (dd, J = 13.2, 2.8, 0.60 H) (major), 3.30–3.07 (m, 1 H), 2.92–2.80 (m, 1.60 H) (major), 2.56 (t, J = 2.8 Hz, 1.40 H), 2.43 (t, J = 6.8 Hz, 0.60 H) (major).

13C NMR (100 MHz, DMSO-d₆): δ = 202.8, 199.8, 173.7, 173.6, 159.2, 158.9, 147.0, 136.1, 127.7, 126.6, 124.3, 119.6, 112.5, 105.4, 105.1, 61.4, 55.6, 55.4, 37.1, 31.6, 30.1, 28.4, 27.6, 27.4.

4-Oxo-4-(2-oxocyclopentyl)butanoic Acid (1g)

A mixture of cyclopentanone (2.6 mL, 30 mmol) and pyrrolidine (3.0 mL, 36 mmol) in benzene (12 mL) was refluxed using a Dean–Stark apparatus overnight. The solvents and excess pyrrolidine were removed in vacuo. The crude enamine and dry triethylamine (4.6 mL, 33 mmol) were dissolved in benzene (10 mL), and to this solution was added dropwise methyl-4-chloro-4-oxobutyrate (3 mL, 33 mmol). The reaction mixture was then heated at reflux for 8 h, cooled to room temperature and filtered through Celite. The filtrate was concentrated in vacuo to give the acylated enamine which was used without further purification. The acylated enamine was dissolved in water (7.5 mL), acetic acid (7.5 mL) and THF (15 mL), and the resultant dark-brown solution stirred at room temperature for 1 h. The solvent was removed in vacuo and the residue purified by column chromatography (petroleum ether/ EtOAc, 3:1) to give 3a as a white solid; yield: 16 mg (70%); mp 162–164 °C; 71% ee (determined by HPLC).

\[ \Delta \nu_{\text{IR}}^{\text{neat}} = 281.0757; \text{found: 281.0676.} \]

HPLC (YM Chiral Amine-C 5-5 μm (25 cm), hexane/i-ProH, 90:10, 0.8 mL/min, 20 °C, 254 nm): \( t_R \) (minor) = 65.4 min, \( t_R \) (major) = 70.4 min.

(5)-6-Methyl-4,5′-dihydrospiro[indene-2,2′-pyran]-1,3′,6′(3H)-trione (3c)

Yield: 13 mg (54%); white solid; mp 166–168 °C; 61% ee (determined by HPLC).

\[ \Delta \nu_{\text{IR}}^{\text{neat}} = 281.0757; \text{found: 281.0676.} \]

HPLC (YM Chiral Amine-C 5-5 μm (25 cm), hexane/i-ProH, 90:10, 0.8 mL/min, 10 °C, 254 nm): \( t_R \) (minor) = 65.4 min, \( t_R \) (major) = 70.4 min.

(5)-6-Methyl-4,5′-dihydrospiro[indene-2,2′-pyran]-1,3′,6′(3H)-trione (3c)
(5)-6-Chloro-4',5'-dihydrospiro[indene-2,2'-pyran]-1,3',6'(3H)-trione (3d)
Yield: 10 mg (40%); white solid; mp 172–174 °C; 68% ee (determined by HPLC).

(5)-4',5'-Dihydrospiro[cyclopenta[a]naphthalene-2,2'-pyran]-1,3',6'(3H)-trione (3e)
Yield: 24 mg (87%); white solid; mp 200–202 °C; 63% ee (determined by HPLC).

6-Oxaspiro[4.5]decane-1,7,10-trione (3g)
Yield: 7 mg (36%); yellow oil; 0% ee (determined by HPLC).

(R)-Spiro[indene-2,3'-isochroman]-1',4'(3H)-trione (3h)
Yield: 18 mg (64%); white solid; mp 140–142 °C; 67% ee (determined by HPLC).

(S)-Methyl 4-(2-Methoxy-1-oxo-2,3-dihydro-1H-inden-2-yl)-4-oxobutanoate (5a)
Yield: 17 mg (66%); colorless oil; 31% ee (determined by HPLC).

(S)-4-(2-Methoxy-1-oxo-2,3-dihydro-1H-inden-2-yl)-4-oxobutanoate (5b)
Yield: 10 mg (38%); colorless oil; 77% ee (determined by HPLC).
1H NMR (500 MHz, CDCl3): δ = 7.73 (d, J = 7.5 Hz, 1 H), 7.64 (t, J = 7.5 Hz, 1 H), 7.50 (d, J = 8.0 Hz, 1 H), 7.39 (t, J = 7.5 Hz, 1 H), 3.68 (d, J = 17.0 Hz, 1 H), 3.64 (s, 3 H), 3.41 (s, 3 H), 3.32–3.08 (m, 3 H), 2.62–2.46 (m, 2 H).

13C NMR (125 MHz, CDCl3): δ = 205.8, 199.5, 173.0, 152.5, 136.2, 134.1, 128.0, 126.5, 124.8, 93.7, 53.6, 51.7, 33.6, 32.6, 27.5.


(10) For molecules containing chiral keto lactones, see:


(16) For selected enantioselective electrochemical processes, see:


(18) CCDC 1834441 (3a) contains the supplementary crystallographic data for this paper. The data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/getstructures.
