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# Electroorganocatalytic asymmetric Diels–Alder cycloaddition of hydroquinones with α,β-unsaturated aldehydes†

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**The concept of combining asymmetric aminocatalysis with electrochemistry remains underexplored. Herein, we report an electrochemically driven Diels–Alder cycloaddition reaction of substituted hydroquinones with a series of enals activated by a TMS-protected prolinol catalyst, leading to optically active products with high yields and perfect enantiomeric ratios up to 99 : 1 e.r.**

Quinones and their derivatives constitute versatile building blocks commonly employed in organic chemistry for the preparation of diverse polycyclic systems.[1] They undergo various additions, cycloadditions and cascades, leading to products of synthetic or biological relevance.[2] They have also been employed as starting materials in asymmetric transformations. In this context, organocatalytic approaches have become increasingly prominent, encompassing various catalytic systems such as aminocatalysis, phosphoric acid catalysis and bifunctional catalysis. These catalysts not only enhance the reaction efficiency, but also provide precise control over enantioselectivity and regioselectivity. This enables the synthesis of complex quinone derivatives with high yields and excellent enantioselectivities, under mild reaction conditions.[3] Notably, quinone and related hydroquinone ring systems are present in natural products exhibiting a wide range of structural complexity. They possess significant biological activity ranging from simple antibiotic to anticancer properties.[4] Electrochemistry is a multidisciplinary science applied across various fields within the physical, chemical, and biological sciences. It is a powerful method, particularly in organic synthesis, for the efficient functionalization of organic molecules.[5] Electrochemical reaction, or electrosynthesis, involves conducting chemical transformations using an electrochemical cell.[6] This technique allows for heterogeneous redox reactions, avoiding the use of stoichiometric amounts of redox reagents and the formation of stoichiometric by-products. One of the key advantages of organic electrochemistry is its ability to offer more sustainable and environmentally friendly alternatives to traditional synthetic methods. By leveraging electricity as a clean reagent, it reduces the reliance on hazardous chemicals and minimizes waste production. This makes electrochemistry a valuable tool in the pursuit of greener and more efficient chemical processes.

Despite advancements in the field of electrochemical organic synthesis, the application of electrochemical methods in asymmetric organocatalysis still remains limited.[7] In 2010, Jørgensen and co-workers demonstrated that electrochemistry is compatible with asymmetric aminocatalysis. They performed an enamine-mediated Michael addition/hemi-acetalization reaction cascade with the corresponding electrophile generated *via* anodic oxidation.[8] In 2024, Dell'Amico performed electrochemical asymmetric radical functionalization of aldehydes in the presence of a redox shuttle.[9] In this context, it is worth noting that the combination of organocatalysis with electrochemistry has been proven to be possible with the existing examples showing the potential of such strategies as a useful tool in the stereocontrolled synthesis of functionalized organic compounds (Fig. 1).

Herein, we present our studies on enantioselective, asymmetric Diels–Alder cycloaddition of hydroquinone with α,β-unsaturated aldehydes. The corresponding dienophile is generated electrochemically, providing the opportunity to perform Diels–Alder cycloaddition. Anodic oxidation of hydroquinones results in the formation of appropriate *para*-quinones, which constitute a group of highly reactive electron-poor dienophiles able to react with electron-rich dienamine intermediates derived from α,β-unsaturated aldehydes.[10]

The feasibility of the reaction was assessed by applying 2,6-dimethylhydroquinone **1a** and 3-methyl-2-butenal **2a** in a $CH_3CN$/$H_2O$/HFIP solvent mixture in the presence of organocatalyst **A** (20 mol%), employing tetrabutylammonium perchlorate as the supporting electrolyte, an RVC electrode as the anode and stainless steel (SS) as the cathode in an undivided electrochemical cell under

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† Electronic supplementary information (ESI) available. CCDC 2383376. For ESI and crystallographic data in CIF or other electronic format see DOI: https://doi.org/10.1039/d5cc00505a

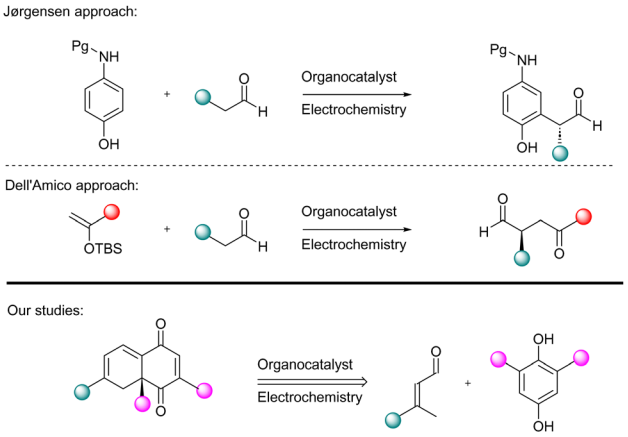



Fig. 1 Previous studies and the synthetic objective of the present work.

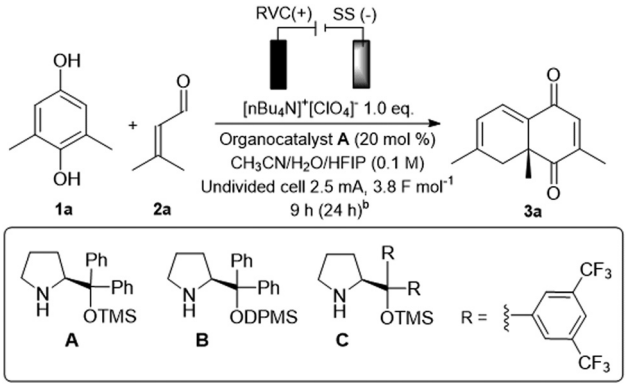
constant current conditions (2.5 mA, 3.8 F $mol^{-1}$). The desired product was formed in 52% yield and with excellent stereoselectivity 99 : 1 e.r. (Table 1, entry 1).

Notably, the anodic oxidation process of 2,6-dimethylhydroquinone **1a** using the above electrochemical setup was achieved in 9 h (monitored by $^1$H NMR) and the reaction was left overnight for full conversion due to the presence of the oxidized analogue of **1a** in the crude reaction mixture. In the next stage of research, we tested other carbon-based electrodes ($C_{(graphite)}$ and $C_{(glass)}$, Table 1, entries 3 and 4) as the anode and stainless steel (SS) as the cathode. Disappointingly, both the yield and enantiomeric excess deteriorated under these conditions.

The influence of different electrolytes on the chemical efficiency and stereoselectivity of the model reaction was also investigated. The reaction was observed to proceed less efficiently in the case of $n$Bu$_4$NBF$_4$, $NaClO_4 \cdot H_2O$ and $LiClO_4$ (43–49% yield, Table 1, entry 5 and Table S1, ESI†), and with comparable efficiency applying other quaternary ammonium salts such as $n$Bu$_4$NPF$_6$ or $n$Bu$_4$NBr (50–51% yield, Table 1, entry 6 and ESI†). Furthermore, the reaction stereocontrol slightly decreased.

Disappointingly, screening of different supporting electrolytes did not bring any significant improvement in the reaction yield. Therefore, we decided to investigate the influence of degassing

Table 1 Optimization and control studies[a]




| Entry | Deviation from standard conditions | Yield (%) | e.r. |
|---|---|---|---|
| 1[c] | None | 52 | 99 : 1 |
| 2[c] | 2.5 mA, 5 h 30 min (24 h)[b], 2.2 F $mol^{-1}$ | 37 | 98 : 2 |
| 3[c] | $C_{(graphite)}$ instead of RVC | 46 | 96 : 4 |
| 4[c] | $C_{(glass)}$ instead of RVC | 47 | 97 : 3 |
| 5[c] | $n$Bu$_4$NBF$_4$ as electrolyte | 43 | 98 : 2 |
| 6[c] | $n$Bu$_4$NPF$_6$ as electrolyte | 51 | 95 : 5 |
| 7[c] | Reaction degassed | 44 | 75 : 25 |
| 8[c] | Reaction degassed, 2 eq. of electrolyte | 38 | 94 : 6 |
| 9[c] | 0.75 eq. of electrolyte | 51 | 99 : 1 |
| 10[c] | Reaction degassed, 2 eq. of electrolyte, 6 h (24 h) | 6 | 94 : 6 |
| 11[d] | $CH_3CN$/HFIP | 63 | 97 : 3 |
| 12[e] | $CHCl_3$/$CH_3CN$/HFIP | 81 | 99 : 1 |
| 13[e] | Catalyst **B**, $CHCl_3$/$CH_3CN$/HFIP | 24 | 99 : 1 |
| 14[e] | Catalyst **C**, $CHCl_3$/$CH_3CN$/HFIP | 54 | 99 : 1 |
| 15[e] | Catalyst **A** (10 mol%), $CHCl_3$/$CH_3CN$/HFIP | 85 | 98 : 2 |
| 16[e] | Catalyst **A** (10 mol%), benzoic acid (10 mol%), $CHCl_3$/$CH_3CN$/HFIP | 85 | 99 : 1 |
| 17[ef] | Catalyst **A** (10 mol%), benzoic acid (10 mol%), $CHCl_3$/$CH_3CN$/HFIP | 56 | 94 : 6 |
| 18[e] | No electricity | No reaction | — |
| 19[e] | No catalyst | No reaction | — |

[a] Standard reaction conditions: **1a** (0.217 mmol, 1.0 eq.) and **2a** (0.651 mmol, 3 eq.) added portionwise (1 eq. every 3 hours) in the presence of $[n\text{Bu}_4\text{N}]^+[\text{ClO}_4]^-$ (0.217 mmol, 1 eq.) and organocatalyst **A** (20 mol%) in $CH_3CN/H_2O$/HFIP (0.1 M). [b] First value refers to the duration of electrolysis. Total reaction time is given in the brackets. [c] Reactions conducted in the solvent mixture 1.5 : 0.5 : 0.1. [d] Reaction conducted in the solvent mixture 1 : 0.05. [e] Reaction conducted in the solvent mixture 0.9 : 0.1 : 0.05. [f] Reaction conditions: **1a** (1.0 mmol, 1.0 eq.) and **2a** (3.0 mmol, 3 eq.), 2.5 mA, 3.8 F $mol^{-1}$, 40 h (4 days) (see footnote b).

(Table 1, entry 7), and increased (Table 1, entry 8) or decreased (Table 1, entry 9) concentration of the supporting electrolyte (for more details see Table S2, ESI†). In general degassing and increased loading of the electrolyte were highly unbeneficial in terms of reaction yield, while reducing the amount of electrolyte gave a slight decrease in the yield of the desired product with the persistence of high enantioselectivity (Table 1, entry 9).

To our delight, evaluation of the solvent mixture showed it to be crucial for the chemical efficiency of the process. Firstly, we identified that the reaction proceeded more efficiently without the water additive (Table 1, entry 11), while the $CHCl_3/CH_3CN$/HFIP solvent mixture allowed the desired product to be obtained in 81% yield and with excellent stereoselectivity of 99 : 1 e.r. (Table 1, entry 12). Organocatalyst **A** proved to be the best in this electrochemical protocol, as the use of a more sterically hindered silyl protecting group as in catalyst **B** or the less nucleophilic aminocatalyst **C** highly suppressed the chemical efficiency of the optimized process (Table 1, entries 13 and 14). Finally, a decreased loading of organocatalyst **A** to 10 mol% (Table 1, entry 15) and addition of benzoic acid, which facilitates dienamine formation (Table 1, entry 16), was evaluated in the model reaction. The latter protocol was the most efficient for the developed process. Furthermore, the model reaction was performed at a 1.0 mmol scale to demonstrate the utility of the method, and the desired product **3a** was obtained in a slightly lower yield and stereoselectivity (Table 1, entry 17). The necessity of the applied current and organocatalyst was confirmed by a control experiment as the cycloaddition product **3a** was not observed in their absence (Table 1, entries 18 and 19).

With the optimized protocol in hand, we next investigated the generality of the process (Fig. 2). A series of structurally diverse α,β-unsaturated aldehydes were tested in the reaction, categorized as follows: uncyclic **2b**, cyclic **2c**–**2e**, heterocyclic **2f**–**2g** and functionalized polycyclic **2h**–**2j**. Notably, the application of enals **2c** and **2e**–**2j** resulted in the formation of products possessing two chiral carbon atoms, while **2d** provided the structure with 3 stereogenic centers.

Initially, *trans*-crotonaldehyde (**2b**) was tested in the model reaction. The desired product **3b** was obtained in 65% yield and a high enantiomeric ratio of 97 : 3 e.r. (Fig. 2). A group of cyclic enals **2c**–**2e** delivered the appropriate cycloaddition products **3c**–**3e** with moderate yields in the range of 42–47% (Fig. 2). Reactions of unsubstituted derivatives (**2c**, cyclohexyl) and (**2e**, cycloheptyl) resulted in the formation of products **2c** and **2e** as single diastereoisomers, while 2-(2-methylcyclohexylidene)acetaldehyde (**2d**) gave a mixture of two diastereoisomers **3d** due to the presence of an additional stereogenic centre at position 2 (Fig. 2). In the next stage of research, two heterocyclic aldehydes **2f**–**2g** were tested and delivered the desired products **3f** and **3g** in 61% and 40% yields, respectively, with high diastereo- and enantioselectivities. Finally, a series of polycyclic precursors of dienes **2h**–**2j** were evaluated in the model electroorganocatalytic approach to achieve further extension of the cyclic system. Successfully, 1,2,3,4-tetrahydronaphthalene-based aldehyde **2h** furnished the desired cycloaddition product **3h** in 62% yield with high diastereo- and enantioselectivities. Surprisingly, stereocontrol of the process was highly diminished when applying heteroaromatic enal **2i** (Fig. 2).

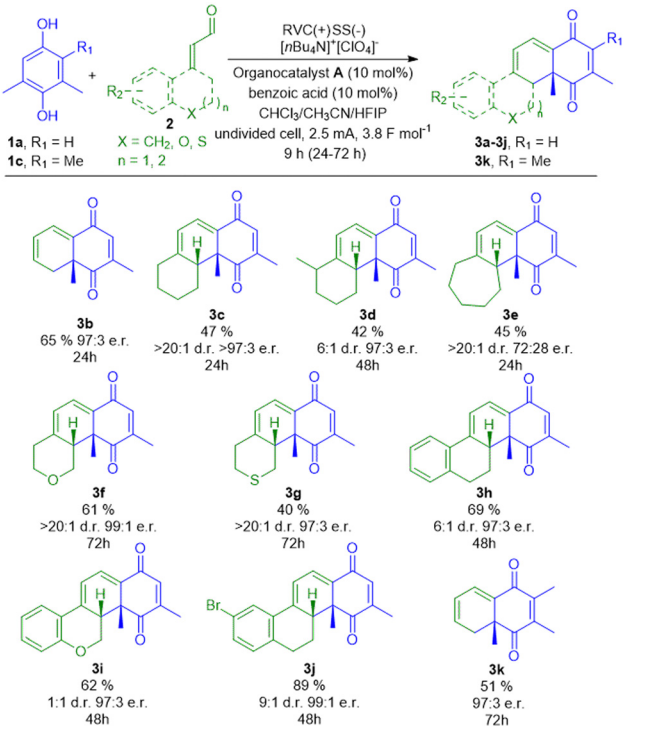


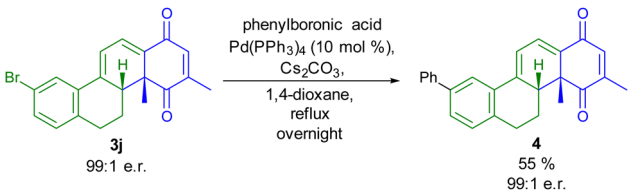

Fig. 2 Scope of the electro/organocatalytic [4+2] Diels–Alder cycloaddition method.

Application of 7-bromo derivative **2j** in the described protocol resulted in the formation of bromo-tetrahydrochrysene-1,4-dione product **3j** in the highest yield of 89% with an excellent enantiomeric ratio of 99 : 1 e.r. Two different quinone precursors were also tested in the described protocol. Trimethylhydroquinone (**1c**) resulted in the formation of the product **3k** in 51% yield as a single diastereoisomer with a high enantiomeric ratio of 97 : 3 e.r. The reaction time was found to be dependent on the structure of the starting enals. Unsuccessful experiments are included in the ESI.† For simple aldehydes such as **2a**, **2b**, **2c**, and **2e**, a reaction time of 24 hours was sufficient to achieve full conversion and to obtain the desired products. However, enals **2f** and **2g** required an extended reaction time up to 72 hours to complete the organocatalytic transformation. In contrast, aldehydes **2h**, **2i**, and **2j** underwent full conversion within 48 hours, affording the corresponding products **3h**, **3i**, and **3j**.

The structure and relative configuration of the product **3c** were unambiguously determined by single crystal X-ray diffraction analysis (Fig. S26, ESI†). The stereochemistry of products **3a**–**3b** and **3d**–**3j** was assigned by analogy and was in accordance with the absolute configuration assigned by Jørgensen and coworkers.[2f,11]

Having demonstrated the synthetic utility of the reaction, cycloadduct **3j** was subjected to Suzuki coupling, resulting in its transformation to 7-phenyl tetrahydrochrysene-1,4-dione derivative **4** in 55% yield. Importantly, the formation of **4** proceeds without deterioration of the enantiomeric ratio of **3j** (Scheme 1).

After experimental confirmation of the structure and relative stereochemistry of the final products **3**, a plausible mechanism for the studied [4+2]-cycloaddition was proposed (Scheme 2).




Scheme 1 Transformation of **3j** to 7-phenyl derivative **4** in Suzuki reaction.

The stereo- and regioselective anodic oxidation and organocatalytic formation of 1,4-diones **3** is proposed to proceed through a sequential process (Scheme 2). The first step involves the electrochemical oxidation of 2,6-dimethylhydroquinone **1a** to generate the dienophilic intermediate **1b**. In the second step, an endo-selective vinylogous nucleophilic addition of an electron-rich dienamine intermediate **I**, formed *via* the condensation of aldehyde **2** with organocatalyst **A**, to quinone **1b** furnishes the zwitterionic intermediate **II**. A second bond-forming event generates the cyclized intermediate **III**. Subsequent deprotonation eventually triggers the regeneration of the aminocatalyst and yields product **3a**. The regio- and endo-selectivity were previously confirmed by Jørgensen *et al.*'s DFT calculations.[2b]

In summary, we have demonstrated a simple and concise access to a series of polycyclic enantiorich products **3** employing an electro/organocatalytic cycloaddition process. The developed reactivity constitutes a facile means for electrosynthesis of **3** in a diastereo- and enantioselective manner. Transformation of the cycloadduct **3j** to 7-phenyl analogue **4** without deterioration of the enantioselectivity confirmed the utility of the developed methodology.

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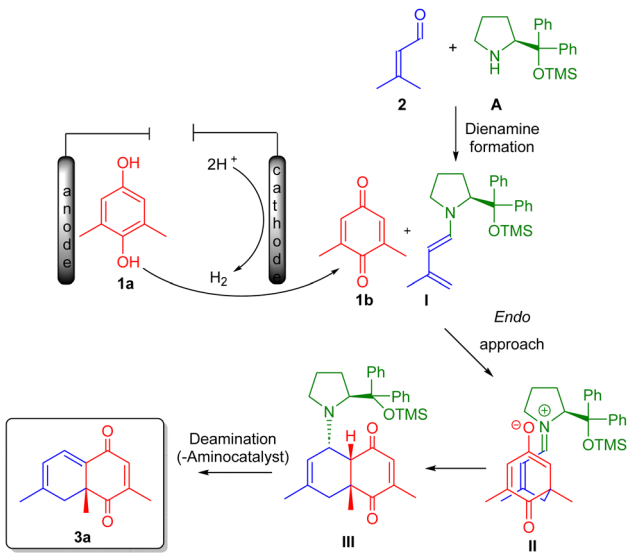


Scheme 2 Proposed mechanism for the electrochemical/organocatalytic reaction.

## Data availability

Data for this article, including NMR FIDs and crystallographic data, are available at **https://rdb.p.lodz.pl/dataverse/W3** and **https://doi.org/10.34658/RDB.ZOXWZA**. Supplementary crystallographic data can be found at The Cambridge Crystallographic Data Centre under CCDC number 2383376.†

## Conflicts of interest

There are no conflicts to declare.

## Notes and references

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11 CCDC 2383376 contains the supplementary crystallographic data for this paper†.

 