Asymmetric Electrochemical Alkenylation by Synergistic Chiral Primary Amine and Naphthalene Catalysis

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ABSTRACT: External tuning of enamine intermediate has significantly expanded reaction space of typical aminocatalysis. Notwithstanding the progress of chemo- and photo-oxidation of enamine intermediate, electro-oxidation was left as a much less explored area, in stark contrast to the prosperous renaissance of electrochemistry in recent years. Challenges mainly come from the reactivity barrier as a consequence of heterogeneous electron transfer, and subtle stereo-control in ionic electrolyte solution under the influence of electric field. Herein, we report asymmetric α-alkenylation of carbonyl compounds using potassium alkenyl trifluoroborate as a model reaction to demonstrate the capability of primary amine catalysis under electrochemical conditions. By employing enamine redox mediator mapping (e-RM[2]) strategy, a new organic mediator, dimethoxyl naphthalene, was found to greatly enhance reactivity. Mechanistic studies uncover an ion-pair interaction between protonated aminocatalyst and anionic substrate that account for the exceptional enantioselectivity. This catalytic system demonstrates the best level of enantioselectivities in electro-oxidative enamine transformations so far.

Introduction

Reactive intermediates are corner-stones for the development of organic reactions, where their generation and manipulations are of paramount importance. The recent renascence of photochemistry[1,2] and electrochemistry[3-6] in organic synthesis has offered powerful tuning strategies to the prominent reactive intermediates in free radical and cationic chemistry. By such external tuning, significant new reactivity can be uncovered with an existing catalytic process. As a prototypical example of covalent and nucleophilic intermediates, enamines readily undergo single-electron oxidation, leading to polarity-reversal reactivity that enables the coupling with nucleophiles under oxidative conditions[7,8]. In the past decades, both chemical[7-18] and photochemical[19-26] oxidation has been well exploited for the SOMO-type aminocatalysis. However, the application of anodic oxidation has surprisingly met with rather limited successes in this type of catalysis (Fig. 1A)[27,28].

With sustainable electricity, electrochemical reaction offers arguably an ideal synthetic pathway in terms of energy consumption and conversion. The merge of aminocatalysis and electrochemistry has been long pursued, but success has been mainly achieved in oxidative enamine transformations wherein the nucleophiles were preferentially oxidized[29-32]. The *in-situ* anodic oxidation of enamine to an open shell SOMO intermediate is easily conceivable and strategically attractive, echoing the tremendous advances in electrochemical free radical reactions as witnessed recently[3-6,33,34]. Unfortunately, simply switching the chemical oxidant to an electrochemical setting led to reduction on both activity and stereoselectivity[8,11,27,28](Fig. 1A), indicating a substantial difference between the homogenous electron-transfer and the electrode electron transfer. Fine tuning and manipulation of the latter is still a great challenge due to the often poorly understood interphase properties[35]. In addition, the compromised enantioselectivity also suggest the generally functioning steric mode under homogenous conditions did not work properly on the electrode double layer in an electrolyte solution (Fig. 1A), requiring a new stereocontrol strategy with aminocatalysis.

In this work, we sought to develop electrochemical SOMO type catalysis using chiral primary-tertiary diamine-type aminocatalysts. Frequently utilized as its acid conjugates, this type of aminocatalysts has been widely applied in a range of oxidative enamine transformations[21-24]. In these processes, its protonated and hence ionic feature would benefit the oxidation of enamine intermediate through proton-coupled electron transfer (PCET). Recently, this feature facilitated the oxidation of *in situ* formed secondary enamine intermediate to α-imino carbocation through a sequence of 2e-2H$^+$ transfer, formulating the first asymmetric electrochemical S_N1 reaction[36]. However, to achieve electrochemical SOMO type catalysis with an α-imino radical intermediate remain elusive under electrochemical conditions. A critical issue is to truncate electron transfer at the stage of forming α-imino radical without further oxidation. Given the function of redox mediators to homogenize electron transfer[35], and the potential benefits of them in enamine oxidation[28], we herein proposed an enamine redox mediator mapping (e-RM[2]) strategy based on our developed redox potential scale of enamine[37]. A systematic map of potential

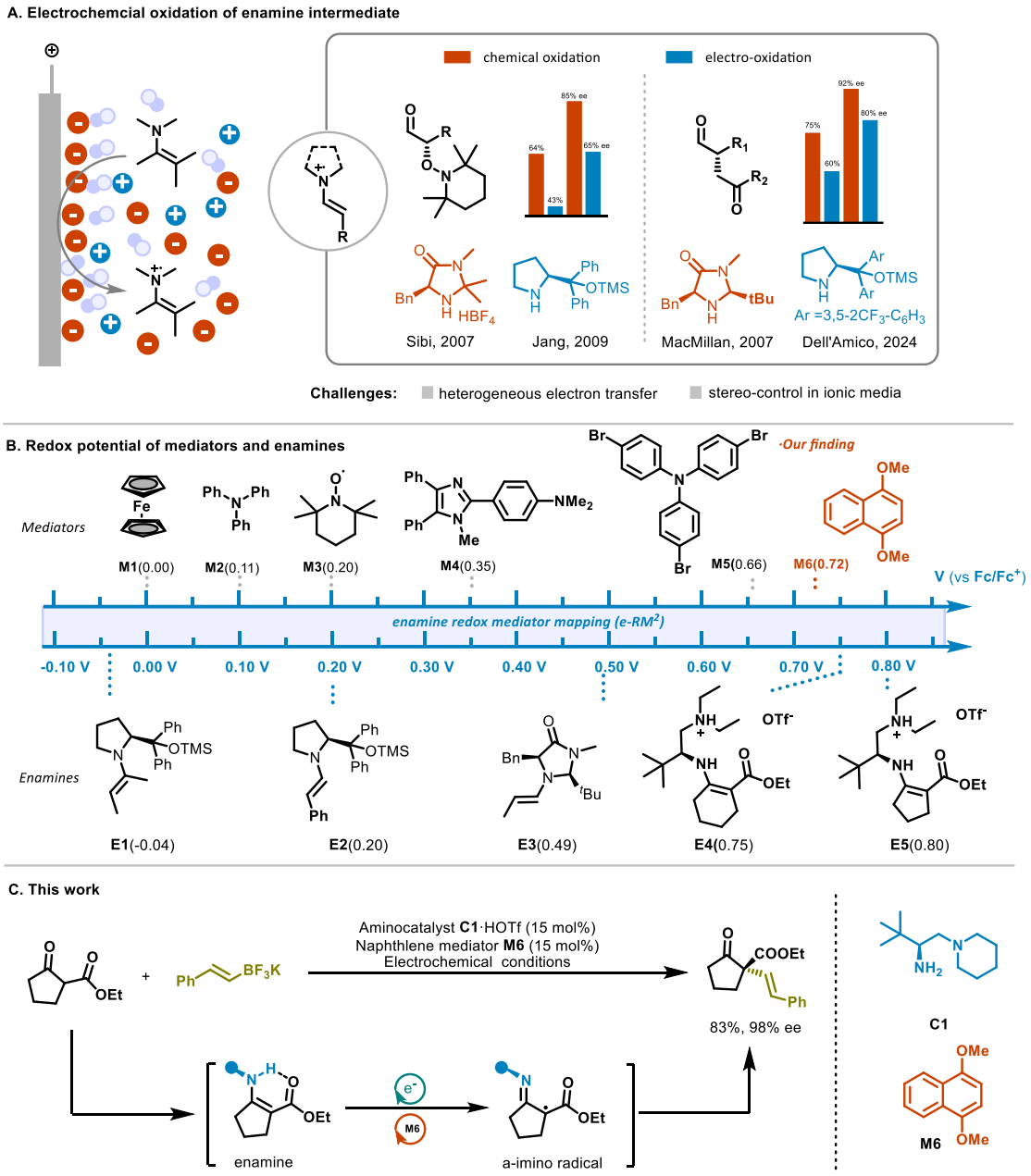
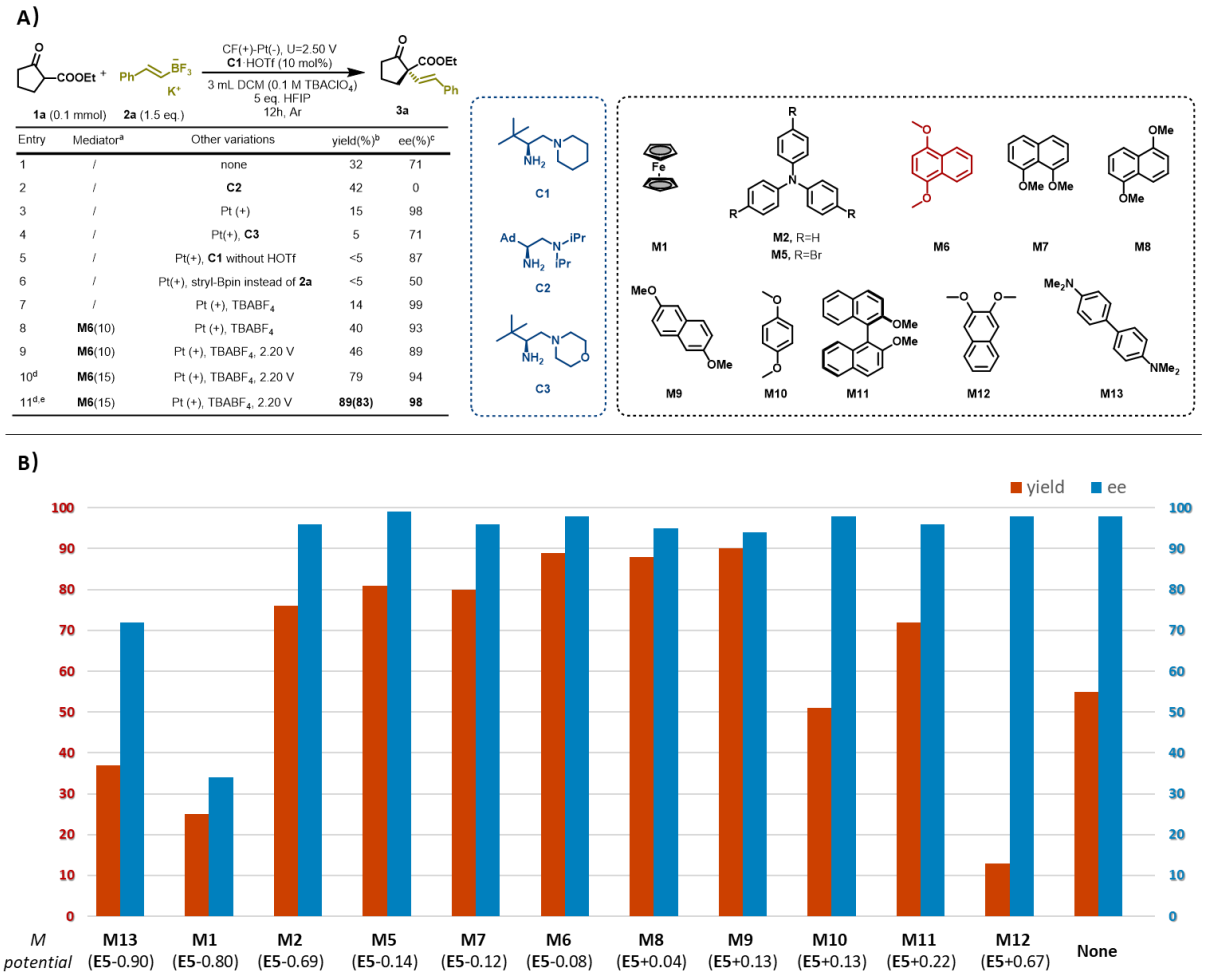


Figure 1. A) Electrochemical oxidation of enamine intermediate. B) e-RM² strategy in redox mediator discovery, and all potentials are calibrated by ferrocene. C) asymmetric electrochemical alkenylation catalyzed by primary amine *via* α-imino radical.

redox mediators[38-40] was constructed according to the redox potentials (Fig. 1B, also in Supporting Information Section 4.3). In e-RM², the matching of redox potential between enamine and mediator serves as an initial selection criterion for further development and optimization. By this approach, we have successfully discovered naphthalene derivatives as a desirable mediator for SOMO catalysis through α-imino radical intermediate. The resulted chiral primary amine and naphthalene synergistic catalysis enables the highly efficient and stereoselective oxidative Suzuki-type coupling with alkenyl trifluoroborates (Fig. 2C). Our mechanistic studies also uncover a distinctive electrostatic interaction with trifluoroborates that dictates the stereo-induction.

Results and discussion

We started our investigation by using the oxidative coupling between 2-oxocyclopentyl carboxylate ester (**1a**) and styryl trifluoroborate (**2a**) as a template reaction. Preliminary experiments were performed under constant voltage of 2.50 V in DCM solution of 0.1 M tetrabutylammonium (TBA) perchloride with hexafluoroisopropinol (HFIP) as the proton source. A quick survey of chiral primary amine catalysts indicated the reaction in the presence of aminocatalyst **C1** gave the desired alkenylated adduct **3a** with 32% yield and 71% *ee* (Fig. 2, entry 1). In contrast, a typical bulky primary aminocatalyst **C2** showed virtually no enantioselectivity (Fig. 2, entry 2), indicating steric effect does not work well in this reaction. With **C1**, a preliminary optimization



Entry	Mediator[a]	Other variations	yield(%)[b]	ee(%)[c]
1	/	none	32	71
2	/	**C2**	42	0
3	/	Pt (+)	15	98
4	/	Pt(+), **C3**	5	71
5	/	Pt(+), **C1** without HOTf	<5	87
6	/	Pt(+), styryl-Bpin instead of **2a**	<5	50
7	/	Pt (+), $TBABF_4$	14	99
8	**M6**(10)	Pt (+), $TBABF_4$	40	93
9	**M6**(10)	Pt (+), $TBABF_4$, 2.20 V	46	89
10[d]	**M6**(15)	Pt (+), $TBABF_4$, 2.20 V	79	94
11[d,e]	**M6**(15)	Pt (+), $TBABF_4$, 2.20 V	**89(83)**	**98**

Figure 2. Reaction optimization. Unless otherwise noticed, all reactions were performed on 0.1 mmol scale of **1a** with 1.5 eq. of **2a**. A) Evolution of the reaction conditions. a) molar percentage of the mediator was included in parenthesis; b) yields were determined by ^{1}H NMR analysis using CH_2Br_2 as internal standard and the data in parenthesis is isolated yield; c) *ee*s were measured using chiral HPLC; d) 15 mol% of **C1** was used; e) molar ratio of **1a** and **2a** was changed to 1.5:1 in 0.1 mmol scale. B) yield and *ee* with different mediators under standard conditions (the same as entry 11). Redox potential shift from that of **E5** is included in parenthesis.

revealed a critical impact of the anodic material. By replacing carbon felt (CF) anode with a Pt electrode, the enantioselectivity was increased to 98% *ee*, albeit with only 15% yield (entry 3). Further efforts to improve activity were all in vain at this stage (Table 1, entries 7, supplementary materials Table S7-8). Nevertheless, several interesting observations were noted that help to reveal the underlying reaction modes. Switching the tertiary amino side chain from piperidine (**C1**) to morpholine (**C3**) with lower basicity (pK_{aH} = 7.15 in water for its conjugated acid *vs* 10.08 for that of piperidine) led to virtually no activity with rather poor enantioselectivity (Fig. 2, entry 4, 5% yield and 71% *ee*). This observation together with the finding that the primary aminocatalyst **C2** was inactive in the absence of TfOH (entry 5) indicated a critical role of the tertiary amine and its protonation status on effective catalysis. In addition, changing the reactive and anionic trifluoroborate to neutral boronic acid pinacol ester (Bpin) also led to an inactive reaction (Fig. 2, entry 6), pinpointing a likely ionic interaction that is functioning in the reaction.

Given the catalytic power of redox mediator in electrochemical processes[38-40], an enamine oxidation mediator was sought after to further improve the reactivity. Recently, we have determined a full scale of redox potential of enamine intermediates[37]. On this basis, a systematic enamine-redox mediator mapping (e-RM^2) was constructed on all the potential redox mediators (Fig. 1B and SI). Following e-RM^2, redox mediators were screened. The frequently utilized mediators such as Ferrocene (Fc, **M1**), and triphenyl amine (**M2**), bearing much lower redox potential (<0.30 V *vs* Fc/Fc$^+$) than that of the targeted keto-enamine **E5** (E_{ox} = 0.80 V *vs* Fc/Fc$^+$) showed less satisfying effect on activity (Fig. 2B). Inspired by the recent finding of biphenyl as mediator[28], we also included electron-rich arenes for our screening. To our delight, methoxyl arenes, particularly naphthalenes, with redox potential around 0.8 V, were identified as the optimal mediators for anodic enamine oxidation. Naphthalene **M6** appeared as an optimal selection in terms of both activity and stereoselectivity. Further modifications on the reaction conditions brought to 89% yield and 98% *ee* in the presence of **C1** and **M6** (Fig. 2A, entries 8-11). It is noted that the enantioselectivity was generally maintained with different derivatives of naphthalene while the activity varied dramatically. For example, the 2,3-dimethoxynaphthalene (**M12**) gave 98% *ee* but only 57% yield, much

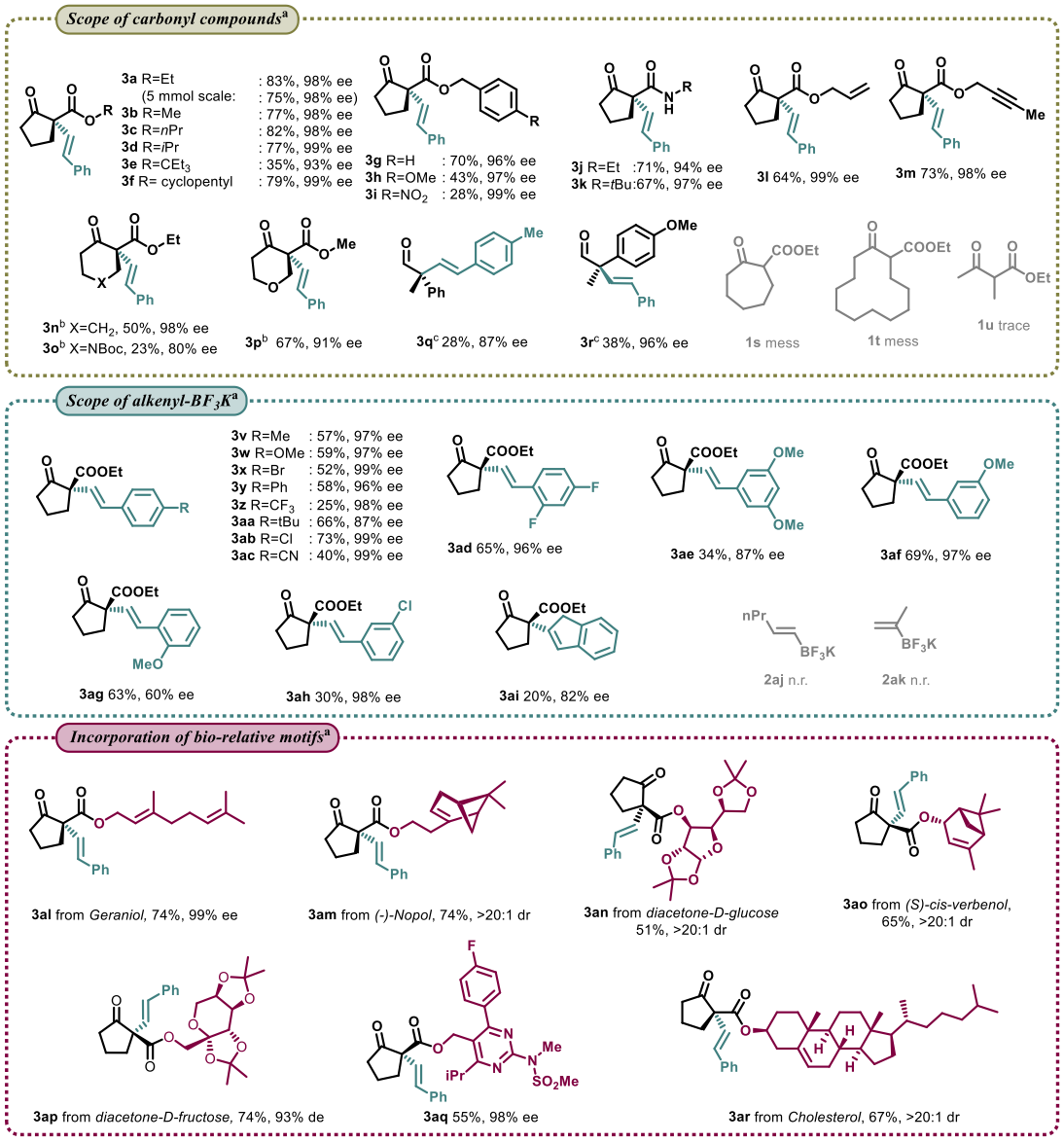


Figure 3. Substrate scope. a) All reactions were performed under standard conditions (1.5 eq. of **1** and 1.0 eq. of **2** in 0.1 mmol scale, 15 mol% **C1** and **M6**, 5 eq. HFIP as proton source, 0.1 M $TBABF_4$ in DCM, Pt as both anode and cathode under constant voltage of 2.20 V, reaction time:12 h) unless otherwise noticed. HPLC analysis was used to determine *ee* and *de* values, and dr was determined by ^1H NMR analysis. All yields refer to isolated yield. b) Reaction time was extended to 36 h. c) $TBAClO_4$ as electrolytes, 25 mol% **C1**, 25 mol% **M6**, 6.0 eq. of **1**.

lower than its other dimethoxy isomers (**M6-9**) (Fig. 2B), a trend at least partially ascribed to the varied redox properties.

Having these optimized conditions, scope of substrates was then examined (Fig. 3). Different β-ketocarbonyl compounds were subjected to this method first. β-Keto-esters ranging from simple ester (**3a-3d**) to very bulky ester (**3e** and **3f**) and benzylic ester (**3g-3i**) can be incorporated to give moderate to good yields and with excellent enantioselectivity for all the cases, indicating a well tolerance to the steric and electronic features of ester side chain. Additionally, gram scale reactions were conducted and no loss of enantioselectivity was observed for **3a**. Besides, the reactions with β-keto-amides bearing either small ethyl or large *tert*-butyl group proceeded smoothly to give the desired adducts with good yields and high enantioselectivity (**3j** and **3k**). Unsaturated C-C bond on the ester chain is also well tolerated in the reaction, showing good yields and high *ee* (**3l** and **3m**). Due to its dominant enol form, cyclohexanone-2-carboxylate is sluggish toward enamine formation comparing with its cyclopentanone counterparts, [41] hence with poor reactivity in oxidative enamine transformations [22,23]. Gratifyingly, this catalytic system showed high enantioselectivity in the reactions of 6-membered-ring keto-esters (**3n**-**3p**) with moderate yields. Moreover, in spite of its tendency undergoing nucleophilic addition[42-45], vulnerable α-branched aldehydes (**3q** and **3r**) can be transformed with satisfying enantioselectivity and no 1,2-addition side product was observed. This is the very first time that radical reactivity is triggered with α-branched aldehyde. Unfortunately, the reactions with β-keto-esters with larger ring (**1s** and **1t**) or acyclic ones (**1u**) gave messy or trace products

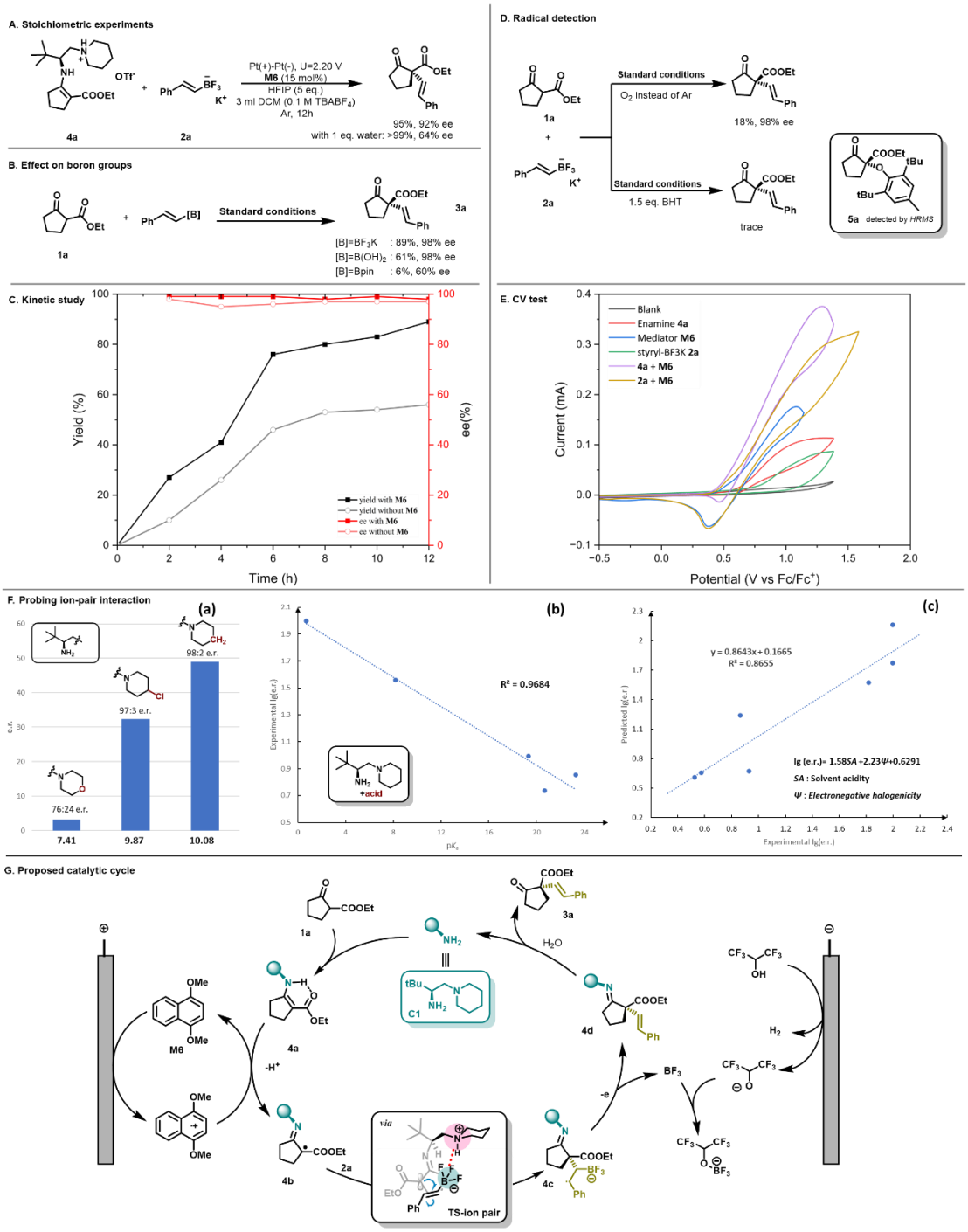


Figure 4. Mechanistic studies. All yields involved are determined by ^{1}H NMR analysis using dibromomathane as internal standard, and *ees* are measured by chiral HPLC. A) stochiometric experiments; B) Effect of different boron groups; C) Reaction profiles of the model reaction; D) Inhibition experiments with radical quenchers; E) CV test. All compounds of interest are of 0.01 M in DCM with 0.1 M $TBABF_4$ as electrolytes, and all tests were performed under Ar; F) Experiments to probe the ion-pair interaction (a) influence of pK_a of tertiary amine side chain in catalyst on e.r.; (b) linear free energy regression (LFER) of pK_a of conjugated acid and lg(e.r.), c) LFER of solvent effect; G) Proposed catalytic cycle.

Next, we examined the scope of alkenyl potassium trifluoroborates. Both electron-withdrawing group (EWG) and electron-donating group (EDG) on *para* position of phenyl ring can be tolerated with high enantio-control (**3v**-**3ac**), while EDG gave better yields than EWG, reminding of the ease of anodic oxidation in the former cases. Multi-substitutions (**3ad** and **3ae**) and different substitution sites (**3af** and **3ah**) except the *ortho*-position (**3ag**) also worked well to give the desired adducts with high enantioselectivity. Apart from terminal alkenyl trifluoroborates, internal alkenyl can be applied in this protocol (**3ai**), the first of such example in this type of transformations[12,34]. Unfortunately, alkenyl trifluoro borates with alkyl substitution did not work in this protocol, possibly resulting from lower stability of alkyl radical. Encouraged by the mild conditions as well as high stereoselective control, we further tried this

electrochemical alkenylation on the late-stage transformations with bio-active moieties. Unsaturated carbon-carbon bonds (**3al**, **3am**, **3ao** and **3ar**), multiple chiral centers (**3am**-**3ap** and **3ar**), and basic pyrimidine (**3aq**) can all be incorporated to give the expected adducts with high level of stereoselectivity.

Control experiments were performed to understand the mechanism. To verify the nature of enamine catalysis, stoichiometric experiments were carried out with the preformed enamine **4a** (Fig. 4A). Directly subjecting **4a** to the optimized conditions in the absence of the aminocatalyst gave the desired adduct **3a** with 95% yield and 92% *ee*, comparable with those under catalytic conditions. The addition of 1.0 equivalent of water to the stoichiometric reaction resulted in surprisingly a large drop of enantioselectivity from 92% *ee* to 64% *ee*, a clear indication of disfavoring polar and protic media effect (*vide infra* for discussions). The observed inactivity of boric ester comparing with its free boric acid and fluoroborate salts also suggest a working ionic interaction for effective reaction in this reaction system (Fig. 4B). The reaction profiles, determined with or without the selected mediator **M6**, clearly indicated that **M6** could effectively enhance the reaction rate, meanwhile show no interference to the stereochemistry under the optimized conditions (Fig. 4C). The reaction in the presence of well-known free radical inhibitors such as oxygen or *tert*-butylphenol (BHT) was either largely suppressed or completely shut down (Fig. 4D) and a radical inhibition adduct **5a** was detected in the latter case, providing direct evidences to a free radical mechanism through an α-imino radical intermediate.

A series of CV tests were conducted to assist in the elucidation of the anodic processes (Fig. 4E). A significant boost of oxidative current was noted when **M6** was treated with enamine **4a**, while the reductive current declined noticeably, an indication of reduced concentration of **M6** radical cation caused by electron transfer with **4a**. However, when treated with styryl trifluoroborate **2a**, reductive current of **M6** remains nearly the same despite the increase of oxidative peak. These observations suggest that the reaction is initialized by a preferential oxidation of enamine in the coexistence of nucleophilic vinyl borate and that **M6** functions by mediating the interphase anodic electron transfer process involving aminocatalytic intermediates. The determined redox potentials of enamine **4a**, **2a** and **M6** is also in line with this scenario, with oxidative potential $E_{p/2}$ of enamine **4a** being 0.81 V, lower than that of **2a** (0.94 V, *vs* Fc/Fc^+) and the better matching between **4a** and **M6** ($E_{1/2}$ = 0.72 V, *vs* Fc/Fc^+) being noted.

Based on the above experimental observations as well as previous studies[22-24], a synergistic aminocatalytic cycle was proposed in Fig. 4G. The reaction was initialized by electrochemical oxidation of *in-situ* generated enamine intermediate **4a** to give an α-imino radical **4b** after a coupled proton loss. A subsequent radical addition to styryl borate, assisted by a delicate yet critical ion pair interaction between the cationic protonated piperidine and anionic trifluoroborate (**TS**), led to a radical intermediate **4c**, which then underwent an oxidative deborination[12,46,47] to give eventually the targeted product. The presence of electron-rich naphthalene **M6** could effectively mediate interphase electron-transfer with aminocatalytic intermediates as illustrated, hence boosting the overall reaction efficiency. The key radical addition step features a critical ion-pair interaction that not only facilitates the addition, but also dictates the facial selection in a full agreement with the experimental observed stereoselectivity (Fig. 4G, **TS**). The observed deteriorative effect water (Fig. 4A) is supportive of this model as water may disrupt the ion pair interaction, resulting in loss of stereocontrol. Indeed, it was noted the reaction preferred polar non-protic solvent in which ion-pair interaction is favored. A good correlation between enantioselectivity and the solvent acidity scale (Catalán's SA) could be obtained (Fig. 4F c)[48,49], underscoring the importance of ionic interactions in the transition state. In addition, a survey of primary aminocatalysts with varied tertiary amine sidechain indicated the more basic side chain such as piperidine (pK_{aH} = 10.08), which tends to exist in its protonated cationic status essential for ion pair interaction, is preferred to the less basic side chains such as morpholine (pK_{aH} = 7.41) or 4-chloropiperidine (pK_{aH} = 9.87). A linear free energy regression (LFER) was obtained between pK_a of conjugate acid of aminocatalyst **C1** and lg(*e.r.*) (Fig. 4F b), the stronger the acidity the better enantioseletivity, a trend also upholding the preference for the charged status. Taken together, these results are in strong support of the ion-pair stereocontrolling model.

Conclusion

In conclusion, we illustrated the viability of electrochemical oxidation of secondary enamine by developing a highly enantioselective and effective alkenylation method. A new organic mediator, 1,4-dimethoxyl naphthalene, discovered through enamine redox mediator mapping (e-RM^2) strategy, was found to promote effectively anodic oxidation of enamine intermediate. The synergistic chiral primary amine and naphthalene catalysis works well for myriad carbonyl compounds with high enantioselectivity. Mechanistic studies uncover a distinctive ion-pair interaction between the protonated catalyst and anionic substrate that dictates the stereoselectivity. This finding may cultivate more advances in electrochemical transformations by aminocatalysis.

ASSOCIATED CONTENT

Supporting Information. Details about the materials and methods, experimental procedures, mechanistic studies, characterization data, NMR spectra and HPLC traces are all available in Supplementary Information. All the data that support the findings of this study are available within the Article and Supplementary Information files. This material is available free of charge via the Internet at http://pubs.acs.org.

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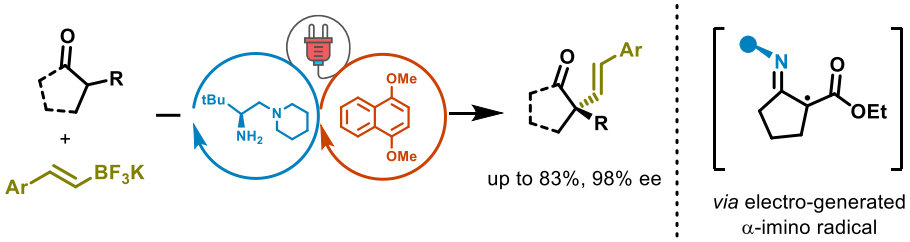

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