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Electrochemical Enantioselective Oxidation of Indoles via Chiral Phosphoric Acid Catalysis in Cooperation with H_3PO_4 in Aqueous Media

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Abstract: Disclosed here is the first catalytic enantioselective electrochemical oxidative rearrangement of indoles for the efficient synthesis of highly enantioenriched spirooxindoles. The *in-situ* generated HBr from substrate oxidation, known to be detrimental to the reaction itself, was perfectly consumed by cathode reduction. Challenges of this process include the difficulty in maintaining the synergy between substrate oxidation and cathode reduction as well as the general incompatibility of a hydrogen bonding catalytic system with the aqueous acidic media. A monophasic system was initially developed, but with little substrate generality. Further analysis of the mechanism and careful optimization allowed the development of a much more general and robust biphasic system that exhibited multiple advantages over chemical oxidation, including broader scope, less waste, milder conditions, and better enantioselectivity. It is also the first demonstration of chiral phosphoric acid catalysis in cooperation with H_3PO_4 in acidic aqueous media.

Introduction

Since the pioneering studies by Akiyama and Terada in 2004,[1] chiral phosphoric acids (CPA) have evolved as a family of broadly powerful catalysts for diverse organic reactions.[2] They have been employed as effective chiral ligands, hydrogen-bond donors, and sources of chiral counter anions. Their extraordinary ability in achieving outstanding asymmetric induction by weak interactions, such as hydrogen bonding, constitutes the key to success. While the design of sophisticated structures of CPAs contributed significantly to their performance, the choice of suitable reaction media often makes a big difference. CPA-based hydrogen-bonding catalysis is typically implemented in non-polar aprotic solvents to minimize their competing and often detrimental influence. Moreover, other hydrogen-bond donors, such as stronger Brønsted acids, are typically incompatible with CPA catalysis. As a result, it is a formidable challenge to implement CPA-based hydrogen-bonding catalysis in polar protic solvents in the presence of a strong inorganic acid.

In the meanwhile, asymmetric electrosynthesis has gained tremendous developments in the past few years.[3-7] The conventional use of stoichiometric oxidants and reductants can be potentially replaced by electricity as a greener and more sustainable alternative. However, current success has been mainly in transition metal catalysis domain, which rely on relatively more robust interaction between chiral catalyst and substrate (Scheme 1a).[3,4] In contrast, asymmetric induction by weak interactions with a chiral organocatalyst in an electrochemical system has met with limited success, partly due to the challenges associated with those unavoidable polar species present in the media, such as electrolytes, that may interfere with the weak but

Scheme 1. Introduction to enantioselective electrosynthesis and our design of oxidative rearrangement of indoles.

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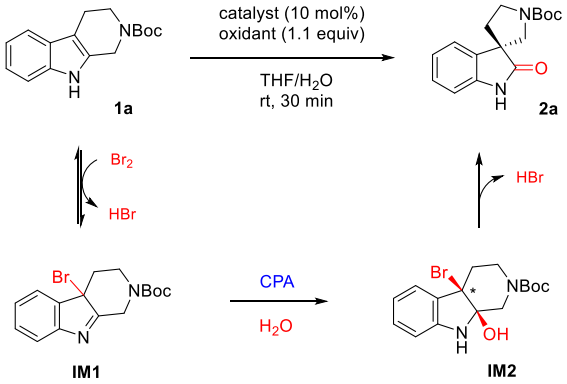
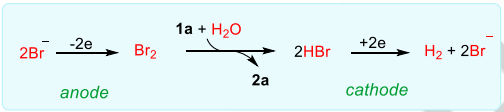


entry[a]	catalyst	oxidant	yield (%)	ee (%)
1	**A1**	Br_2	>95	7
2	**A1**	$^nBu_4NBr_3$	>95	11
3	**A1**	$^nBu_4NBr_3$[b]	>95	20
4	–	Br_2	>95	–
5[c]	**A1**	current (3 mA)	>95	73
6[d]	**A1**	current (3 mA)	>95	4



Scheme 2. Preliminary results. [a] Reaction conditions: **1a** (0.05 mmol), oxidant (0.055 mmol), (*S*)-**A1** (10 mol%, THF (3 mL), H_2O (0.4 mL), rt, 30 min, yield was determined by crude ^1H NMR, and ee value was determined by chiral HPLC. [b] Slow addition of $^nBu_4NBr_3$ in THF (0.75 mL) over 30 min. [c] Pt anode and cathode, constant current, 2.2 F mol^{-1}, $^nBu_4NBr$ (0.1 M), undivided cell. [d] HBr (2.0 equiv) was added.

crucial enantiodetermining interactions.[5-7] In this context and as our continued efforts,[7] here we report the first CPA catalysis in acidic aqueous media for electrosynthesis. The synergistic cooperation with inorganic phosphoric acid (H_3PO_4) to achieve high efficiency and enantiocontrol was also demonstrated for the first time.

Oxidative rearrangement of indoles to spirooxindoles was chosen as a model reaction for our study, as it represents an important process that converts readily available substrates to highly valuable complex biologically active molecules.[8-10] Although great process has been achieved in the development and application of this process in the past few decades, there still remains very limited success in developing a catalytic enantioselective variant (Scheme 1b). Moreover, previous asymmetric protocols uniformly required the use of stoichiometric chemical oxidants.[9,10] In this context, the advantages of electrosynthesis further inspired us to develop a greener and more sustainable approach by electrochemical oxidation.

Results and Discussion

It has been well-known that electrochemical oxidation of Br^- can be employed to replace chemical oxidants, such as Br_2.[3,7,11,12] To prove the feasibility of green oxidation approach, we first examined this enantioselective process with stoichiometric Br_2 as oxidant and mixed THF/H_2O as solvent to mimic the electrochemical condition (Scheme 2). With **A1** (structure shown in Table 1) as the catalyst, the reaction of **1a** successfully generated the desired product **2a** in quantitative yield, but with essentially no enantioselectivity, no matter with Br_2 or its analogue $^nBu_4NBr_3$ (entries 1−2). We also tried slow addition of oxidant, but with no significant improvement (entry 3). Next, a control experiment in the absence of **A1** showed similar results, suggesting a strong background reaction that might explain the low enantiocontrol (entry 4). From the proposed mechanism of this process,[10] it is clear that two equivalents of HBr can be generated from this system, which may outcompete CPA to facilitate this process and cause low enantiocontrol. We were also curious about the absence of such dramatic influence of HI generated from the use of NIS in the chemical oxidation protocol.[10] Indeed, control experiment indicated that NIS could oxidize HI into I_2, thus avoiding the influence of the generated HI (see the SI for details).

Nevertheless, despite the discouraging chemical oxidation results, we reasoned that an electrochemical oxidation system may fix the problem caused by the generated acid HBr, as the anodic oxidation is accompanied by cathodic reduction, which converts H^+ to H_2 and thus neutralizes the reaction system (Scheme 2, blue box). To test this hypothesis, we did preliminary study using electricity as oxidant. Gratifyingly, the enantioselectivity was significantly enhanced (73% ee, entry 5). A control reaction by the addition of two equivalents of HBr to this system led to almost complete loss of enantiocontrol (entry 6), thus consistent with the above analysis on the influence of HBr in the chemical oxidation. Overall, the preliminary study clearly highlighted the advantage of electrochemical system for this process by synergizing the two half reactions in electrodes.

The above preliminary outcome using **A1** as catalyst, $^nBu_4NBr$ as both electrolyte and mediator, and THF/H_2O as solvent was used as a starting point for further optimization (Table 1, entry 1). Variation of the anode material to graphite felt (GF), glassy carbon (GC) or carbon rod (CR) resulted in decreased yield and ee (entries 2). However, almost same results were observed with nickel as cathode (entry 3). Other CPAs were also examined. Replacing the spirocyclic backbone to BINOL-based counterpart (**B1**) led to significant decrease in enantioselectivity (entry 4). However, changing the side arm to anthracene (**A2**) improved the enantioselectivity to 92%, suggesting the reaction was sensitive to the catalyst steric environment (entry 5). After additional screening, catalyst **A4** was identified as the best catalyst (entry 7). Solvents also showed influence on this reaction. Ethyl acetate resulted in a slight decrease in enantioselectivity, but acetonitrile led to a substantial drop to 11% ee (entries 9−10). However, acetone gave comparable results with THF (entry 11), and more importantly, it led to higher conductivity, so it was employed for further study. Finally, decreasing the loadings of catalyst and water provided the optimal outcome (entry 12).

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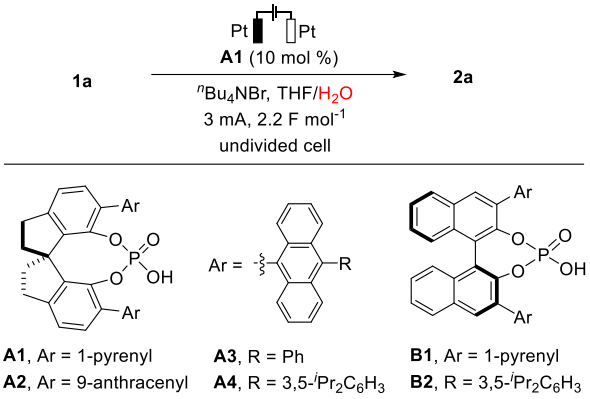
Table 1. Condition optimization.[a]

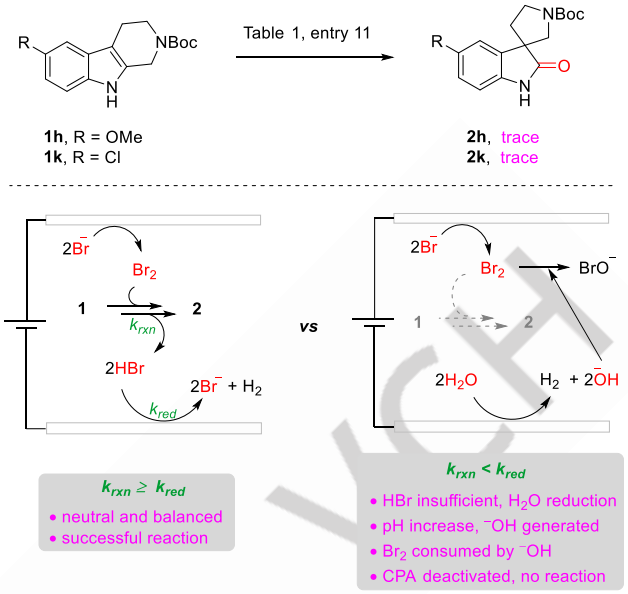


A1, Ar = 1-pyrenyl
A2, Ar = 9-anthracenyl
A3, R = Ph
A4, R = 3,5-^{i}Pr$_2$C$_6$H$_3$
B1, Ar = 1-pyrenyl
B2, R = 3,5-^{i}Pr$_2$C$_6$H$_3$

Entry	deviation from the conditions	yield (%)	ee (%)
1	--	>95	80
2	GF/GC/CR as anode	30–72	72–79
3	Ni instead of Pt as cathode	>95	80
4	**B1** in place of **A1**	>95	44
5	**A2** in place of **A1**	>95	92
6	**A3** in place of **A1**	>95	94
7	**A4** in place of **A1**	>95	95
8	**B2** in place of **A1**	>95	93
9	**A4**, EtOAc in place of THF	>95	84
10	**A4**, CH3CN in place of THF	>95	11
11	**A4**, acetone in place of THF	>95	92
12[b]	**A4**, acetone in place of THF	>95	96

[a] Reaction conditions: **1a** (0.05 mmol), (*S*)-**A1** (10 mol%), ^{n}Bu$_4$NBr (0.3 mmol, 0.1 M), THF/H$_2$O (3.0/0.1 mL), Pt anode (10 mm × 10 mm × 0.2 mm), Pt cathode (10 mm × 10 mm × 0.2 mm), constant current, 2.2 F mol^{-1}, undivided cell, yield was determined by crude ^{1}H NMR, and ee value was determined by chiral HPLC. [b] **A4** (5 mol%), H$_2$O (0.05 mL).

With the optimized protocol, we started to explore the reaction scope. However, to our surprise, this protocol was not general at all. For example, variation of the electronic properties on the indole ring had a drastic influence on reactivity. Substrates **1h** and **1k** showed completely no reactivity under the above conditions (Scheme 3). We reasoned that this might be due to unbalanced synergy between substrate oxidation and cathodic reduction. In the ideal situation, the indole oxidation should not be slower than cathodic reduction ($k_{rxn} \geq k_{red}$), thus the whole system is slightly acidic and the generated HBr is reduced in cathode. However, if this balance is broken (e.g., $k_{rxn} < k_{red}$), there is insufficient HBr generated for cathodic reduction. Consequently, to maintain electron balance, water would be reduced instead, which generates hydroxide ($^{-}$OH) and turns the system into alkaline. The generated hydroxide not only quenches the CPA catalyst, but also further causes consumption of Br$_2$ by forming BrO^{-}, which shuts down the indole oxidation. In principle, such an issue might be alleviated by adjusting the current. However, it is tedious to tune these parameters for each substrate. Thus, a more general protocol applicable to all the substrates would be highly desirable.



Scheme 3. Preliminary examination of substrate generality and analysis.

We envisioned that a biphasic system allowing physical separation of the indole oxidation and cathodic reduction might be a possible solution to the above issue (Table 2). We then employed a mixture of DCM and H$_2$O as solvent. NaBr was chosen as a source of bromide and electrolyte as well, since it has a good solubility in aqueous phase. Unfortunately, the results were irreproducible (entry 1), suggesting partial water reduction in the cathode might be still involved to cause an unstable pH value of the system. In this context, we reasoned that the addition of an external acid should ensure an acidic medium, despite its possible interference with CPA in asymmetric induction. Thus, various Brønsted acids of different strengths were examined, including weak acid AcOH and strong inorganic acids HCl, H$_2$SO$_4$, and H$_3$PO$_4$. Among them, HCl and H$_2$SO$_4$ showed neither obvious improvement nor negative effect (entries 2−3). However, AcOH was able to improve the enantioselectivity (93% ee), but with almost no increase in yield (entry 4). To our delight, H$_3$PO$_4$ proved superior, resulting in both excellent yield and enantioselectivity (entry 5). Moreover, the results were reproducible, with either one or two equivalents of loading (entry 6). We believe that the ability of H$_3$PO$_4$, together with its conjugate bases, to serve as a potential buffer to stabilize the acidity of the reaction system might contribute to its extraordinary performance. Furthermore, to briefly test the generality, **1h** and **1k** were subjected to this new protocol. Both resulted in excellent efficiency and enantioselectivity (entries 7−8), thereby illustrating improved generality of this biphasic binary acid system. It is also worth noting that, to the best of our knowledge, the combined use of CPA and H$_3$PO$_4$ for effective enantioselective catalysis has not been demonstrated before.[2]

Table 2. Further optimization of a biphasic acidic system.[a]

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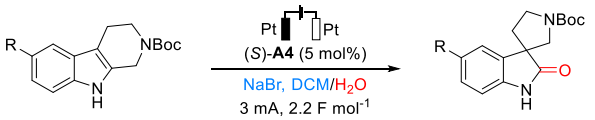
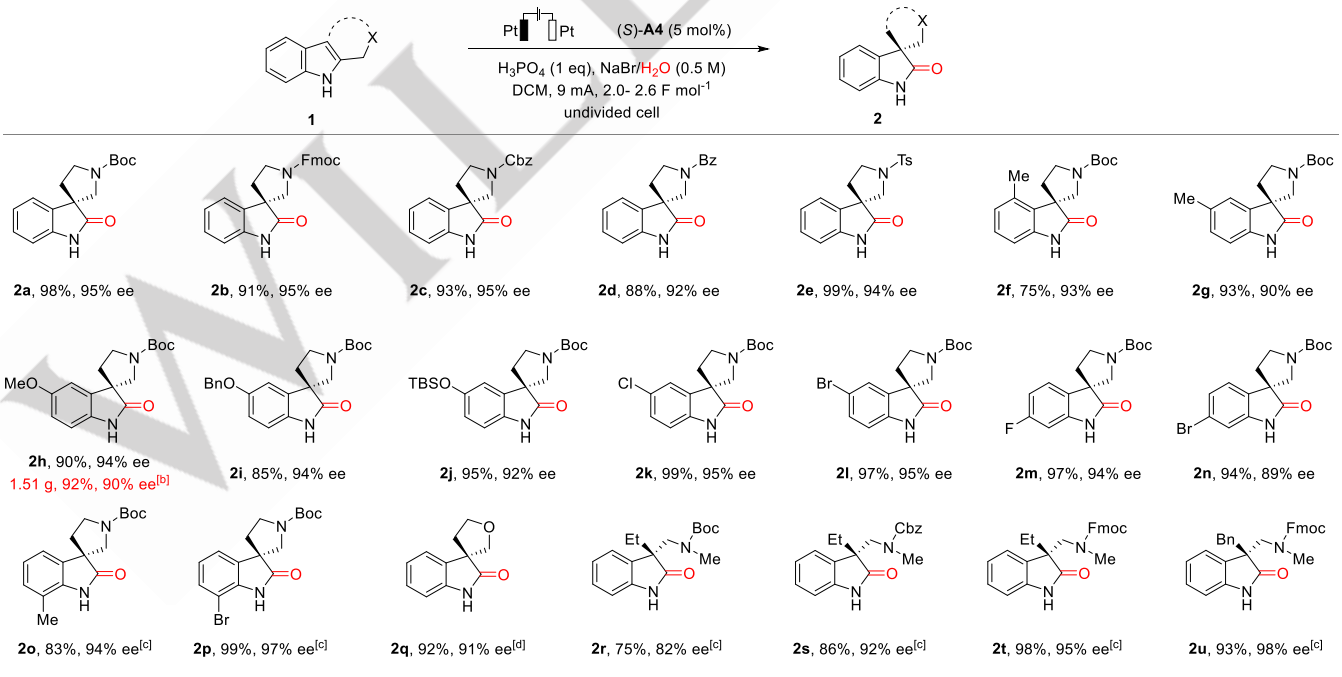


entry	substrate	additive	yield (%)	ee (%)
1	**1a**	–	72–84	76–85
2	**1a**	HCl	79	85
3	**1a**	H_2SO_4	83	86
4	**1a**	HOAc	79	93
5	**1a**	H_3PO_4	>95	95
6[b]	**1a**	H_3PO_4	>95	95
7[b]	**1h**	H_3PO_4	>95	94
8[b]	**1k**	H_3PO_4	91	92

[a] Reaction conditions: **1** (0.05 mmol), (*S*)-**A4** (5 mol%), NaBr/H_2O (2.5 mL, 0.5 M), DCM (1 mL), additive (2 equiv), Pt anode (10 mm × 10 mm × 0.2 mm), Pt cathode (10 mm × 10 mm × 0.2 mm), constant current, 2.2 F mol^{-1}, undivided cell, yield was determined by crude ^1H NMR, and ee value was determined by chiral HPLC. [b] H_3PO_4 (1 equiv).

With the newly optimized biphasic protocol, we next examined a wide range of different indole substrates for the enantioselective electrochemical oxidative rearrangement (Scheme 4). These reactions were smoothly enlarged to 0.3-mmol scale, along with a higher electric current of 9 mA. Different protecting groups on the nitrogen of the tetrahydro-*β*-carbolines, such as Boc, Fmoc, Cbz, Bz, and Ts, were all well-tolerated under the mild conditions (**2a**–**2e**). Moreover, various substituents at different (4- to 7-) positions of the indole ring, including both electron-donating and electron-withdrawing ones, all led to excellent outcomes (**2f**–**2p**). It is worth noting that simple deprotection of **2h** could generate the natural alkaloid horsfiline with ease.[13] This electrochemical system has a number of advantages over our previously reported chemical oxidation protocol.[10] Other than the use of green electricity, the new conditions showed a broader substrates scope. For example, substrates bearing a C4- or C7-substituent (e.g., **2f**, **2o**–**2p**) were unsuccessful before, but they reacted smoothly to provide the desired products with excellent enantioselectivity and efficiency under the present electrochemical system. Moreover, tetrahydrofuranyl-sprooxindole **2q**, representing another important family of substructures,[14] could also be easily synthesized with high enantiopurity. In contrast, such molecules were obtained with sub-optimal enantiocontrol under the previous chemical oxidation system.[10] Of note, the previous chemical oxidation system strictly required careful operation at low temperature to achieve high enantioselectivity, but the new electrochemical condition worked efficiently at ambient temperature. Finally, the monophasic system could also be applied to indoles without ring fusion in the 2,3-positions, leading to the corresponding oxindoles (**2r**–**2u**) bearing a non-spiro all-carbon quaternary stereocenter.[15] However, a 2-aryl-substituted indole may form the 3-brominated imine product, which was unreactive toward further rearrangement (see more details in the SI). Importantly, a gram-scale synthesis of **2h** with a reduced catalyst loading resulted in equally high yield and enantioselectivity, illustrating the practicability of this electrochemical process. It is also worth mentioning that all these examples demonstrated exceptionally high Faradaic efficiency, mostly exceeding 80%.



Scheme 4. Reaction scope. [a] Reaction conditions: **1** (0.3 mmol), (*S*)-**A4** (5 mol %), DCM (6 mL), H_3PO_4 (1 equiv), NaBr/H_2O (0.5 M, 6 mL), Pt anode (15 mm × 15 mm × 0.2 mm), Pt cathode (15 mm × 15 mm × 0.2 mm), 9 mA, 2.0-2.6 F mol^{-1}, undivided cell, isolated yield. [b] **1** (5 mmol), (*S*)-**A4** (2 mol%). [c] (*R*)-**B2** was used. [d] The monophasic conditions (Table 1, entry 12) were applied.

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Next, cyclic voltammetry of both the monophasic and biphasic systems was measured (Figure 1). In the monophasic system, substrate **1a** showed higher oxidation potential than $^{n}Bu_4NBr$, suggesting the indole oxidation was performed indirectly by the *in-situ* generated oxidant from bromide (Figure 1a). Upon mixing with **1a**, the solution of $^{n}Bu_4NBr$ exhibited a catalytic current, suggesting consumption of the intermediary oxidant (e.g., Br_2) by reacting with **1a**. For the biphasic system, we examined the effect of additives (Figure 1b). The addition of H_3PO_4 had no influence on the cyclic voltammetry curve of NaBr. In contrast, the addition of NaOH caused an obvious change featuring a higher oxidation current, which might be due to the consumption of the generated Br_2 by NaOH.

Control experiments were also performed to probe the role of bromide (Figure 1c). Replacing NaBr with $NaNO_3$, an alternative electrolyte, led to no reaction. However, the addition of a catalytic amount of NaBr to this system restored the reactivity. These observations implied that NaBr not only served as an electrolyte, but also a mediator, which was consistent with our proposed mechanism involving Br_2 as oxidant. Notably, increasing the NaBr concentration did not lead to further improvement (see more details in the SI).

Then we investigated the role of H_3PO_4. Two electrolysis reactions of **1a** were performed in parallel, with and without H_3PO_4, under otherwise identical standard conditions (Figure 1d). In the absence of H_3PO_4, the pH value of the aqueous phase increased obviously over time. In the meanwhile, the product enantioselectivity was mediocre and unstable. In contrast, with H_3PO_4, the same reaction showed almost constant pH value. resulting the inferior and unstable enantioselectivity. While in the presence of H_3PO_4, the pH value of the aqueous phase remained almost no change before reaction completion. Moreover, the product ee value was also constant and excellent. These observations undoubtedly confirmed the role of H_3PO_4 as a buffer to stabilize the acidity of the reaction system, which was crucial to the excellent outcome.[16]

Based on the above results, a possible mechanism is proposed (Figure 1e). The reaction begins by anodic oxidation of the bromide in the aqueous phase. The resulting Br_2 enters the organic phase to oxidize the substrate with the CPA catalyst controlling the enantioselectivity (see more details in the SI for the relative distribution of bromine between phases). The rearrangement product was generated with concomitant release of HBr, which then enters the aqueous phase. Cathodic reduction of the generated HBr balances the charge and acidity.

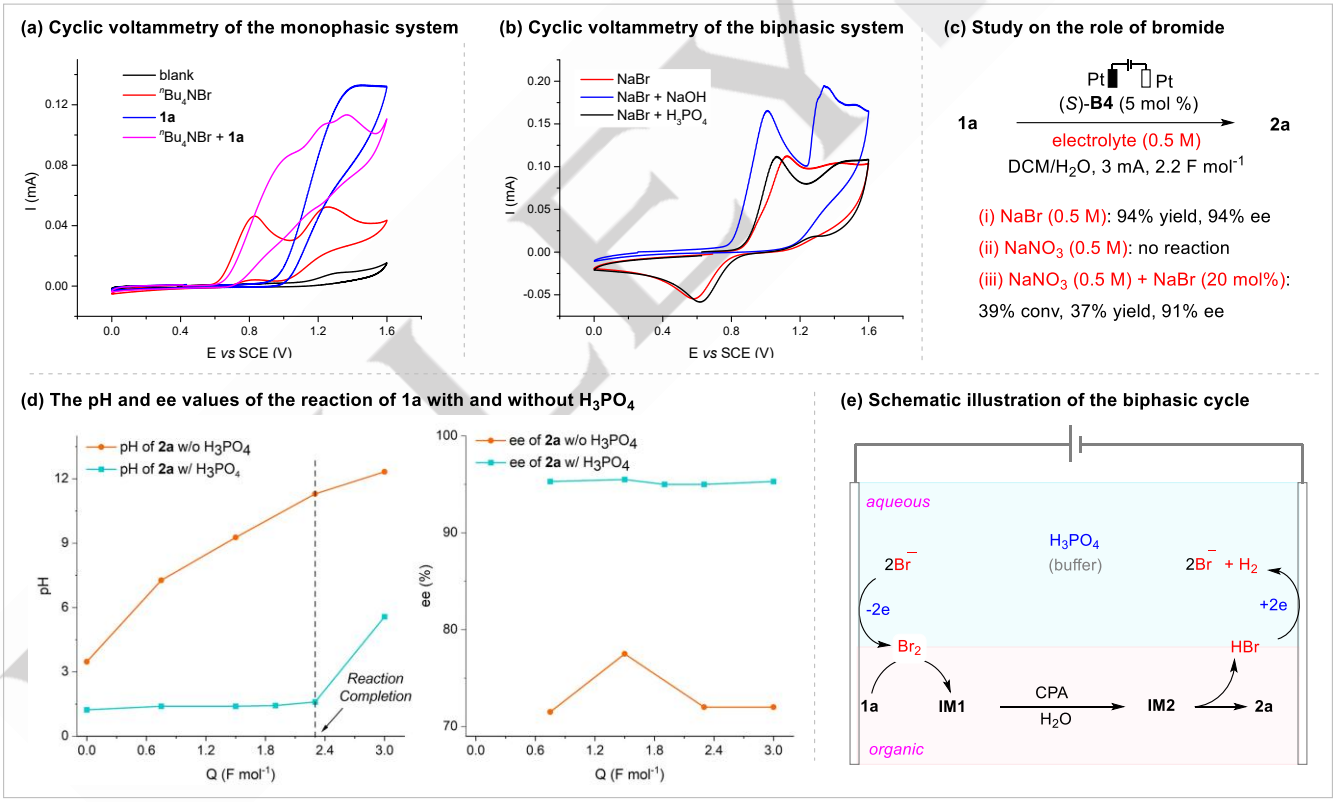

Figure 1. Mechanistic studies.

Conclusion

In summary, we have developed the first catalytic enantioselective electrochemical oxidative rearrangement of indoles, leading to green and efficient synthesis of diverse highly enantioenriched spirooxindoles. The synergy between indole oxidation and cathode reduction proved critical to the success. The *in-situ* generated HBr from oxidative rearrangement proved to be detrimental to the reaction itself, but it can be perfectly consumed by cathode reduction. However, the initially developed monophasic system could not maintain this delicate balance of reaction rates, thus lacking generality. Nevertheless, careful mechanism analysis and condition optimization led to a successful improvement into a much more general biphasic

system. This new protocol exhibited multiple advantages over the previous chemical oxidation approach, including less waste, broader scope, and milder conditions. The choice of H_3PO_4 as an additive not only ensured good reproducibility and robustness of this protocol but also improved the chemical efficiency and enantioselectivity. This is also the first demonstration of CPA catalysis in cooperation with H_3PO_4 in aqueous media. The unusual enhancement in performance by H_3PO_4 could be explained by the formation of a hypothetical heterodimer with CPA. Mechanistic and control experiments confirmed that NaBr served as both electrolyte and mediator. The development of other organocatalytic enantioselective electrosynthesis methods by weak interactions is ongoing in our laboratories.

Acknowledgements

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Keywords: electrosynthesis • chiral phosphoric acid • chirality • organocatalysis • asymmetric catalysis

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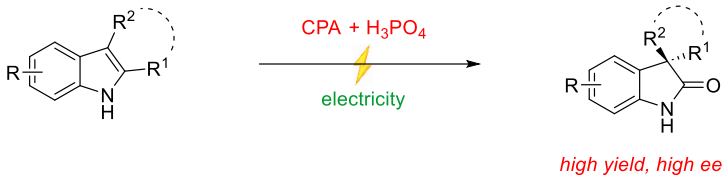

high yield, high ee

• no chemical oxidant • CPA-H_3PO_4 cooperation (unprecedented)
• little waste • aqueous media • mild conditions • broad scope

A binary organic-inorganic acid cooperative catalytic system has been developed to achieve highly enantioselective electrochemical oxidative rearrangement of indoles. The use of electricity as an oxidant in this case showed several advantages including environmental benignity and improved enantiocontrol. A biphasic electrolysis system contributes to the general substrate scope by physically separating the chiral organic acids from the achiral inorganic acids.