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Electrochemically driven stereoselective approach to *syn*-1,2-diol derivatives from vinylarenes and DMF†

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We have developed an electrochemically driven strategy for the stereoselective synthesis of protected *syn*-1,2-diols from vinylarenes with *N,N*-dimethylformamide (DMF). The newly developed system obviates the need for transition metal catalysts or external oxidizing agents, thus providing an operationally simple and efficient route to an array of protected *syn*-1,2-diols in a single step. This reaction proceeds *via* an electrooxidation of olefin, followed by a nucleophilic attack of DMF. Subsequent oxidation and nucleophilic capture of the generated carbocation with a trifluoroacetate ion is proposed, which gives rise predominantly to a *syn*-diastereoselectivity upon the second nucleophilic attack of DMF.

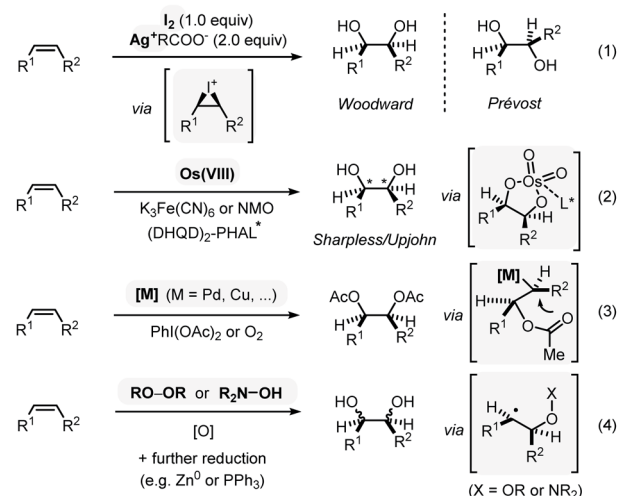
Introduction

The dihydroxylation of alkenes is a fundamental and straightforward transformation for the preparation of 1,2-diols, which is widely used in the preparation of key intermediates in fragrances, pharmaceuticals and functional materials.¹ There are several classical methods that are capable of achieving this goal, including the Woodward–Prevost reaction^{2a–c} and the epoxidation followed by ring-opening,^{2d} in which both reactions proceed *via* cyclic intermediates that define the stereochemistry of the product (eqn (1) in Scheme 1A). A concerted *syn*-dihydroxylation mediated by OsO₄ along with its asymmetric version, the Sharpless dihydroxylation, has also been recognized as the most widely used synthetic method for 1,2-diols (eqn (2) in Scheme 1A).³ Despite these landmark achievements, the replacement of the use of an expensive and highly toxic osmium catalyst led to the dioxxygenation of alkenes employing other metal-based catalysts which has successfully been developed in the presence of stoichiometric chemical oxidants such as PhI(OAc)₂ or dioxygen (eqn (3) in Scheme 1A).⁴ More recently, transition-metal free approaches such as peroxide⁵ or radical-mediated protocols⁶ have emerged as the alternative synthetic routes to 1,2-diols, although it is sometimes difficult to predict stereochemical outcome (eqn (4) in Scheme 1A).

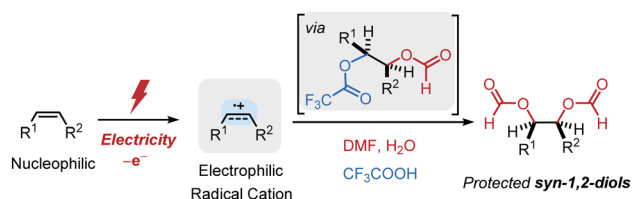
Most of these precedent examples however still rely on the use of transition metals for the requisite redox process or otherwise require additional synthetic steps for the preparation of reaction mediators. In addition, an employment of

a chemical oxidant system (*e.g.* hypervalent iodines) often leads to limited functional group compatibility. In this regard, we envisioned an electrochemical alkene oxidation as an ideal approach. Electrocatalytically driven organic synthesis allows to precisely select the redox potential for use, which circumvents selectivity and compatibility issue that often arise from its

(A) Previous approaches: alkene dioxxygenation with chemical oxidants



(B) This work: Electrochemical alkene *syn*-diformyloxylation promoted by TFA



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Scheme 1 Synthetic approaches to 1,2-diols from alkenes.



purely chemical counterparts.⁷ Despite recent efforts in the development of electrochemical dialkoxylation,⁸ it is highly desirable to develop a conventional and stereoselective approach for 1,2-diol derivatives using feedstock chemicals.

Herein, we report an electrochemical *syn*-diformyloxylation of vinylarenes using DMF as an oxygen source (Scheme 1B). This newly developed catalyst-free approach provides a straightforward and efficient route to a wide range of protected *syn*-1,2-diols in a single step. Electrochemical oxidation of alkenes to its radical cation enabled the direct addition of DMF, in which the formyloxy group derived from DMF can readily be converted into hydroxyl group.⁹ Subsequent oxidation and a facile nucleophilic capture of the generated carbocation with a trifluoroacetate ion is proposed to grant high *syn*-diastereoselectivity upon second nucleophilic attack of DMF.

Results and discussion

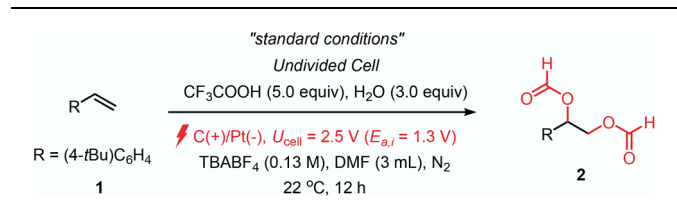
We set out to investigate our proposed olefin diformyloxylation by choosing 4-*tert*-butylstyrene (**1**) as the model substrate (Table 1). After optimization, we observed that the application of a constant cell voltage of 2.5 V (corresponding to an anodic potential of 1.3 V vs. SCE) enabled the formation of a formyl protected diol **2** in 90% yield (entry 1). The optimal conditions employed trifluoroacetic acid (TFA, 5.0 equiv.) and water (3.0 equiv.) as additives, TBABF₄ as the electrolyte, carbon felt and platinum plate as the anode and cathode respectively, in DMF. A control experiment without applied potential revealed that electric current is necessary for reactivity (entry 2). The reaction efficiency was significantly diminished when the reaction was conducted in the presence of molecular sieves, suggesting that

stoichiometric amount of water is requisite for the reaction (entry 3). We found that the employment of acids weaker than TFA were detrimental to the reaction (entries 4 and 5). On the other hand, acids stronger than TFA were productive, albeit with slightly reduced efficiencies (entries 6 and 7). Switching the solvent from DMF into CH₃CN significantly hampered the reactivity, even under high excess amount of DMF (entries 8 and 9). We have also found that the reactivity was not significantly affected when electrolysis was conducted under a constant current of 2 mA (entry 10). Notably, the reaction under O₂ atmosphere was not beneficial for the desired transformation, showing a significant drop in reaction efficiency (entry 11). Similarly, the reactivity was found to be slightly diminished when the reaction was conducted open to air (entry 12).

To investigate the scope and functional group compatibility of the current diformyloxylation protocol, an array of terminal vinylarenes were initially examined (Table 2). Vinylarenes with different functional groups such as simple alkyls (**2–4**), acetoxy (**5**), ester (**6**) and halogen (**7–9**) groups at *para*-position were well tolerated. An *ortho*-substituted vinylarene (**10**), 2-vinylnaphthalene (**11**) and 1,1-disubstituted olefin (**12**) were also smoothly participated in the reaction without difficulties. Importantly, vinyl heterocycles derived from dibenzofuran (**13**) and carbazole (**14**) were also applicable to the current protocol, while pyridine, quinolone and thiophene derived vinyl heteroarenes were reluctant to participate in the reaction mainly due to the formation of polymeric side products. Interestingly, 1,2-diacetoxylation (**15**) product was obtained when *N,N*-dimethylacetamide (DMA) was employed as a solvent. Moreover, the reactivity toward biorelevant structures was examined to illustrate the installation of protected 1,2-diol group as a late-stage synthesis, furnishing estrone (**16**) and tyrosine (**17**) derivatives. It was also notable to see that a readily oxidizable electron rich alkene such as phenyl vinyl ether,¹⁰ could also be engaged in this reaction (**18**).

To explore the stereoselectivity of the current procedure, we next set out to examine the scope of various internal alkenes. As summarized in Table 2, diformyloxylation of a wide range of internal alkenes granted access to products bearing vicinal stereogenic centers with good diastereocontrol. Dioxygenation of acyclic 1,2-disubstituted alkenes provided formyl-protected *syn*-diol products in good to excellent diastereomeric ratios (**19–24**, >7 : 1). Notably, substrates having labile groups on allylic positions underwent desired transformations without dissociation of the leaving groups (**21–23**). The cyclic alkenes such as dibenzosuberone and indene were viable substrates as well, albeit in somewhat diminished diastereoselectivity (**25–26**, >4 : 1, diastereomeric ratios). Interestingly, the reaction was found to be highly chemoselective towards a more readily oxidizable, electronically rich alkene when a substrate bearing multiple alkenes was tested. For example, cinnamyl cinnamate gave a mono-dioxygenated product **27** with high chemo- and diastereoselectivity. Trisubstituted alkenes were also reacted efficiently to afford the corresponding products in good diastereoselectivity (**28–29**). However, tetrasubstituted or unactivated alkenes derived from simple hydrocarbons were found to be recalcitrant to the current dioxygenation method (see

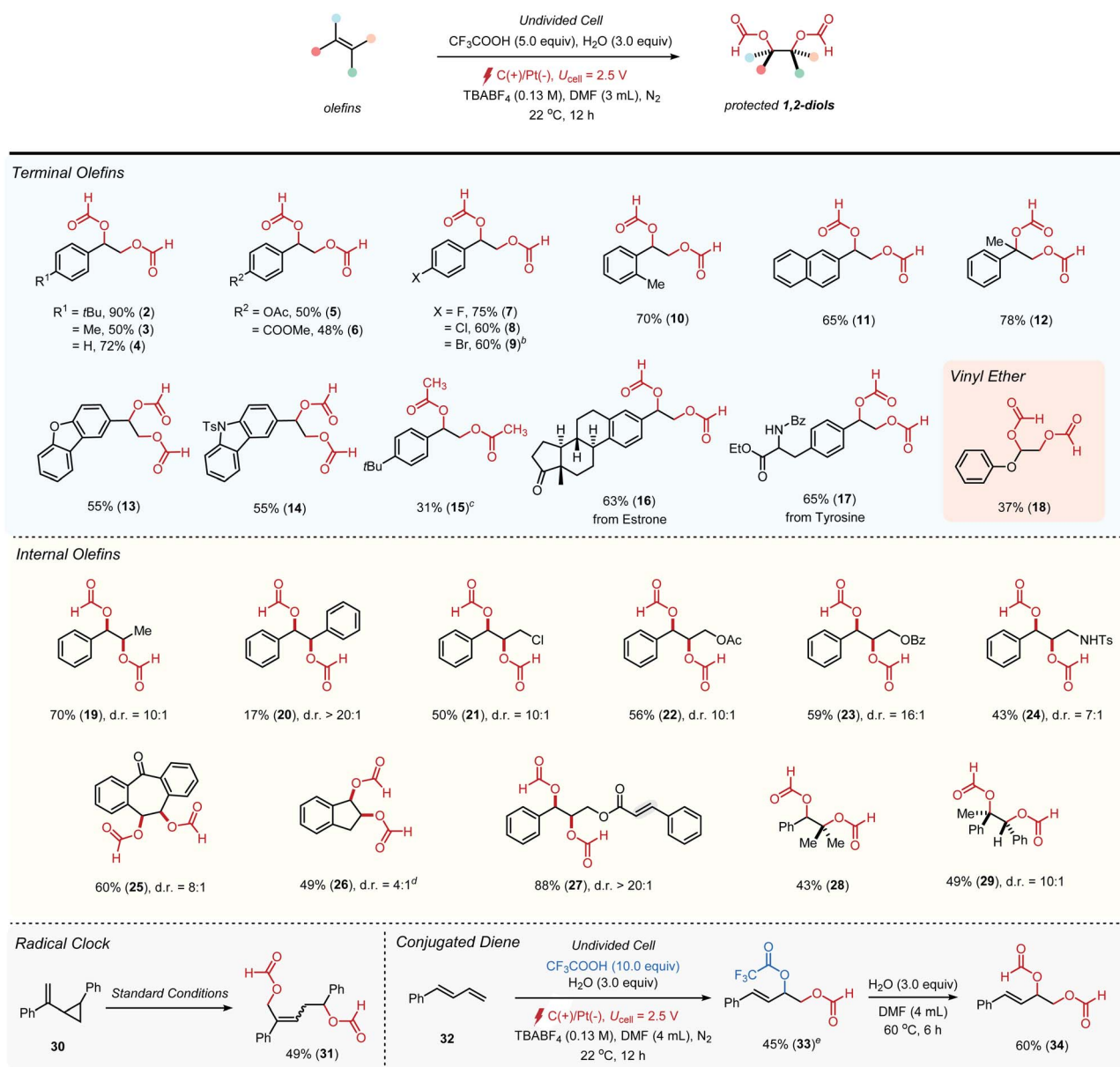
Table 1 Reaction parameter optimization^a



Entry	Variation from "standard conditions"	Yield of 2 (%)
1	None	95 (90)
2	No applied voltage	<5
3	With 4 Å molecular sieves	33
4	CH ₃ COOH instead of TFA	<5
5	HCOOH instead of TFA	31
6	HOTf instead of TFA	60
7	HNTf ₂ instead of TFA	50
8	DMF (20 equiv.) in CH ₃ CN (0.05 M)	25
9	DMF (10 equiv.) in CH ₃ CN (0.05 M)	15
10	Under constant current (I _{cell} = 2.0 mA)	75
11	Under O ₂ atmosphere (balloon, 1 atm)	45
12	Under air atmosphere	70

^a **1** (0.2 mmol, 1.0 equiv.), CF₃COOH (1.0 mmol, 5.0 equiv.), H₂O (0.6 mmol, 3.0 equiv.), TBABF₄ (0.1 M), DMF (3 mL); cell voltage (U_{cell} = 2.5 V); yields determined by ¹H NMR (isolated yields in parenthesis).



Table 2 Substrate scope of electrochemically driven olefin dioxygenation^a

^a Isolated yields are reported. Optimal conditions from Table 1 used. Diastereoselectivity was determined by ¹H NMR spectra of crude reaction mixture. ^b Yield determined by ¹H NMR using 1,2-dimethoxyethane as an internal standard. ^c *N,N*-Dimethylacetamide (DMA) was used as a solvent. ^d 10 equiv. of TFA was used. ^e 5% of 33 was also obtained along with 32.

Scheme S1 in ESI† for unsuccessful substrates). The electrochemical diformyloxylation tested positive in the radical clock experiment with cyclopropyl-substituted alkene **30**, implying the intermediacy of a benzylic radical during the reaction.

We have also found that the reaction took place selectively at the terminal position when 1,3-diene was employed as a substrate (**32**). Different from conventional vinylarene substrates, however, the dioxygenation product **33** possessing a trifluoroacetoxy group at 3-position was obtained as the major product (45%) along with 5% of the desired product (**34**). This observation led us to further investigate the possible

intermediacy of our reaction. As hypothesized, we were able to observe the formation of desired diformyloxylation product **34** upon treatment of **33** with DMF in the presence of water.

The uncommon diastereoselectivity trend observed in this catalyst-free approach piqued our interest in elucidating its mechanism. The reaction under deuterated DMF-*d*₇ solvent revealed that the formyl groups in the product originate from DMF, as we envisioned at the outset (Fig. 1A). In contrast, we found that the reaction with deuterated formic acid did not result in incorporation of deuterium on both formyl groups (Fig. 1B). These findings suggested that the engagement of



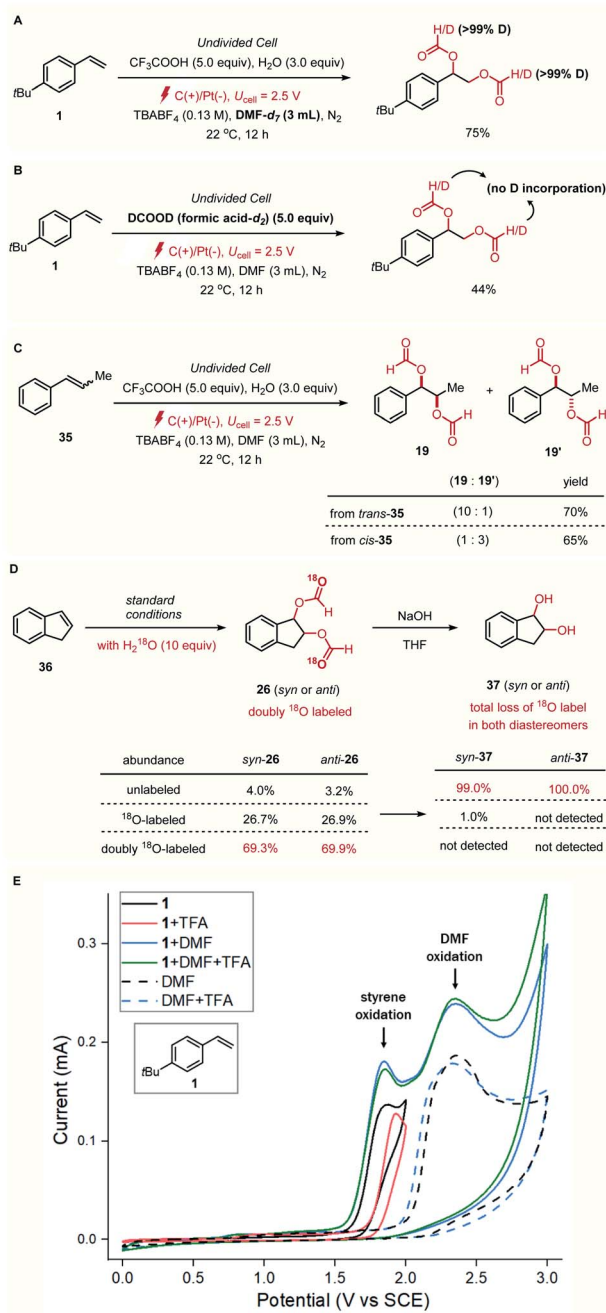


Fig. 1 Mechanistic investigations. (A) Deuterium labeling experiment with DMF-d_7 . (B) Deuterium labeling experiment with formic acid- d_2 . (C) Diastereoselectivity test with isomeric vinylarene substrates. (D) O^{18} -labeling experiments. (E) Cyclic voltammetric experiments.

formic acid with the olefin radical cation is less conceivable, in which the formic acid is initially generated by hydrolysis of DMF in the presence of strong acid.^{9a,11} Notably, the stereo-outcome of this reaction was dependent on the alkenylic geometry of the starting materials, with the major isomers irrespectively arising from *syn*-diformyloxylation. For example, *trans*- and *cis*- β -methylstyrene (*trans*- and *cis*-35) both gave corresponding *syn*-diformyloxylation products with 10 : 1 and 3 : 1 of diastereomeric ratios respectively (Fig. 1C). We note that this retention of

diastereoselectivity upon choice of the stereoisomeric starting materials is unusual compared to previous examples that employ different alkene oxidation strategies.¹²

To elucidate the origin of the oxygen atoms, we performed an isotopic labeling study with indene (36) as a substrate, using 97% O^{18} enriched water as an additive (Fig. 1D). The relative amounts of doubly-labeled diformyloxylation products (>69.3%) with singly-labeled (<26.9%) and unlabeled (<4%) products were determined for both diastereomers (*syn*- and *anti*-26), using high-resolution mass spectroscopy (HRMS). On the other hand, hydrolysis of the formyloxy groups resulted in significant removal of the oxygen 18-label, leading to the formation of unlabeled diol as the major product for both diastereomers (*syn*- and *anti*-37). These results suggest that both oxygens for the hydroxyl group originate from DMF during the reaction, not from water.

Cyclic voltammetry (CV) data showed that the oxidation of alkene 1 to the corresponding alkene radical cation results in a feature at around $E_{\text{p}/2} = 1.7 \text{ V}$ (vs. SCE; Fig. 1E, black line). The addition of TFA, DMF, or both did not cause significant anodic peak shift of this redox event in thermodynamically more feasible way, implying that the alkene substrate is directly oxidized on the carbon anode during the reaction. We also recognized the possibility of an oxidation of DMF prior to the alkene. However, such mechanism is proved to be difficult because of high oxidation potential of DMF ($E_{\text{p}/2} = 2.1 \text{ V}$, dashed black lines), even in the presence of TFA (dashed blue lines).

On the basis of these experimental results and precedent literature,¹³ a mechanistic rationale is shown in Fig. 2. First, electrochemical oxidation of the alkene substrate **A** generates the alkene radical cation **B** (the oxidation potentials E_{ox} for the

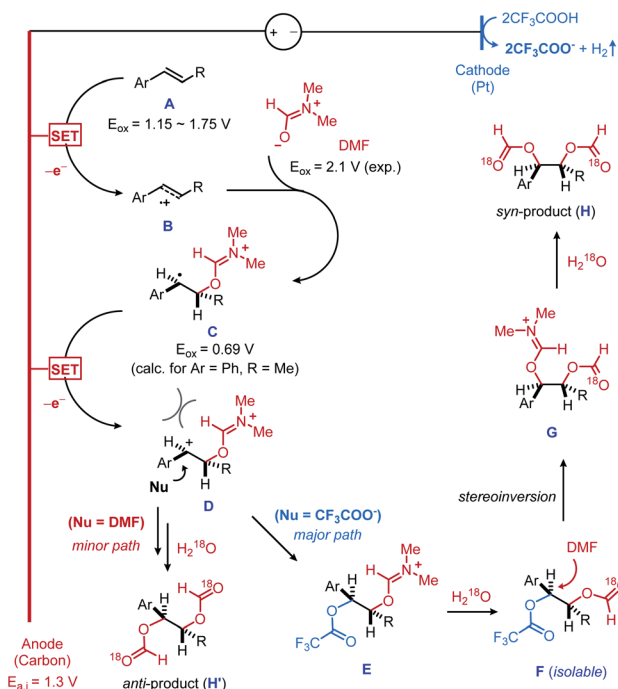


Fig. 2 Mechanistic rationale.



different vinylarenes tested range from 1.15 V to 1.75 V vs. SCE).¹⁴ The low potential threshold for such electron transfer is reported to be 0.5 V lower than the thermodynamic potential of the substrate,¹⁵ which supports that our measured initial anodic potential ($E_{a,i} = 1.3$ V vs. SCE) is above the onset potential of alkene oxidation. As an additional note, the anodic potential was maintained throughout the reaction, showing 1.22 V of the final anodic potential ($E_{a,f}$). This result suggests that the desired reactivity can be achieved at the low potential threshold of the alkene oxidation. The nucleophilic trapping of **B** with DMF produces the carbon-centered radical **C**, which is concurrently oxidized into the dication **D** on a carbon anode. Indeed, the second anodic oxidation is calculated to be thermodynamically more feasible than the first oxidation ($E_{ox} = 0.69$ V vs. SCE, when Ar = Ph and R = Me).¹⁶ A facile nucleophilic capture of sterically biased dication **D** by trifluoroacetate ion would result in the predominant formation of an *anti*-dioxxygenated intermediate **F**, upon hydrolysis of iminium intermediate **E**. A nucleophilic displacement of trifluoroacetate group¹⁷ from an isolable intermediate **F** by DMF eventually furnishes a *syn*-diformyloxylated product **H** followed by the second hydrolysis. It should be noted that the high diastereoselectivity observed in linear alkene substrates suggests that the formation of **E** occurs prior to the erosion of diastereocontrol caused by C–C bond rotation. The reactivity trend upon the choice of acid observed in Table 1 is likely related to the final nucleophilic displacement step. Moreover, the role of TFA in affecting diastereoselectivity was also verified by a series of control experiments with internal alkene substrate, where TFA is replaced by other acids.¹⁸ We also recognized the possibility of a nucleophilic attack of **D** directly from DMF to give *anti*-diformyloxylated product (**H'**). However, this pathway is considered to be less likely because trifluoroacetate is presumably a better nucleophile than DMF to capture dicationic intermediate **D** mainly due to its anionic character. This is also consistent to the predominant *syn*-diastereoselectivity of the current diformyloxylated protocol.

Conclusions

In conclusion, we devised an electrooxidative strategy that grants access to formyl-protected *syn*-1,2-diols from vinylarenes and DMF. This reaction is initiated by the electrochemical oxidation of the alkene substrates followed by the nucleophile attack of DMF. Mechanistic studies imply that trifluoroacetate ion is presumably engaged in the nucleophilic capture of the carbocation intermediate, which gives rise to high *syn*-diastereoselectivity. A simple deprotection of formyl protecting groups from the dioxxygenated product was also presented, highlighting synthetic utility of this electrochemical method toward a variety of 1,2-diols. We anticipate this electrochemical synthetic approach promoted by trifluoroacetic acid will be broadly applicable in further development of nucleophilic olefin functionalization reactions.

Author contributions

S. H. P. and D. S. C. performed the experiments and analysed the data. H. K. conceived the project, analysed experimental

data and performed the calculations. The manuscript was written by H. K. and S.-g. L. and S. H. P. contributed to the editing.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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- 18 A set of control experiments was conducted where TFA is replaced by other acids using an internal alkene (*trans*-35) as a substrate. Both reactivity and *syn*-selectivity was decreased upon treatment of other acids, supporting that the mechanistic role of TFA is important in the final nucleophilic displacement step. See ESI† page S12 for details.

