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Article

One-Pot Transformation of Salicylaldehydes to Spiroepoxydienones *via* the Adler–Becker Reaction in a Continuous Flow

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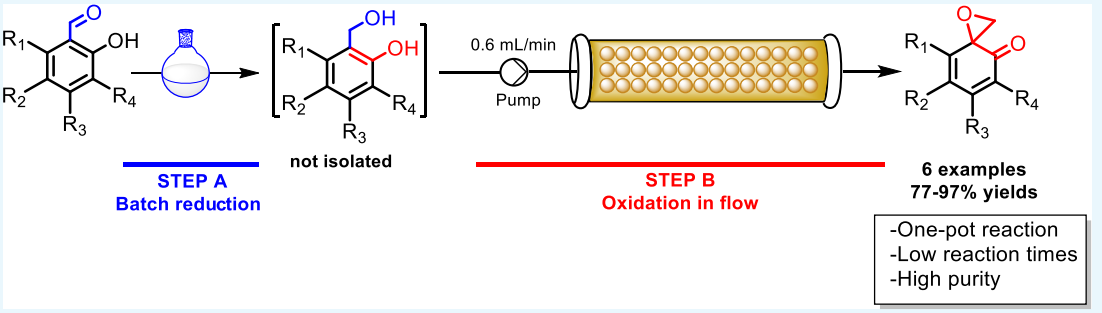

ABSTRACT: The Adler–Becker reaction is a useful approach for the oxidative dearomatization of salicylic alcohols to spiroepoxydienones and has been applied in the total synthesis of several natural products. Despite the advantages, the substrate and product instability under the reaction conditions can decrease the reaction efficiency, leading to lower yields. Herein, we report the Adler–Becker reaction in a continuous flow for the transformation of reduced salicylaldehydes into spiroepoxydienones in a one-pot approach. For that, a heterogeneous oxidant based on periodate is developed, leading to an efficient continuous flow process, with higher productivity and shorter reaction times, when compared with batch conditions.

INTRODUCTION

Oxidative dearomatization of phenols is a useful methodology for the creation of complex organic building blocks from simple precursors. An important example is the classic Adler–Becker reaction that transforms salicylic alcohols into spiroepoxydienones, mediated by periodate (Figure 1A).[1,2] This is a simple procedure starting from readily available salicylic alcohols via reduction of the corresponding salicylaldehyde[3−6] or salicylic acid[7,8] or *ortho*-hydroxymethylation of phenols,[9,10] which, in combination with a cheap oxidant, have been used in several total synthesis of natural compounds.

Other modifications to the Adler–Becker reaction have been reported such as one-pot oxidative dearomatization/acylnitroso cycloaddition[11] and in situ elimination under basic conditions of salicylic alcohol as dichloroacetate to quinone methide followed by epoxidation with H_2O_2.[12]

Spiroepoxydienones are reported as key intermediates for the total synthesis of several bioactive natural products such as (−)-4-hydroxyzinowol,[13] triptolide,[14] platencin,[15] ovalicin,[16] and (+)-hirsutic acid[17] (Figure 1B).[18,19] In addition, due to their diverse chemical reactivity, spiroepoxydienones are valuable intermediates for the generation of complex molecular architectures (Figure 1C).[11,20−24] For example, when not protected, spiroepoxydienones (substituted in positions C-5 and C-6) can undergo Diels–Alder cycloaddition, forming cycloadducts by dimerization or in the presence of an external dienophile, providing a powerful methodology for the synthesis of compounds containing the bicyclo[2.2.2]octane ring system (Figure 1C) with a notable contribution by Singh and Johnson, among others groups.[11,13,22] Due to their versatility, spiroepoxydienones can be quite unstable in the presence of light since photochemical isomerization can occur forming the respective salicylaldehyde (Scheme 1).[1,25,26] Despite the rich chemistry of the formed spiroepoxydienones, their instability under the oxidative reaction conditions as well as the broad instability of the starting salicylic alcohols limits the use of this valuable transformation as a robust synthetic methodology.

Nowadays, flow reactions are gaining considerable interest due to their numerous advantages, such as higher safety, better mixing, more efficient heat transfer, chemoselectivity, reactions under extreme conditions (temperature, pressure), photochemical and electrochemical transformations, and easy scale-out.[27−29] The combination of flow chemistry and supported catalysis can additionally increase the process sustainability due to easier recyclability of the catalyst and higher product purity.[30] In line with our previous studies under flow conditions,[31−35] we

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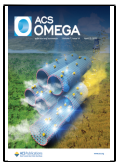


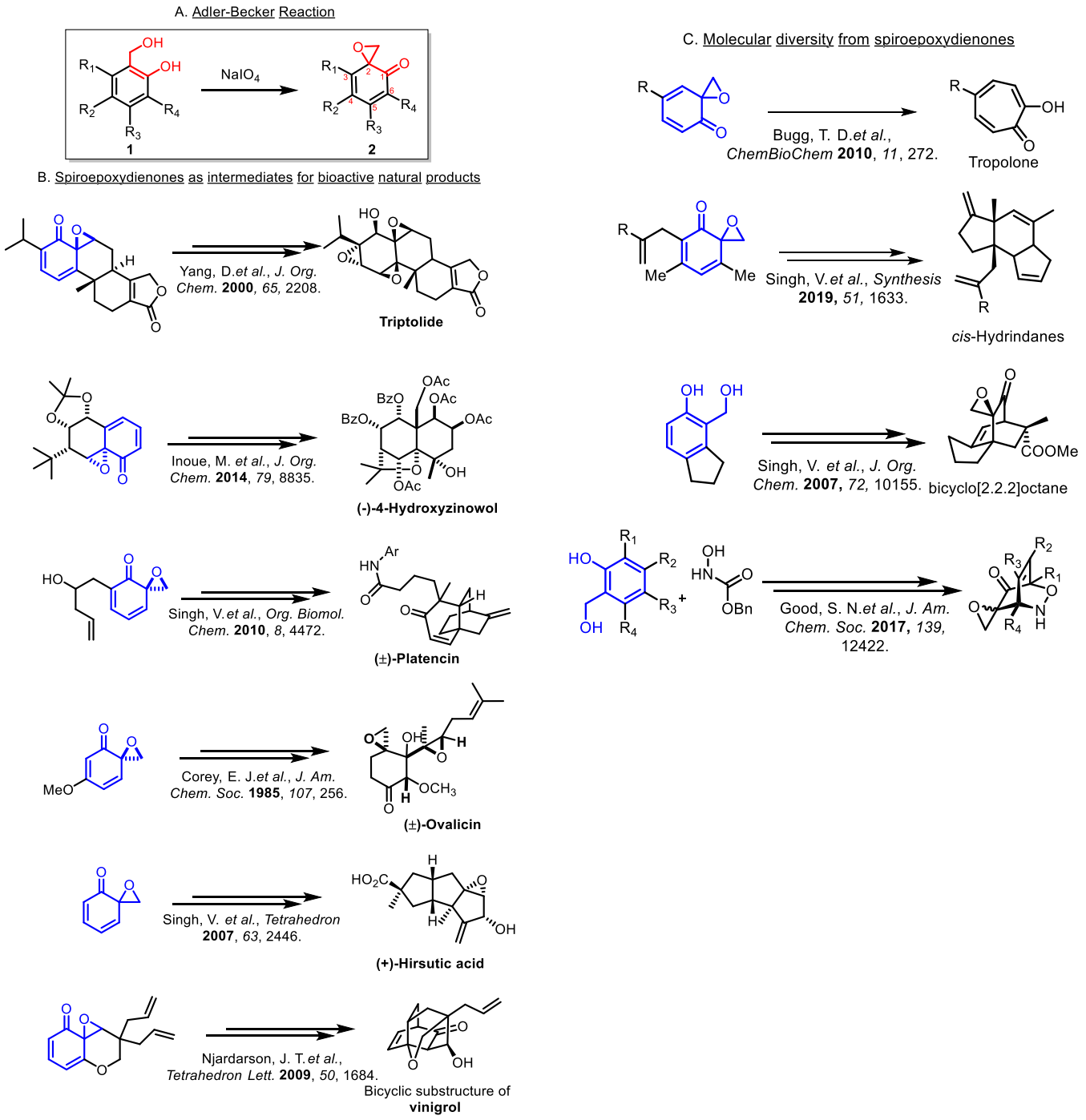
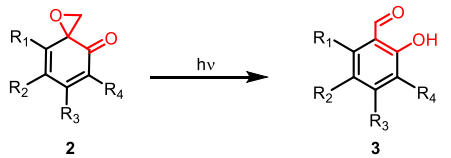


Figure 1. Synthesis of spiroepoxydienones *via* the Adler−Becker reaction (A) and application as a versatile intermediate for the total synthesis of bioactive compounds (B) and as a tool for molecular diversity (C).[1,2,11,13,15−24]

Scheme 1. Photochemical Isomerization of Spiroepoxydienones[1]



explored the possibility to apply the Adler−Becker reaction under flow conditions, in a way to improve reaction yields, minimize side reactions, and also facilitate the isolation step of spiroepoxydienones since these compounds can be quite unstable.

Here, described the Adler−Becker reaction using a packed-bed flow reactor,[30] where the supported oxidant is grafted on an insoluble solid resin. Since the supported oxidant is limited to the flow reactor, no further separation of the product from the reaction mixture is needed, thus improving the yield, product purity, and reaction time, when compared with the Adler−Becker original conditions under batch conditions.

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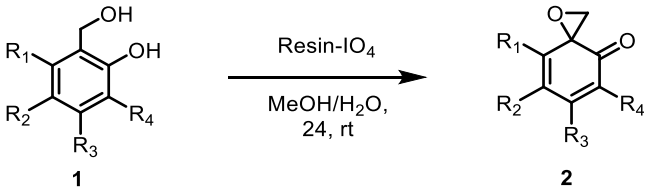
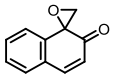
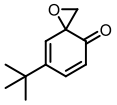
Table 1. Adler–Becker Reaction under Batch Conditions Using Sodium Periodate and Resin-IO_4 as Oxidants[abc]



1 2

Product	Yield (%)[a] (Resin-IO_4 as oxidant, 1.1 equiv.)[b]	Reported [c] ($NaIO_4$ as oxidant, 1.1 equiv.)
 2a	82	50 [21]
 2b	40	77 [1]

[a]Overall yield of the isolated product. [b]Aldehyde (0.6 mmol), $NaBH_4$ (1.1 equiv), and MeOH (3 mL). After 1 h, H_2O (3 mL) and then resin-IO_4 were added (0.66 mmol of IO_4, 1.1 equiv). After 24 h of reaction, the product was isolated by filtration followed by extraction with dichloromethane (DCM). [c]The reported procedure was performed as follows: to an aqueous solution of sodium periodate (0.61 mmol), the substrate (0.6 mmol) dissolved in 3 mL of methanol was added. After 24 h of stirring, methanol was evaporated, and the final product was obtained by extraction with DCM.

Scheme 2. Continuous Flow Adler–Becker Reaction Performed in a Packed-Bed Reactor

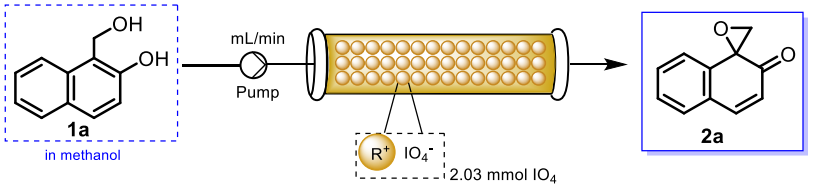
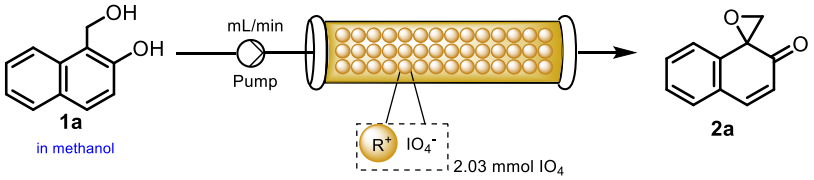


Table 2. Study of the Continuous Flow Adler–Becker Reaction[a]



entry	alcohol (mmol/mL)	flow (mL/min)	yield (%)[b]	productivity[c] (mmol/h)	residence time (min)[d]
1	0.29	0.4	40	2.79	2.2
2	0.06	0.2	73	0.51	4.4
3	0.02	0.2	75	0.16	4.4
4	0.02	0.4	80	0.33	2.2
5	0.02	0.6	76	0.48	1.5

[a]After each run, the resin was replenished with an aqueous solution of 1 M periodic acid. Resin: 1.56 g (2.03 mmol of IO_4); reactor volume: 0.885 mL. [b]Yield of the isolated product. [c]Productivity = [flow rate (mL/min)*concn (μmol/mL)*yield(%)/100].[36] [d]Residence time = [reactor volume]/[flow rate].

RESULTS AND DISCUSSION

Batch Optimization. The study was initiated by the reaction optimization under batch conditions using sodium periodate as an oxidant and 2-naphthol-1-methanol (**1a**) as a model substrate since it has an extended aromatization of the aromatic ring at the positions C-5 and C-6 that avoid the product dimerization. In addition, it is considered that the second aromatic ring stabilizes the resulting spiroepoxide, decreasing the photochemical rearomatization of the spiroepoxide to the aldehyde (Scheme 1). The solvent screening (Figure S1 in the Supporting Information, SI) showed that methanol and acetone were the best tested solvents to this reaction (89 and 88% yield, respectively, of **2a**). Other ketones, acetates, and alcohols were also tested as solvents, resulting in very low yields, even for 48 h reaction. Due to the high solubility

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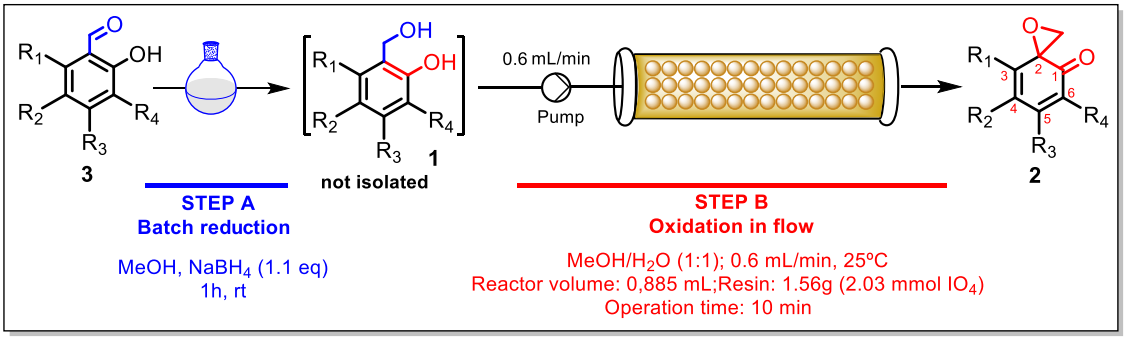
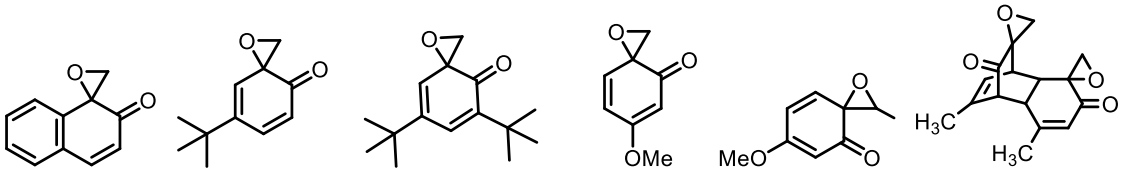
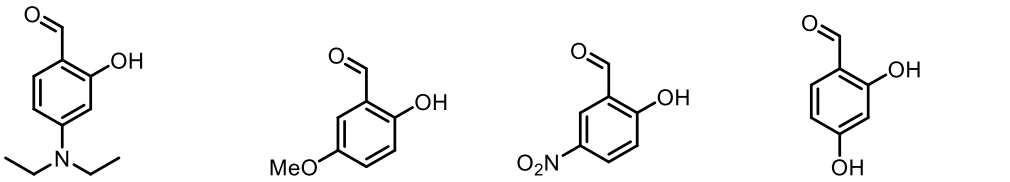
Scheme 3. Substrate Scope of the Adler–Becker Flow Reaction



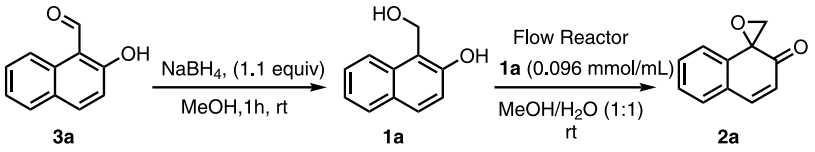


2a, 95% **2b**, 83% **2c**, 77% **2d**, 83% **2e**, 93% **2f**, 76%



3g, no reaction (product degradation) **3h**, no reaction **3i**, over reaction (product degradation) **3j**, over reaction (product degradation)

Table 3. One-Pot Preparation of Spiroepoxidienone 2a Starting from Salicylic Aldehydes 3a[a]



3a 1a 2a

entry	flow rate (mL/min)	yield (%)[c]	productivity (mmol/h)[d]	residence time (min)[e]
1	0.2	69.0	0.80	4.4
2	0.4	65.6	1.53	2.2
3	0.6	78.0	2.71	1.5
4	0.8	25.1	1.16	1.1
5	0.6 2 turns[b]	95.0	3.30	2.9

[a]Reaction conditions: Aldehyde **3a** (0.6 mmol), $NaBH_4$ (1.1 equiv), and MeOH (3 mL) in batch. After 1 h, add H_2O (3 mL), then enter to flow reactor. Resin: 1.56 g, **1a** (0.096 mmol/mL); reactor volume: 0.885 mL; after each run, the resin was replenished with an aqueous solution of 1 M periodic acid. [b]Flow adduct recirculated in the flow reactor for a second time. [c]Yield of the isolated product **2a**. [d]Productivity = [flow rate (mL/min)*concn (mmol/mL)*yield(%)/100].[36] [e]Residence time = [reactor volume]/[flow rate].

of salicylic alcohols in methanol, this solvent was chosen to continue the study.

In a way to further explore the continuous flow approach, sodium periodate was immobilized in solid support, namely, Ambersep resin, and tested for the Adler–Becker reaction in batch. As described in Table 1, when resin-IO_4 is used in bach conditions, low yields can be obtained when compared with sodium periodate, which can be explained by the less available periodate anion when the resin is used.

Continuous Flow. In a way to decrease the reaction time and increase the product purity due to the instability of the products spiroepoxides **2**, the Adler–Becker reaction was tested in a continuous flow approach (for more information, see the SI). Ambersep was used as a polymer-supported base bearing a periodate anion (IO_4^-) as an oxidating agent that was prepared starting from a commercial ion exchange resin (OH form) and flushed with periodic acid (Scheme 2).

It was possible to obtain good yields and isolate the final product just by simple solvent evaporation, without further workup or chromatography. The reaction optimization was performed by testing different flow rates and substrate concentrations (Table 2).

At a low concentration (0.02 mmol/mL), the reaction efficiency was not linear with the flow rate variation since the yield for 0.4 mL/min (80%) was higher than that for 0.2 or 0.6 mL/min (75 and 76%, respectively, Table 2). At a higher

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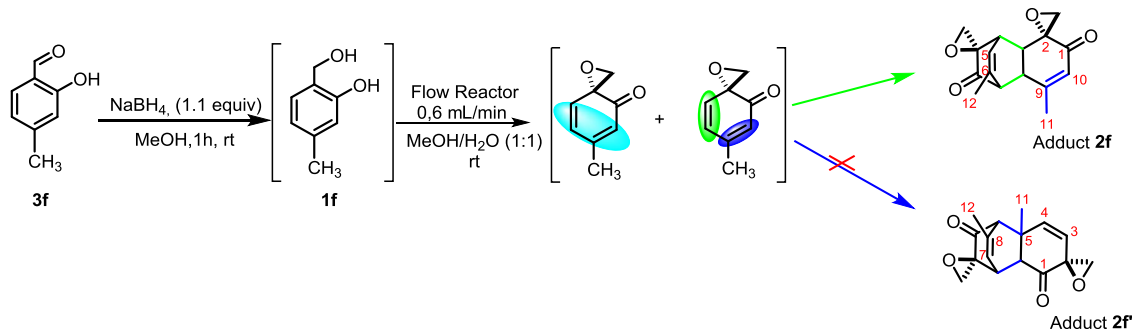
Scheme 4. Formation of the Diels−Alder Adduct for Substrate 3f



concentration, 0.29 mmol/mL (entry 1, Table 2), the productivity increased to 2.79 mmol/h, although the yield decreased to 40%. Despite high similarity of results with different concentrations and flow rates, the best yield was obtained when a 0.02 mmol/mL solution was used at a 0.6 mL/min flow rate. In these conditions, it was possible to replenish the flow reactor at least six times without loss of efficiency by flushing with a 1 M periodic acid solution.

Although the yield in batch is slightly higher (82% in batch vs 80% in flow, Tables 1 and 2, respectively), the flow reaction has several advantages: (a) lower reaction times, from hours in batch to minutes in flow; (b) since the oxidant is retained on the reactor, no workup is needed and only solvent evaporation is required to isolate the product in higher purity (see Figure S15 for the comparison of batch and flow product purity).

One-Pot Adler−Becker Reaction: From Salicylic Aldehydes to Spiroepoxydienones. Salicylic alcohols are typically obtained by the reduction of aldehydes or carboxylic acids[21,37] and, due to their instability, they are usually prepared freshly before the Adler−Becker reaction. To avoid the isolation step of salicylic alcohols **1**, a new approach was studied, where the reduction of aldehydes **3** and subsequent oxidation into spiroepoxidienone **2** were performed in one pot (Scheme 3). For that, the reduction of silicic aldehyde was performed under batch conditions, with $NaBH_4$ in methanol. After that, the crude reactant solution was submitted directly to the flow reactor (Table 3).

In this approach, it was possible to increase the substrate concentration to 0.096 mmol/mL, resulting in a higher productivity (2.71 mmol/h, entry 3, Table 3). Unexpectedly, higher residence times (entries 1 and 2, Table 3) did not increase the reaction yield or the productivity possibly due to the higher contact of the substrate with the oxidant. In a way to increase the residence time without decreasing the flow rate, the reaction mixture was recirculated in the flow reactor for one more cycle. In this way, the yield increased up to 95% also with higher productivity (3.30 mmol/h, entry 5, Table 3). This flow methodology allowed better yields, product purity, and lower reaction times, when compared with batch conditions (Table 1, resin-IO_4 as an oxidant, 24 h, 82% yield, and 0.019 mmol/h productivity). In these conditions (0.6 mL/min, for two cycles), the reaction scope was investigated for the aldehydes **3a−f**, resulting in the corresponding spiroepoxidienones **2** in very good yields for aldehydes **3a−f** (Scheme 3).

Compound **2e** was shown to be particularly unstable (see the SI for NMR); even when prepared freshly from the respective aldehyde, degradation was observed. An attempt to purify this compound by column chromatography was performed although it completely degraded on the column. In addition, aldehydes **3g−j** resulted in product degradation in step B (Scheme 3) or no reaction was observed.

For substrate **3f** that contains a methyl group at *para* position, C-5 was observed the formation of the Diels−Alder adduct **2f** (Schemes 3 and 4). This result can be explained by the facile dimerization of spiroepoxydienones when positions C-5 and C-6 are not protected.[1,38] The exclusive formation of the stereoselective adduct **2f** was reported previously by Adler[38] and confirmed by ^{1}H NMR (see the SI) since the presence of only two olefinic protons (H5 and H10) versus three olefinic products of adducts **2f′** (H3, H4, and H7) was observed. The structure of compound **2f** was confirmed by X-ray analysis (Figure 2). The diastereoselectivity of this reaction can be justified by steric effects since the reactive dienophile is the less substituted and less hindered one (Scheme 4). Although spiroepoxydienone **2d** (Scheme 3) is substituted in the same position C-5 as compound **2f**, the Diels−Alder adduct is not observed. This can be explained by electrodonating character of the methoxy group, thus inhibiting the Diels−Alder dimerization.

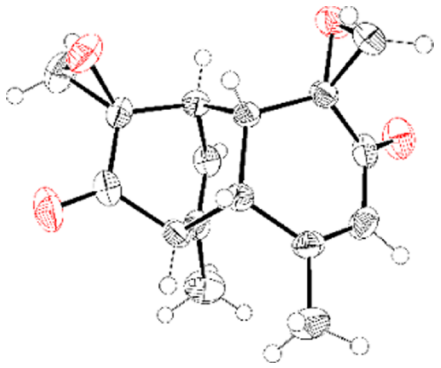


Figure 2. X-ray analysis: ORTEP-3 diagram of compound **2f** (asymmetric unit), using 50% probability level ellipsoids.

CONCLUSIONS

We describe, for the first time, the Adler−Becker reaction in a continuous flow process that allows obtaining spiroepoxydienone from salicylic aldehydes without the need to isolate the intermediary alcohol. Although this is not a general methodology for all salicylic aldehydes, when compared with batch conditions, the flow process allows higher reaction efficiency, resulting in higher yields, without the need to purify the resulting product by chromatography. This can be a valuable tool in total synthesis since it can avoid unnecessary steps in purification, increasing the overall yield.

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EXPERIMENTAL SECTION

All of the solvents were distilled before use. All chemicals were purchased from Aldrich or Alfa Aesar. ^{1}H and ^{13}C NMR spectra were recorded in $CDCl_3$ on a Bruker ARX 300 spectrometer at 300 and 75 MHz, respectively. Chemical shifts are expressed in ppm relative to tetramethylsilane (TMS). The coupling constants (J) are reported in Hz. High-resolution mass spectra were recorded in a Thermo Scientific Q Exactive hybrid quadrupole-Orbitrap mass spectrometer (Thermo Scientific Q Exactive Plus). Chiral high-performance liquid chromatography (HPLC) analysis was performed using a Shimadzu pump (LC-20AT) and a diode array detector (DAD SPD-M20A), with a commercial Lux 5 μm cellulose-3 chiral column, 250 × 4.6 mm column (90:10 hexane/isopropanol).

X-ray Details. The data was collected at room temperature (296(2) K) on a Bruker D8 Venture diffractometer equipped with a Photon 100 CMOS detector and an Oxford cryostream cooler using graphite-monochromated Mo Kα radiation (λ = 0.71073 Å). The data was processed using the APEX3 suite software package, which includes integration and scaling (SAINT), absorption corrections (SADABS[39]), and space group determination (XPREP). Structure solution and refinement were done using direct methods with the programs SHELXT-2014/5 and SHELXL-2018/3[40,41] inbuilt in APEX and WinGX-Version 2021.3[42] software packages.

Preparation of Resin-IO_4 as an Oxidant Reagent under Batch Conditions. In an empty glass column, 1.9772 g of Ambersep 900 resin (in a hydroxide form) was added and washed with water until the pH becomes neutral. After that, the column was passed through a periodic acid aqueous solution (1 M) to exchange the hydroxyl ions of the resin to the periodate anions until the pH turns from neutral to acidic (1.3 mmol IO_4/g of resin). Swelling of the resin was not observed.

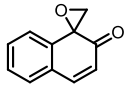
General Procedure for the Synthesis of Spiroepoxydienones from Salicylaldehydes with Resin-IO_4 as an Oxidant under Batch Conditions (Table 1). An appropriate amount of salicylic aldehyde **3** was dissolved in MeOH (0.6 mmol in 6 mL), and $NaBH_4$ (1 equiv) was added. The mixture was stirred at room temperature for 1 h. Afterward, water (6 mL) and HCl (100 μL of 0.1M HCl) were added to neutralize the reaction medium. Then, resin-IO_4 (0.66 mmol of IO_4, 1.1 equiv) was added, and the mixture was stirred overnight at room temperature. The resin-IO_4 was filtered, and the solvent was evaporated to afford product **2** as a solid.

Description of the Continuous Flow System. In an empty HPLC column (250 mm × 4.6 mm), 1.56 g of Ambersep 900 resin (in a hydroxide form) was added and passed through methanol (capacity of the column: 1.2 mL of methanol); after that, the column was washed with a periodic acid aqueous solution (1 M) to exchange the hydroxyl ions of the resin with the periodate anions (1.3 mmol IO_4^- per g of resin). Swelling of the resin was not observed. Then, the column was washed with a solution of methanol/water in a ratio of 1:1, and the substrate was injected as a solution in methanol/water (1:1) at different flow rates at 25 °C. After each run, the resin was replenished with a 1 M periodic acid solution. The concentration of ions IO_4^- per gram of resin was calculated by the volume of periodic acid necessary to acidify the resin in the hydroxide form.

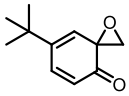
Optimization of Conditions for the Continuous Flow Adler–Becker Reaction (Table 2). 1-(Hydroxymethyl)-naphthalen-2-ol **1a** (0.6 mmol) was dissolved in MeOH and passed through the reactor at different flow rates and concentrations. After that, methanol was evaporated to afford 2*H*-spiro[naphthalene-1,2′-oxiran]-2-one **2a** as a white solid without further purification.

General Method for the Synthesis of Spiroepoxydienones from Salicylaldehydes (One-Pot Reaction) under Flow Conditions (Scheme 3). In a flask, 0.6 mmol salicylic aldehyde **3** dissolved in 6 mL of methanol was added; then 1 equiv of $NaBH_4$ was added, and the mixture was stirred for 1 h at room temperature. After the reaction was complete (by TLC), 6 mL of water and HCl (100 μL of 0.1 M HCl aqueous solution) were added to neutralize the reaction. The resulting mixture was injected directly into the reaction flow system, with a flow rate of 0.6 mL/min at 25 °C. The reaction mixture that exited the flow system was collected and injected for a second time at the same flow rate. After that, methanol was evaporated and the aqueous solution was extracted with 3 × 100 mL of dichloromethane. After solvent evaporation, spiroepoxydienones **2** was obtained in a pure form without chromatographic purification, as characterized by NMR.

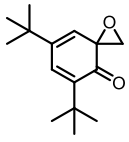
Characterization of the Spiroepoxydienones. 2a.[21] White solid; yield: 95%; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.61 (d, J = 10.0 Hz, 1H), 7.47−7.33 (m, 3H), 7.31−7.19 (m, 1H), 6.35 (d, J = 10.0 Hz, 1H), 3.40 (d, J = 8.1 Hz, 1H), 3.14 (d, J = 8.1 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 194.37, 145.78, 137.45, 131.87, 130.49, 129.72, 128.68, 125.56, 123.59, 77.51, 77.09, 76.66, 63.73. HRMS (ESI): calcd for $C_{11}H_7O_2$ $[M]^-$: 171.0452; found: 171.0443.



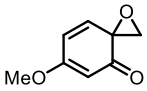
2b.[1] Yellow solid; yield: 83%; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.28 (d, J = 10.2 Hz, 1H), 6.20 (d, J = 10.2 Hz, 1H), 5.75 (s, 1H), 3.26 (d, J = 8.1 Hz, 1H), 3.09 (d, J = 8.1 Hz, 1H), 1.11 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 195.52, 148.23, 143.09, 129.78, 125.97, 59.37, 34.54, 28.63. HRMS (ESI): calcd for $C_{11}H_{13}O_2$ $[M]^-$: 177.0921; found: 177.0913.



2c.[1] Yellow solid; yield: 77%; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.07 (d, J = 2.4 Hz, 1H), 5.66 (d, J = 2.4 Hz, 1H), 3.19 (d, J = 8.1 Hz, 1H), 2.99 (d, J = 8.1 Hz, 1H), 1.18 (s, 9H), 1.10 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 194.39, 147.62, 144.47, 136.77, 127.48, 59.00, 34.77, 34.66, 29.13, 28.70. HRMS (ESI): calcd for C15H21O2 $[M]^-$: 233.1547; found: 233.1545.



2d.[43] White solid; yield: 83%; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.04 (d, J = 10.1 Hz, 1H), 5.80 (d, J = 10.1 Hz, 1H), 5.29 (s, 1H), 3.45 (s, 3H), 2.99 (d, J = 7.9 Hz, 1H), 2.77 (d, J = 7.9 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 192.69, 171.61, 139.55, 127.37, 100.68, 57.77, 56.32, 55.48. HRMS (ESI): calcd for $C_8H_8NaO_3$ $[M + Na]^-$: 175.0366; found: 175.0362.



2e.[16] Brown solid; yield: 93%; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.36 (dd, J = 10.3, 2.5 Hz, 1H), 6.20 (d, J = 10.3 Hz, 1H), 5.54

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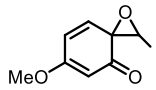
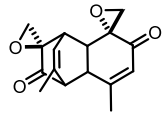
(d, J = 2.5 Hz, 1H), 3.73 (s, 3H), 3.45 (q, J = 5.3 Hz, 1H), 1.40 (d, J = 5.3 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 193.51, 170.78, 137.57, 127.98, 100.43, 67.31, 60.04, 56.16, 14.56. HRMS (ESI): calcd for $C_9H_{10}NaO_3$ $[M + Na]^-$: 189.0528; found: 189.0518.



2f.[38] Yellow solid; yield: 76%; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.14 (d, J = 6.6 Hz, 1H), 6.07 (s, 1H), 3.39 (s 1H), 3.32 (d, J = 9.0 Hz, 1H), 3.11 (d, J = 6.1 Hz, 1H), 2.90−2.82 (m, 2H), 2.81−2.74 (m, 2H), 2.62 (d, J = 9.0 Hz, 1H), 2.03 (s, 3H), 1.69 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 204.08, 192.12, 156.84, 138.72, 129.55, 126.17, 58.76, 58.28, 57.94, 57.65, 53.70, 43.32, 41.37, 38.06, 22.85, 21.76. HRMS (ESI): calcd for $C_{16}H_{16}NaO_4$ $[M + Na]^-$: 295.0946; found: 295.0936.



■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acsomega.1c05559.

Flow system description; and NMR spectra and X-ray data of compound **2f** (PDF)

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Notes

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