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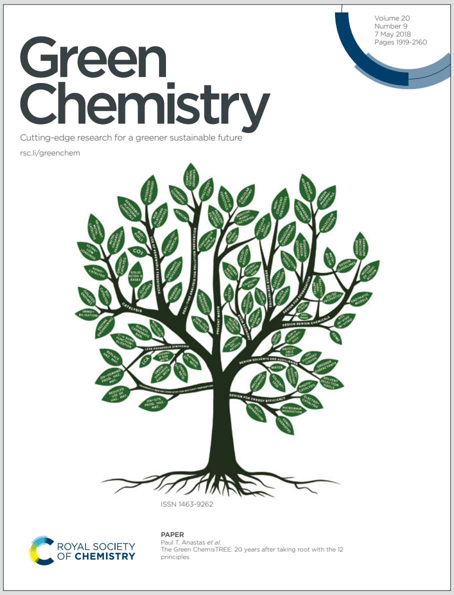

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Direct Anodic (Thio)Acetalization of Aldehydes with Alcohols(thiols) under Neutral Conditions and Computational Insight into the Electrochemical Acetals Formation

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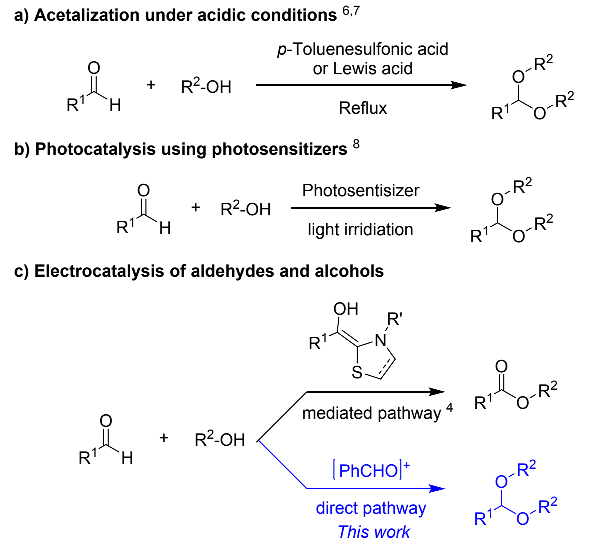
A versatile protocol for acetals/thioacetals production by means of direct electrochemical oxidation is developed under neutral conditions, providing (thiol)acetals with good functional group tolerance and wide scope from both aldehydes and (thio)alcohols. DFT calculations reveal that direct electron transfer from anode plays a key role for carbonyl activation during this acid free acetalization process.

Recent concerns on environment pollution and energy over-consumption in chemical production have drawn significant attentions, which appeal greener and more sustainable synthetic approaches to relieve the environment crisis.[1] Electrochemical organic synthesis is such a process, which utilizes electrons as an effective catalyst to achieve functional group interconversion with high chemoselectivity and functional group compatibility under mild conditions.[2] Specifically, direct electron transfer from electrodes without a mediator can avoid the recontamination during product formation, offering a simpler and more attractive opportunity for organic synthesis.[3] Inspired by successful anodic oxidative coupling of aldehydes and alcohols,[4] we have been exploring the potential transformation of aldehydes via electrochemical activation. To our surprise, anodic oxidation of benzaldehyde in ethanol without mediators leads to acetals formation. Such a transformation has not yet been reported in previous work,[4,5] possibly due to the NHC-mediated Breslow intermediate formation, which undergoes a different reaction pathway after electrochemical activation. (Thiol)acetals are important synthetic intermediates which are widely used as carbonyl protection in multistep synthesis. A conventional procedure for (thio)acetal production generally requires stoichiometric Bronsted or Lewis acid as carbonyl activator along with refluxing conditions.[6] Recent efforts devoted to develop more efficient Lewis acid[7] or utilize photocatalysis strategy[8], these procedures had either limited scope to thioacetals/acetals or caused potential metal and chemical pollution. Herein, we report a general and direct acetalization/thioacetalization method from aldehydes and alcohols/thiols by using an electrochemical process under neutral conditions without mediators.

The initial investigation for the acetalization optimization was performed from benzaldehyde **1** and ethanol, as summarized in Table 1. Considering the reaction equilibrium between acetal **2** and aldehyde **1**, the maximum conversion of benzaldehyde was achieved in a divided cell under constant current of 1 mA (1.75 V vs. Ag/AgCl, Fig. S2), giving acetal **2** as the sole product in 91% yield (Table 1, entry 1).



Scheme 1. Acetalization of aldehydes

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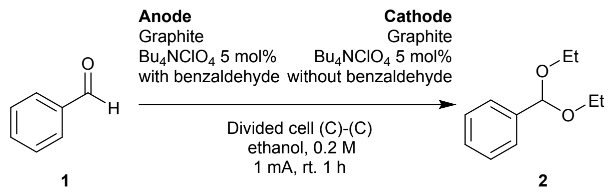
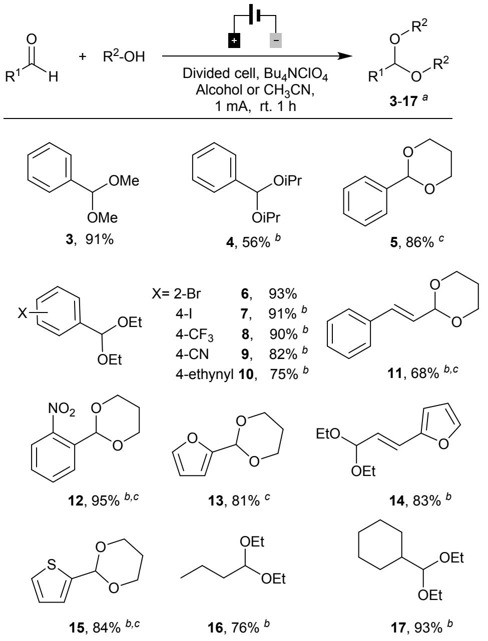
Table 1. Condition optimization of acetalization reaction from benzaldehyde and ethanol.[a]



Entry	Deviation from standard condition	Time (h)	Conv (%)	Yield [b] (%)
1[c]	none	1	92	92(91)
2	Without electric current	0.5	0	0
3	Bu_4NBr	0.5	86	85
4	Bu_4NBF_4	0.5	44	44
5	Bu_4NClO_4	0.5	89	88
6	Reaction at 50 °C	0.5	84	81
7	Pt anode instead of C anode (5 mol% Bu_4NBF_4)	0.5	14	14

[a] Reaction conditions: **1** (1.0 mmol), Bu_4NClO_4 (5 mol %), ethanol (5 mL) [anode], Bu_4NClO_4 (5 mol %), ethanol (5 mL) [cathode] in an H-type divided cell with two graphite electrodes and separated by a Nafion-117 membrane, rt, 1 h under air. [b] The yield was determined by GC with dodecane as the internal standard. [c] Isolated yield is in the parentheses.



[a] Reaction conditions: **1** (1.0 mmol), Bu_4NClO_4 (5 mol %), alcohol (5 mL) [anode], Bu_4NClO_4 (5 mol %), alcohol (5 mL) [cathode] in an H-type divided cell with two graphite electrodes separated by a Nafion-117 membrane, 1 mA, rt. 1 h, yield of isolated product; [b] Constant current, 2 mA; [c] Reaction using 1,3-propanol (1.5 mmol), performed in 5 mL CH_3CN.

Scheme 2. Electrochemical acetalization of aldehydes and alcohols

It should be mentioned that the reaction did not work without electricity (entry 2). The reaction proceeded smoothly in air with ammonium salts as the support electrolyte, and the best yield obtained when Bu_4NClO_4 was used (entries 3-5). However, the higher temperature influenced the equilibrium of acetalization, which decreased the yield of **2** (entry 6). Graphite electrodes were proved to be the more economical and efficient electrodes (entry 7). The electrolysis in a divided cell was more efficient than in an undivided cell, this could be related to the formation of cationic species, which then play as real catalyst in the acetalization reaction (for more details on control experiments of electrolysis time and yields of **2**, see SI, Table S2). While the cathodic electrode in an undivided cell may quench the positively charged species.

Upon the optimal condition established, electrochemical acetalization from various aldehydes with alcohols under standard conditions were screened, as shown in Scheme 2. First, several alcohols were submitted for acetalization reactions with benzaldehyde **1**, the steric hinderance effect from *iso*-propanol was observed, forming **4** in a moderate yield. Excellent isolated yield was obtained from 1,3-propandiol in CH_3CN solvent, which was more efficient than the alcohol solvent itself, giving **5** featuring a 1,3-dioxane motif. Then, substituted benzaldehydes were investigated, both electron rich and deficient functions were tolerated, affording the corresponding acetals **6**-**9** in excellent yields. Interestingly, some acid sensitive substrates, for instance, 4-ethylnylbenzaldehyde and cinnamyl aldehyde reacted with alcohols to generate the corresponding acetals **10**-**12** in good yields. Heteroarene aldehydes and aliphatic aldehydes were also compatible with the standard reaction conditions, producing acetals **13**-**17** smoothly.

Moreover, this protocol readily expands the reaction scope to thiol derivatives, since the thioacetal products are also widely applied as synthetic intermediates or coupling reagents for elaborated molecular structures.[9] Generally, better results were observed when thiols were used as nucleophiles with benzaldehyde **1** under similar conditions in CH_3CN, acetals **18**-**20** were obtained with excellent yields in all cases (Scheme 3). Notably, 1,3-dithiane derivatives **22**-**29**, which were key acylating reagents in Corey-Seebach reactions, produced from 1,3-dithiols and different aldehydes in excellent yields. It is also interesting to see that secondary thiols and thiols with an ester functional group tolerate in such transformation to generate acetal **21** and **30**, respectively. In addition, electrochemical thioacetals preparation are also successful, affording **31** and **32** in good yields.

The applicability of the new electrochemical transformation process was further evaluated, as shown in scheme 4. The typical (thio)acetals **5** and **20** were prepared in gram-scale without compromising the yields and chemoselectivity under similar conditions. In addition, gram-scale synthesis of thioacetals **22**-**28** were also successful (reaction performed on 30 mmol of aldehydes, 1 M solution in MeCN), which demonstrated the high applicable potency of the electrochemical process.

As an expand of the current electrochemical synthetic approach, the carbon nucleophile was investigated to construct C-C bonds under the anodic electrolysis. When Ruppert-Prakash reagent (CF_3SiMe_3) was used as the carbon

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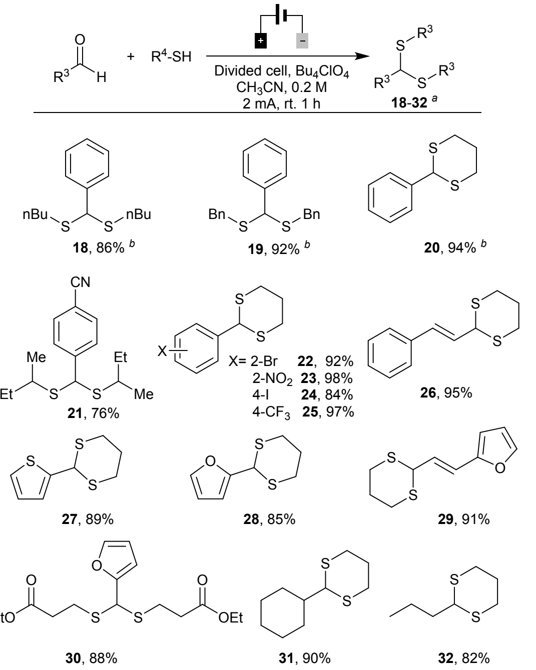
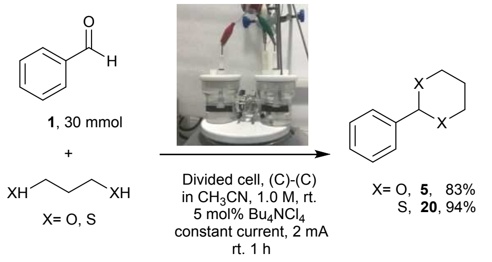
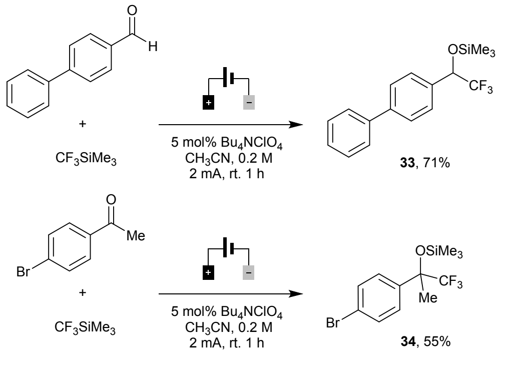


[a] Reaction conditions: Aldehydes (1.0 mmol), Bu_4NClO_4 (5 mol %), thiols (1.5 mmol), CH_3CN (5 mL) [anode], Bu_4NClO_4 (5 mol %), CH_3CN (5 mL) [cathode] in an H-type divided cell with two graphite electrodes and separated by a Nafion-117 membrane, constant current 2 mA, rt. 1 h, yield of isolated product; [b] Constant current 1 mA.

Scheme 3. Electrochemical (thio)acetalization of aldehydes and thiols.



Scheme 4. Gram-scale synthesis of (thio)acetals.



Scheme 5. Electrochemical trifluoromethylation of Carbonyl Compounds.

nucleophile, trifluoromethylation of both aldehyde and ketone proceeded smoothly in high efficiency without further optimization of the reaction conditions (Scheme 5), which avoid the traditional activation by Lewis acids or NHC carbene.[10] The results manifested that anodic oxidation could behave as Lewis acid surrogates to promote the nucleophilic attack of small molecules.

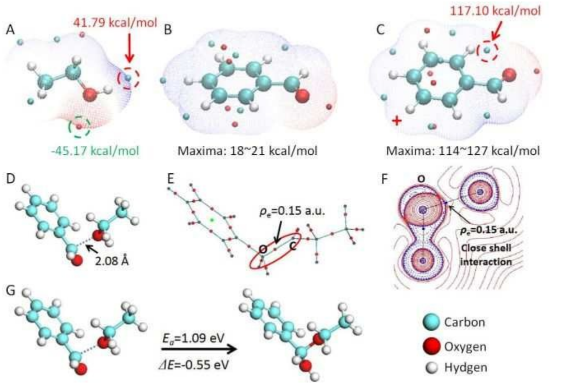


Figure 1. Geometric and electronic structures for the formation of hemiacetal intermediate from CH_3CH_2OH and $[PhCHO]^+$. Electrostatic potential surface of CH_3CH_2OH, PhCHO, and $[PhCHO]^+$ (A-C), reaction complex $[PhCHO\cdots CH_3CH_2OH]^+$, (D), Critical points distribution of reaction complex $[PhCHO\cdots CH_3CH_2OH]^+$ (E), Laplacian distribution ($\nabla^2\rho_r$) for C-O interaction in $[PhCHO\cdots CH_3CH_2OH]^+$ complex (F), reaction process for the formation of hemiacetal intermediate (G).

Previously reported acetalization processes of aldehydes and alcohols by means of thermodynamic or photocatalytic processes involve some acidic species, which were believed as the real catalysts (Scheme 6a).[8a, 11] To understand how the electrochemical acetalization works under neutral conditions. The frontier orbital energies of CH_3CH_2OH, PhCHO, and $[PhCHO]^+$ were calculated to elucidate the reaction pathway. Meanwhile, the electrostatic potential distribution maps (with extreme points) of those three compounds were also plotted (Fig. 1).

The calculation results clearly demonstrate that the frontier orbital energy between CH_3CH_2OH and **1** has huge barrier, which makes the direct reaction between CH_3CH_2OH and benzaldehyde **1** unfeasible. However, under the electrochemical anodic activation, if **1** undergoes one electron oxidation to generate intermediate $[PhCHO]^+$, the calculated energy barrier between the LUMO orbital of $[PhCHO]^+$ and HOMO orbital of CH_3CH_2OH is only 0.04 eV,

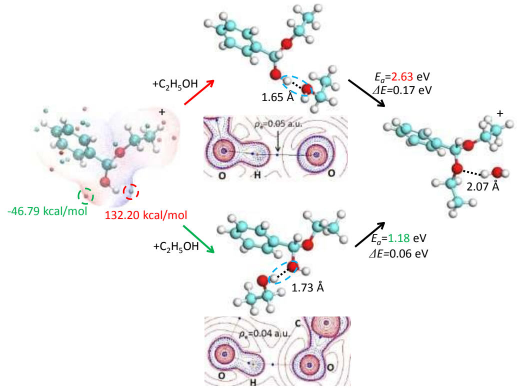


Figure 2. Different reaction pathways for the formation of acetal product.

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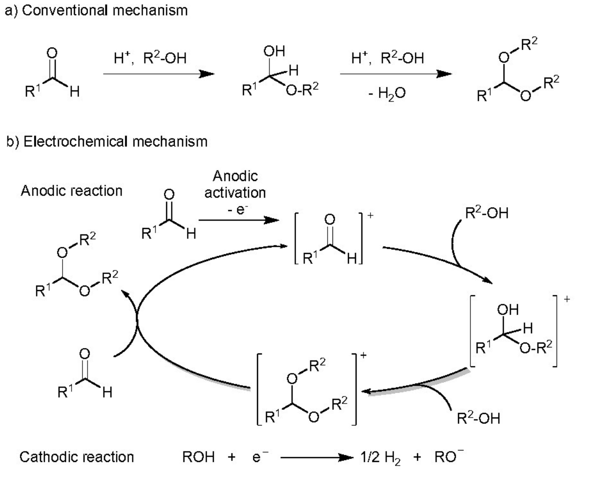
indicating that two species can interact effectively. Moreover, the electrostatic potential extreme points distribution of $[PhCHO]^+$ changes dramatically as compared to **1**. Specifically, a distinct minimum point appears on one side of its molecular plane (the red circle in Fig. 1c). This minimum point exactly matches the maximum point (the green circle in Fig. 1a) near the O atom in the CH_3CH_2OH, which is the reaction region of those two compounds. Further calculations show that the reaction between $[PhCHO]^+$ and CH_3CH_2OH does occur in this region, O atom in CH_3CH_2OH directly interacts with the C atom in $[PhCHO]^+$, forming a $[PhCHO\cdots CH_3CH_2OH]^+$ intermediate (Fig. 1d), and the distance between C-O bond is calculated to be 2.08 Å. Electron density topological analysis using Atom in molecules (AIM)[12] indicates that there exists a bond critical point (BCP) between 'O' and 'C' atom, and the electron density for this point is 0.15 a.u. Contour map of the Laplacian distribution ($\nabla^2\rho_r$) shows that the BCP is located in the positive region, thus $[PhCHO\cdots CH_3CH_2OH]^+$ is a typical closed shell interaction. Next, the hydroxyl 'H' atom from CH_3CH_2OH shifts to the carboxyl 'O' atom of PhCHO, and the 'O' atom bonds to the carboxyl 'C' atom from **1**, forming a stable $[PhCH(OH)OCH_2CH_3]^+$ hemiacetal intermediate. The activation energy for the hemiacetal intermediate formation is calculated to be 1.09 eV.

The $[PhCH(OH)OCH_2CH_3]^+$ hemiacetal intermediate can further interact with the ethanol in the reaction system forming the final acetal **2** in two different reaction pathways from different reaction sites. The corresponding reaction intermediates can be formed, which are stabilized by hydrogen bond interaction (Fig. 2). The activation energy of hydrogen bond between the hydroxyl group of hemiacetal and the 'O' atom in the ethanol is calculated to be 2.63 eV (Figure. 2 in the red arrow pathway), which is unfavorable from the kinetic point of view. While the activation energy of the hydrogen bond formed from the 'H' atom (from ethanol) and 'O' atom (from hemiacetal) is estimated to be only 1.18 eV (Fig. 2 in the green arrow pathway), which is almost equivalent to the activation energy for hemiacetal formation (1.09 eV). Therefore, the positively charged benzaldehyde formed by electrochemical process can smoothly react with the ethanol in the system to form the positive charged acetal, which undergoes cation ion exchange with **1** to form acetal **2** and regenerate $[PhCHO]^+$ (Fig. S2).

Moreover, control-experiments showed that even short-time electrolysis, followed by rigid stirring could promote the reaction to good yield (see Table S2). Such results indicated that anodic electrode triggered some cationic species as real catalyst. The positively charged species could easily undergo cation ion exchange with aldehyde to regenerate the catalysts to promote the reaction (SI, Fig. S3).

Based on above results, a plausible reaction mechanism was proposed for the electrochemical acetalization, as shown in Scheme 6b. Initially, the anodic oxidation of aldehyde produces a positively charged $[RCHO]^+$, which could readily react with the first alcohol to form corresponding $[hemiacetal]^+$. Further reaction between the charged hemiacetal and the second alcohol proceed smoothly to produce $[acetal]^+$. Then, cation ion exchange between aldehyde and $[acetal]^+$ occurs to give acetal and regenerate $[RCHO]^+$ simultaneously. On the cathode, alcohol was reduced to generate H_2 and alkoxyl anion.



Scheme 6. Acetalization reaction pathways.

Conclusions

In summary, we developed a simple and efficient (thio)acetalization approach from aldehydes and (thiol)alcohols by anodic electrochemical oxidation. Both aromatic and aliphatic (thio)acetals were obtained in high yields with complete selectivity. The electrochemical (thio)acetalization reaction is insensitive to air and could be performed in gram scale even with some acid sensitive functional groups, making it an attractive method for (thio)acetal synthesis. DFT calculations together with control experiments suggest that the anodic activation of aldehydes is a key step, which promotes the acetalization reaction by generating positively charged catalytic cation species.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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Notes and references

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Direct anodic (thio)acetalization of aldehydes and alcohol(thiols) has been developed under neutral conditions.