Electrochemically site-selective alkoxylation of twisted 2-arylbenzoic acids *via* spirolactonization

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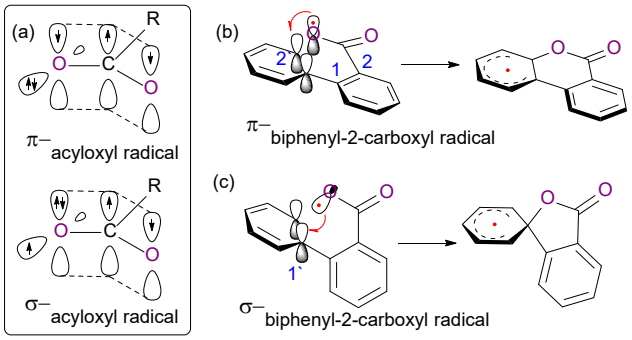
The *Electrochemical Cross-Dehydrogenative Coupling* (ECDC) of twisted biphenyl-2-carboxylic acids with aliphatic alcohols provides 4`-alkoxyspirolactones which isomerize, under mild basic conditions, to give 4`-alkoxy-2-phenylbenzoic acids. This site-selective alkoxylation was readily adapted to 1-mmol scale and is environmentally friendly, as no terminal oxidants are needed and H_2 is the only residue. The suitability of diphenic acid derivatives in this two-step protocol is noteworthy, especially for axially chiral substrates that can be functionalized with retention of the configuration and of the enantiomeric purity. We have proposed a plausible mechanism based on experimental pieces of evidence that support the single-electron oxidation of the carboxylate, formed by deprotonation of the biphenyl-2-carboxylic acids with 2,6-lutidine, and DFT calculations that suggest a very fast spirocyclization of the intermediate σ-aroyloxyl radical. Competing pathways to benzocoumarins were also examined by computational studies.

Introduction

The high occurrence of benzoic acids in Nature with a variety of functionalization makes these stable and inexpensive compounds highly attractive substrates in organic synthesis.[1] In this context, the single-electron oxidation of arylcarboxylic acids has recently become a convenient and predictable tool to activate these substrates for a range of transformations.[2] In contrast to aliphatic and alicyclic acyloxyl radicals that undergo extremely fast decarboxylation ($k > 10^9$ s^{-1} at 25 ˚C),[3] the extrusion of CO_2 from aroyloxyl radicals is much slower ($k \sim 10^6$ s^{-1} at 25 ˚C).[4] This different reactivity has been attributed to the σ-ground state of aliphatic acyloxyl radicals, whose orbital symmetry favors the decarboxylation, while for most aroyloxyl radicals the ground state is π and the decarboxylation is symmetry forbidden (Scheme 1a).[5] Therefore, electrophilic *O*-centered aroyloxyl radicals tend to react intramolecularly, either in HAT processes regenerating the carboxylic acid ($k \sim 10^7$ $M^{-1}s^{-1}$ at 25 ˚C) or in fast addition to adjacent aromatic rings. Among benzoic acids are biphenyl-2-carboxylic acids, in which, after single-electron oxidation, the resulting aroyloxyl radicals usually undergo intramolecular addition at C-2` to give benzocoumarins after further oxidation.[6]

This reactivity of biphenyl-2-carboxyl radicals was previously ascribed to the better overlapping of the frontier orbitals for the planar biphenyl π radical (Scheme 1b). The corresponding σ-acyloxyl radical approach would result in an orthogonal overlap between the interacting orbitals, which would not be effective for the cyclization at C-2`. However, when the twisted conformation of biphenyl-2-carboxyl radicals is particularly stable, the spirocyclization can be favored in virtue of the frontal overlapping of the $\sigma$-acyloxyl radical with the $\pi$-orbital of the aromatic ring at C-1`(Scheme 1c).[7]



Scheme 1 Orbital overlapping in the cyclization of π- and σ-biphenyl-2-carboxyl radicals.

A few years ago, we demonstrated that this dehydrogenative lactonization can be induced by visible light, using the Fukuzumi catalyst and $(NH_4)_2S_2O_8$ as the terminal oxidant (Scheme 2a).[8] Interestingly, Luo and coworkers improved this protocol by using a cobalt complex in substoichiometric amounts to recycle the acridinium photocatalyst.[9] The same transformation of biphenyl-2-carboxylic acids has been lately accomplished using Kolbe anodic oxidation.[10] Very recently, the group of Samec demonstrated that *ortho*-position blocked biphenyl-2-carboxylic acids can be transformed into the corresponding spirolactones using two complementary oxidative photocatalytic protocols (Scheme 2b).[11] This transformation attracted our attention because the starting biaryl compounds are abundant as by-products after the bio-refinery of lignin,[12] and the spirolactone motif is found as the core of several natural products and bioactive compounds.[13] Importantly, the spirolactone moiety can be further elaborated into a variety of functionalities.

The activation of carboxylic acids by anodic oxidation dates back to the independent pioneer studies of Faraday and Kolbe in the XIX century.[14] Organic electrochemistry has experienced important advancements in the last decades and nowadays has

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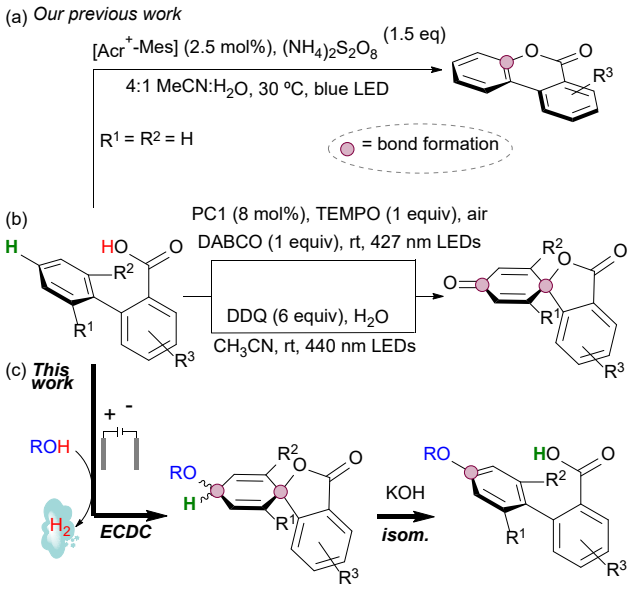


Scheme 2 (a) Our previous work to form benzo-3,4-coumarins. (b) Previous work for the spirolactonization. (c) This work.

become a fundamental tool for synthetic organic chemists.[15] The use of electricity as a reagent in an organic transformation is environmentally benign and cost-effective, explaining the current renaissance of electro-organic synthesis. Moreover, the precise control based on redox potentials can give access to reaction intermediates only accessible by this method under safe and predictable conditions, opening novel pathways in organic synthesis.[16] Continuing with our interest in the reactivity of aroyloxyl radicals,[8,17] we decided to examine the anodic oxidation of *ortho*-position blocked biphenyl-2-carboxylic acids in the presence of aliphatic alcohols (Scheme 2c).

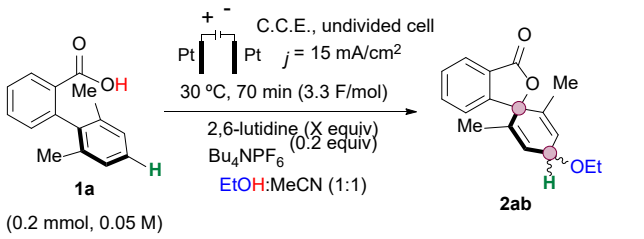
According to the above-commented precedents, we anticipated that the preference for the twisted conformation of the substrates would favor the spirocyclization of the acyloxyl radical, followed by a second anodic oxidation to yield a cyclohexadienyl cation that would be trapped by the alcohol. Importantly, this *Electrochemical Cross-Dehydrogenative Coupling (ECDC)* approach avoids the use of harmful terminal oxidants and minimizes the waste produced, H_2 being the only by-product. Interestingly, the isomerization of the resulting spirolactone would give rise to the selective remote alkoxylation of starting 2-phenylbenzoic acids at C-4`, a transformation that has been eluded to date, opening new avenues for remote functionalization of this important family of compounds.

Results and discussion

Optimization of the ECDC reaction.

We set out to investigate our proposed ECDC, by choosing biphenyl-2-carboxylic acid **1a**, with both *ortho* positions blocked by methyl groups, as the model substrate in a 1:1 EtOH/MeCN mixture (Table 1).

Table 1 Optimization of the reaction conditions of the ECDC



Entry	2,6-lutidine	Variation of the conditions	% Yield **2ab**[a]
1	-	none	47
2	-	7.5 mA/cm², 4.0 F/mol	48
3	-	6.7 mA/cm², 2.8 F/mol	57
4	-	15 mA/cm², 8.4 F/mol	34
5	-	anode of graphite	18
6	-	cathode of graphite	50 (48)
7	0.2 equiv	cathode of graphite	74
8	**0.2 equiv**	**none**	**81 (74)**
9	2 equiv	EtOH:MeCN (1:50)	41
10	0.5 equiv	EtOH:MeCN (1:3)	69
11	0.2 equiv	only EtOH as solvent	68 (54)
12	0.2 equiv	$NaClO_4$ as electrolyte	70
13	0.2 equiv	Bu_4NBr as electrolyte	nr
14	-	10 equiv of HFIP	nr
15	0.2 equiv	15 °C	(56)
16	0.2 equiv	40 °C	(55)

[a]GC yield using durene as an internal standard. Isolated yields are given in parenthesis. nr = no reaction. HFIP: 1,1,1,3,3,3-hexafluoroisopropanol. A sand bath was used to control external temperature.

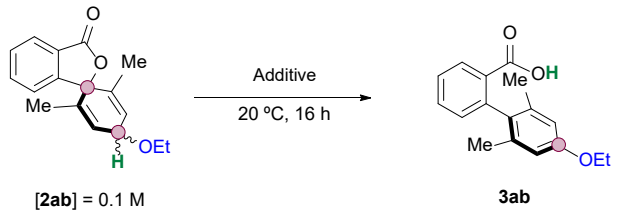
After screening some initial conditions (see ESI), we observed that reduced amounts of Bu_4NPF_6 (0.2 equiv) were enough to ensure good conductivity, and using platinum electrodes (anode and cathode), the formation of the spirolactone **2ab** with selective ethoxylation at the C-4` position occurred in 47% yield (entry 1, Table 1). Variation of the current density and charge passed (entries 2-4) or the material of the electrodes (entries 5-6), slightly improved or even diminished the initial yield.

Since the single-electron oxidation of carboxylates is usually much easier than that of carboxylic acids, we examined the impact of 2,6-lutidine in the outcome of the reaction. The use of substoichiometric amounts of this hindered organic base significantly improved the yield of spirolactones **2ab**, which were obtained as a 1:1 diastereomeric mixture (entry 8). Remarkably, the use of a graphite cathode under similar conditions (entry 7), gave a slightly lower but still synthetically useful yield of **2ab**. Increasing the equivalents of 2,6-lutidine to 0.5 or 2 equivalents did not improve the outcome of the reaction (entries 9-10) and further optimization of solvent, electrodes, supporting electrolyte, additive, or reaction temperature, gave poorer results (entries 11-16).

Optimization of the isomerization.

With the optimized conditions for the synthesis of **2ab** in hand, it was submitted to acidic conditions for isomerization. Notably, only partial isomerization was achieved using AcOH at room

Table 2 Optimization of the isomerization reaction



[**2ab**] = 0.1 M **3ab**

Entry	Variation of the conditions	Ratio **3ab:2ab**[a]
1	AcOH	58:42
2	AcOH, 45 ˚C	decomposition
3	AcOH:EtOAc (1:1)	16:84
4	AcOH:EtOAc (1:10), 72 h	80:20
5	AcOH:CH_2Cl_2 (1:10)	57:43
6	AcOH:EtOH (1:10)	50:50
7	TFA:CH_2Cl_2 (1:10)	decomposition
8	KOH (2 equiv), EtOH	60:40
9	KOH (10 equiv), EtOH	73:27
10	**KOH (10 equiv), EtOH, 45 ˚C**	**>98:2 (>99%)**

[a] Ratio obtained by ^{1}H-NMR. Isolated yields are given in parenthesis.

temperature overnight and the increase of the temperature to 45 ˚C resulted in decomposition of the sample (entries 1-2, Table 2). The addition of different co-solvents at different temperatures and reaction times (entries 3-6) could not afford complete conversion, not even the use of TFA, which promoted the formation of several byproducts (entry 7). Thus, the isomerization was attempted using alkaline conditions (entries 8-10). To our delight, the use of 10 equivalents of KOH in EtOH at 45 ˚C overnight provided the desired isomerized product **3ab** in quantitative yield after simple crystallization of the product.

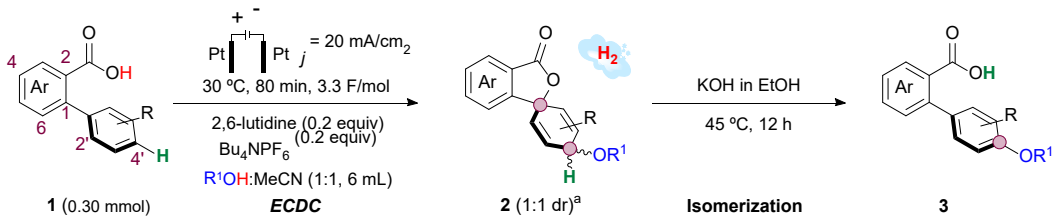
Scope and limitations of the ECDC/isomerization protocol

Having optimized the reaction conditions for the ECDC of acid **1a** with EtOH, and the isomerization of spirolactone **2ab**, we investigated the substrate scope for this two-step protocol (Scheme 3). The use of the optimized ECDC conditions in the presence of MeOH afforded spirolactone **2aa** in 78% yield. By increasing the hydrophobicity of the alcohol (*n*-PrOH, *i*-PrOH, *t*-BuOH) a decrease of the yield was observed for the formation of **2ac** (68%), **2ad** (53%), and **2ae** (37%), respectively. This drop in the reaction yield might be related to a lower conductivity of the reaction media, as indicated by the increasing voltage of the electrochemical cell when passing the same current density throughout these experiments (j = 20 mA/cm^2). Alkyl-, aryl-, and halogen-substituted acids performed well under the ECDC reaction conditions to give compounds **2b**-**2f**, including the 2-phenylnicotinic acid derivative **1g** that delivered the corresponding spirolactone **2g**. Unfortunately, the presence of a nitro group was not tolerated under our optimized electrochemical conditions (**2q**) and the thiophene-2-carboxylic acid derivative **1r** remained intact, probably due to the high angular tension that would result from having two fused 5-membered rings. Interestingly, acid **1h** bearing a single alkyl group at C-2' provided spirolactone **2h** in 38% yield accompanied by 31% of benzo-3,4-coumarin, with loss of the isopropyl group. This result was examined in more detail using DFT calculations and will be commented on the ESI. Remarkably, having a methyl group at C-6 resulted in a smooth spirocyclization (**2i**, **2j**), although in lower yield for the challenging acid **1k** that is unsubstituted at C-2' (**2k**, 32%), due to the side formation of the corresponding benzocoumarin. In addition, for this group of substrates, the presence of a methyl (**1i**) or methoxy group at C-2' (**1j**) significantly increased the diastereomeric ratio of the obtained spirolactones (65:35 for **2i**, and 81:19 for **2j**). For product **2j**, nOe interactions revealed the *cis*-spirolactone as the major diastereoisomer (details are given in ESI).

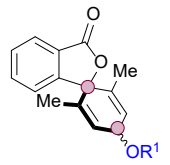
In line with these results, naphthyl derivative **1l** with a methyl group at C-6 provided compound **2l** in good yield and enhanced diastereoselectivity (71%, 63:37 dr), while product **2m** was obtained in a more moderate yield with almost no diastereoselection (54%, 54:46 dr). Notably, acid **1s** failed to give the desired spirolactone under our reaction conditions. Instead, benzocoumarin **2s'** was obtained in moderate yield as a 2:1 mixture of regioisomers. Since the steric demands of **1s** and **1m** are similar yet their outcome is very different, we reasoned that the dearomatization of the adjacent naphthyl ring requires less energy to give **2m** than that of the phenyl ring to give **2s**.

The twisted conformation of all the previous substrates was imposed by steric repulsion in the *ortho*-position blocked biphenyl-2-carboxylic acids. We thus decided to examine the commercially available diphenic acid (**1n**), a symmetric molecule for which a -CO_2H group is present at C-2`, with a much lower steric demand than *i*-Pr group (A-values of 1.2 vs 2.2), but with almost orthogonal phenyl rings.[18] It is worth mentioning that diphenic acid derivatives can be found in herbs and fruits and exhibit a range of therapeutic properties.[19] After using our optimized conditions in the ECDC of **1n** with MeOH, we were pleased to isolate the spirolactone **2n** in good yield, with the second -CO_2H group intact. The same protocol was also successfully conducted with the more congested 6,6'-dimethyl-2,2´-diphenic acid (**1o**) and its monomethyl ester derivative **1p**,[20] providing the spiro compounds **2o** and **2p** in good and moderate yields, respectively.

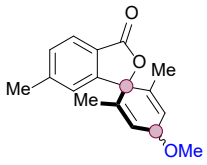
The obtained spirolactones (**2aa**-**2p**) were submitted to our mild optimized conditions for the isomerization, providing the corresponding 4`-alkoxybiphenyl-2-carboxylic acids (**3aa**-**3p**) in excellent yields. Notably, after acidic workup, pure products were obtained either from direct acidulation and crystallization from the reaction mixture or by simple extraction with EtOAc. It is worth mentioning that the isomerization of **2n** and **2o** provided the expected mono-methoxylated diphenic acid derivatives **3n** and **3o**, de-symmetrized with respect to the substrates **1n** and **1o**. Furthermore, the mild conditions used for this isomerization (45 ˚C) made it possible that **2p** furnished methyl ester **3p** in excellent yield, while at a higher temperature (60 ˚C) diacid **3o** was obtained after complete saponification.



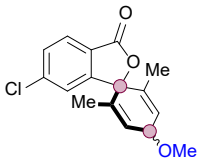
ECDC scope



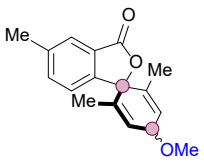
R^1 = Me (**2aa**), 78%
R^1 = Et (**2ab**), 74%
R^1 = ^{n}Pr (**2ac**), 68%
R^1 = ^{i}Pr (**2ad**), 53%
R^1 = ^{t}Bu (**2ae**), 37%



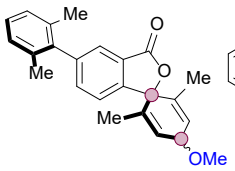
2b, 70%



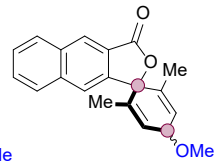
2c, 60%



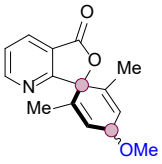
2d, 37%



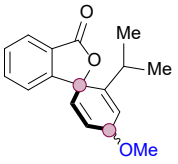
2e, 54%



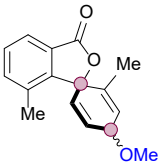
2f, 59%



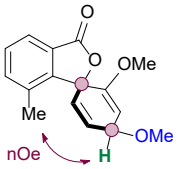
2g, 51%[b]



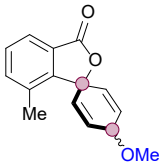
2h, 38%[c]



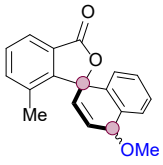
2i, 62%, 65:35 dr



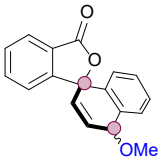
2j, 63%,81:19 dr [d]



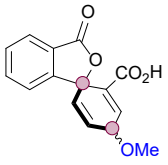
2k, 32%,[e] 55:45 dr



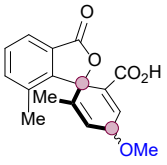
2l, 71%, 63:37 dr



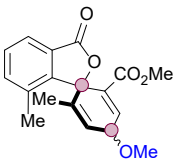
2m, 54%, 54:46 dr



2n, 63%

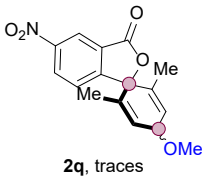


2o, 67%



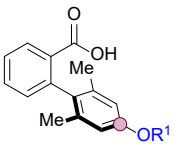
2p, 34%

Unsuccessful results

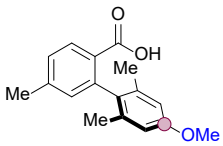


2q, traces

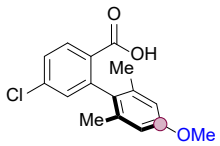
Isomerization scope



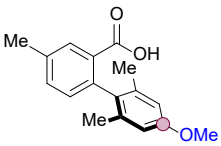
R^1 = Me (**3aa**), 92%
R^1 = Et (**3ab**), >99%
R^1 = ^{n}Pr (**3ac**), >99%
R^1 = ^{i}Pr (**3ad**), 92%
R^1 = ^{t}Bu (**3ae**), >99%



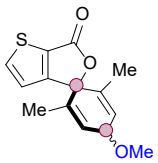
3b, 90%



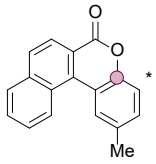
3c, 66%



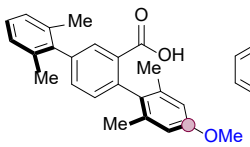
3d, 79%



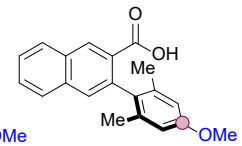
2r, 0%



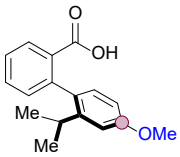
2s', 28%, 2:1 rr[f]



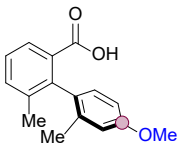
3e, 93%



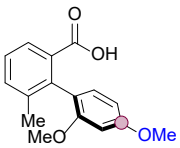
3f, 89%



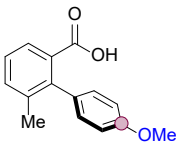
3h, 84%



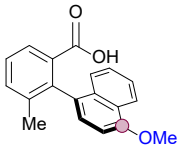
3i, >99%



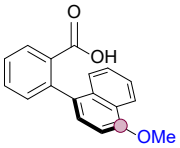
3j, 67%



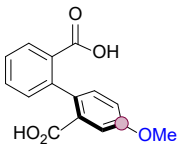
3k, >99%



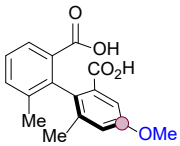
3l, 82%



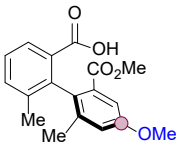
3m, 86%



3n, 91%



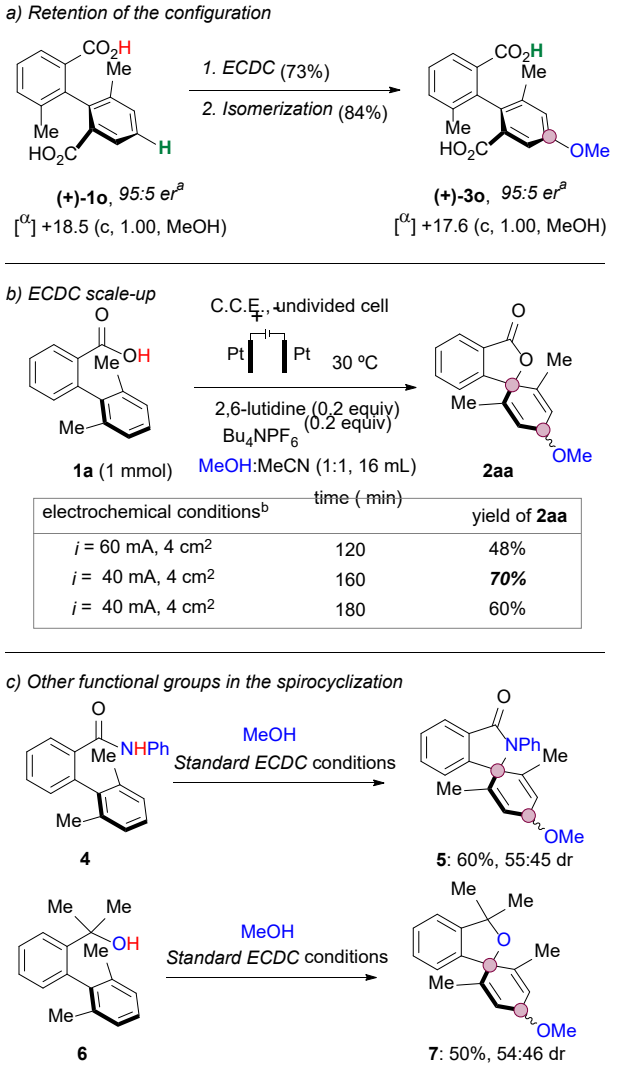
3o, 92%



3p, 83%

Scheme 3 Substrate scope for ECDC and isomerization. [a]unless otherwise noted, the diastereoselectivity of compounds **2** ranges from 45:55 to 55:45 dr. [b] ^{1}H NMR yield using durene as internal standard. A single diastereoisomer was isolated in a 14% yield (see ESI for details). [c]31% of benzo-3,4-coumarin (**2h'**) was also isolated. [d] nOe-d$_1$ experiment performed for compound **2j** irradiating C-4'-H of the major and minor diastereoisomers: nOe with C-5-Me was only observed for the major diastereoisomer. [e]13% of 10-methyl-6*H*-benzo[c]chromen-6-one (**2k'**) was also isolated. [f] spirolactone **2s** was not isolated and 28% of a 2:1 rr of 2-and 4-methyl-6*H*-naphtho[2,1-*c*]chromen-6-one (**2s'**) was isolated instead. *denotes the position of the methyl group in the regioisomeric structure. See structures of compounds **2h**`and **2k**` in the ESI.

To examine the enantioespecificity of our two-step ECDC/isomerization protocol, we prepared the enantioenriched acid **(+)-1o** following a reported procedure.[21] Remarkably, when this chiral substrate was submitted to our optimal ECDC conditions, followed by isomerization, the 4`-methoxy derivative **(+)-3o** was obtained in good yield (Scheme 4a) and, most importantly, retaining the enantiopurity (HPLC analysis, see ESI for details) and absolute configuration (optical rotation). Notably, this two-step protocol would be valuable for the preparation of other 4`-alkoxy-1,1`-biaryl-2,2`-dicarboxylic acids with axial chirality, which have found broad applications as ligands in asymmetric catalysis.[22]



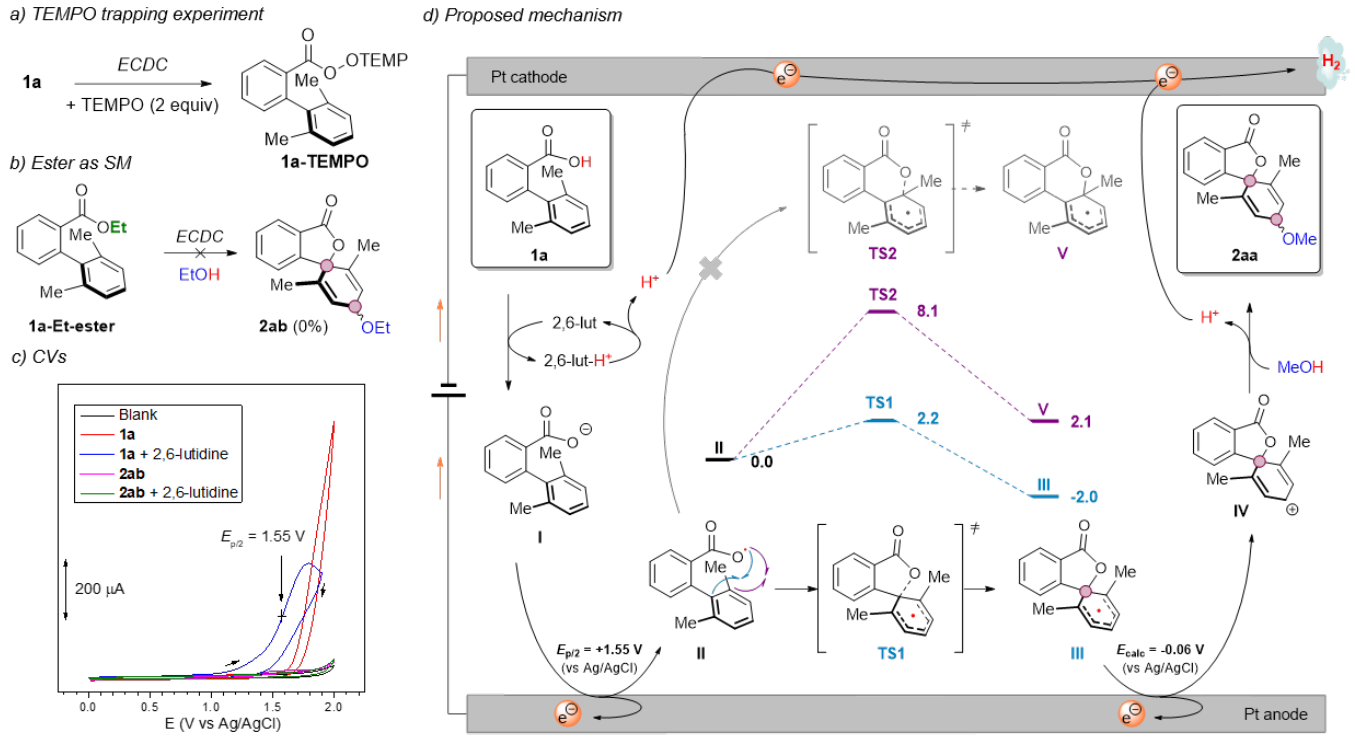
Scheme 4 Further evaluation of the ECDC reaction. [a] Enantiomeric ratio obtained from HPLC analysis of the corresponding diesters. [b] Area referred to one face of the anode (see ESI for set up details).

To further evaluate the synthetic usefulness of our ECDC protocol, we scaled up the reaction to 1 mmol of **1a**. After adaptation of the set-up and small optimization of the electrochemical conditions (see ESI for details), spirolactone **2aa** was obtained in 70% yield (Scheme 4b) and the corresponding methoxy-substituted acid **3aa** in 86% yield. More importantly, we demonstrated that this ECDC protocol could be extended to substrates different from carboxylic acids. For example, carboxamide **4** was smoothly transformed into the spirolactam **5** and the tertiary alcohol **6** into the spirophthalane **7** (Scheme 4c).[23]

Mechanistic investigations

Mechanistic studies were performed to propose a plausible mechanism for this reaction. When 2 equivalents of TEMPO were added to the optimal conditions, the corresponding **1a-TEMPO** adduct was isolated in quantitative yield (Scheme 5a), and when the **1a-Et ester** was submitted to optimized ECDC conditions, no reaction was observed (Scheme 5b). Both experiments suggest the necessity of an acid moiety for the reaction to proceed and the formation of an acyloxyl radical intermediate under these reaction conditions. Moreover, to the light of these experiments, and the observed oxidation potentials for biphenyl and sodium benzoate (> +1.80 V and + 1.55 V *vs* Ag/AgCl, respectively, see ESI), the single-electron oxidation of the dimethylphenyl ring (Ar^2), followed by nucleophilic addition of the carboxylate group is less likely. The cyclic voltammogram analysis of substrate **1a** in the presence of 2,6-lutidine showed a significant shift to a lower onset oxidation potential (Scheme 5c, E_{onset} from 1.60 V to 1.05 V vs Ag/AgCl).[24] This result is in accordance with the easier oxidation of the carboxylate anion and explains the positive impact of the organic base on the reaction outcome. Importantly, it was also observed that the oxidation of spirolactone **2ab** occurred at much higher potentials (E_{onset} > 1.90 V vs Ag/AgCl) than acid **1a** in the presence of 2,6-lutidine, explaining the lack of significant overoxidation observed with this protocol.

DFT calculations were also performed to gain more insight about the reaction mechanism. As indicated above, we had some evidences that suggested the generation of biphenyl-2-carboxyl radicals in our process. There are some literature reports about the transformation of biphenyl-2-carboxyl radicals to give intramolecular additions to the adjacent aromatic ring at either C-1' (spirocyclization)[7,11] or C-2' (formation of benzocoumarins).[6,8,10] Therefore, we evaluated both reaction pathways and the results of our calculations are shown in Scheme 5d. The formation of cyclohexadienyl radical **III** by spirocyclization of radical **II** through transition state **TS1** is a thermodynamically spontaneous process (ΔG = -2.0 kcal/mol) with a low activation barrier of 2.2 kcal/mol, which suggests that this transformation should be very fast. The alternative intramolecular reaction of radical **II** by formation of a new bond between the oxygen radical and the C-2' atom is kinetically less favored, the energy of **TS2** being 5.9 kcal/mol higher than the one for **TS1**. Moreover, radical **V** is thermodynamically less stable than the starting radical **II** (ΔG = +2.1 kcal/mol). These observations are consistent with the experimental data, since spirolactones **2a**-**2g** were the only products detected when acid **1a** was used as starting material. However, the formation of a benzocoumarin by-product was observed in the reaction with substrate **1h**, bearing an isopropyl group at atom C-2', and this result is discussed in the ESI.



Scheme 5 (a) Optimized ECDC reaction in the presence of a radical trap such as TEMPO. (b) ECDC reaction performed using **1a-Et-ester**. (c) Cyclic voltammograms (CVs) of acid **1a** and spirolactone **2ab** in the absence and in the presence of 2,6-lutidine. (d) Proposed mechanism including Gibbs free energy profile (in kcal/mol) for two possible reaction pathways for the cyclization of radical **II**, obtained from DFT calculations at the B3LYP-D3/6-311G(d,p) level with acetonitrile as solvent using the SMD model. Experimental ($E_{p/2}$) and calculated (E_{calc}) potentials for the single electron oxidation of **I** to **II** and **III** to **IV**, respectively, were also included.

With all these precedents in hand, we propose a plausible mechanism (Scheme 5d) in which 2,6-lutidine forms the carboxylate **I** that suffers the first single-electron oxidation on the surface of the anode to form the twisted acyloxyl radical **II**, which undergoes a fast spirocyclization through **TS1**.

Once the spirocyclization has taken place, we assume that radical **III** could be further oxidized at the anode to give the corresponding carbocation **IV**, which would then be trapped by a molecule of MeOH furnishing the final product **2aa**, which is resistant to oxidation. We have estimated an oxidation potential of -0.06 V (vs Ag/AgCl)[25] from the variation of the calculated Gibbs free energies of the radical **III** and the corresponding cation **IV** (see the ESI for details). This value is clearly lower than the experimental oxidation potential that we had measured for the carboxylate of acid **1a** to give radical **II** ($E_{p/2}$ = +1.55 V Ag/AgCl). Therefore, the electrochemical oxidation of radical **III** should be a feasible process under our reaction conditions. Concomitant cathodic two-electron reduction of the liberated protons, with 2,6-lutidine acting as a proton shuttle, causes the release of hydrogen gas (H_2) as the only residue.

The ease with which radical **II** undergoes the spirocyclization could be due to the twisted conformation imposed by the two methyl groups located at C-2' and C-6'. In addition, we have studied the spin density distribution obtained from the calculations of the vibrational frequencies of radical **II** and the results are depicted in Figure 1. As expected, the electrophilic

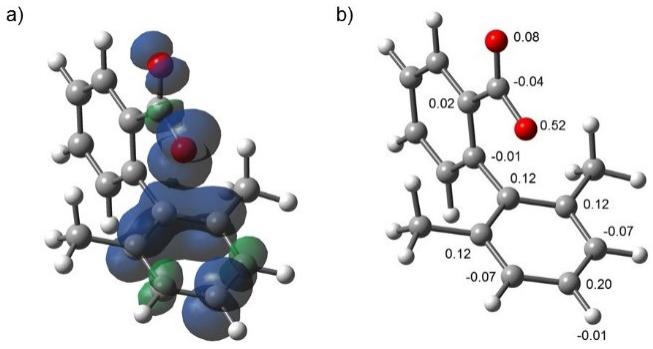


Figure 1 Spin densities of radical **II**, obtained from DFT calculations at the B3LYP-D3/6-311G(d,p) level with acetonitrile as solvent using the SMD model. For the sake of clarity, only values of spin density different from 0 are included in Figure 1b.

oxygen radical seems to have σ-character, which facilitates its interaction with the Ar[2] ring at C-1' by an effective frontal overlapping of the orbitals. Most of the spin density (0.52) is located on the reacting oxygen atom (O-1). The spin density on the carbonylic oxygen atom (O-2) is very small (0.08) and the two C-O bond lengths are different, the bond with O-2 (1.230 Å) being shorter than the one with O-1 (1.300 Å). These data suggest that there is no delocalization of the oxygen radical through the carbonyl group. Instead, the oxygen radical interacts with the Ar[2] ring (Figure 1), resulting in the development of significant spin density on atoms C-1' (involved

in the spirocyclization), C-2', C-6' (*ortho* positions) and C-4' (*para* position).

Experimental

See detailed experimental procedures in the ESI.

Conclusions

In conclusion, we have demonstrated that the electrochemical oxidation of twisted biphenyl-2-carboxylic acids in the presence of aliphatic alcohols is a convenient method to selectively prepare 4`-alkoxyspirolactones, avoiding terminal oxidants and $H_2$ being the only residue. The straightforward isomerization of the spirolactones under mild conditions allows the formation of 4`-alkoxy-2-phenylbenzoic acids. Remarkably, axially chiral diphenic acid derivatives do not racemize with this protocol, which opens new opportunities in asymmetric catalysis for the site-selective functionalization of these chiral ligands. We have collected experimental evidence that supports the intermediacy of biphenyl-2-carboxyl radicals obtained by single-electron oxidation of the corresponding carboxylate during our mechanistic study. Moreover, our DFT calculations indicate that these twisted benzoyloxyl radicals have a σ-character with significant transfer of spin density to the adjacent phenyl ring, favoring an exergonic and very fast spirocyclization. This study paves the way to examine amides and alcohols instead of carboxylic acids as substrates of this electrochemical transformation and the use of redox mediators to expand the scope of nucleophiles, a work that is currently under progress in our laboratory.

Author Contributions

The experiments and the analysis of data were conducted by M. E.-B. and I. B. The computational studies were performed by D. G. The project was conceived by J. C. G.-G., and directed by I. B. and J. C. G.-G. The manuscript was written by I. B., D. G., and J. C. G.-G. All authors discussed the results and approved the final version of the manuscript.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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