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## Accepted Article

**Title:** Electrochemical [4+2] Annulation-Rearrangement-Aromatization of Styrenes: Synthesis of Naphthalene Derivatives

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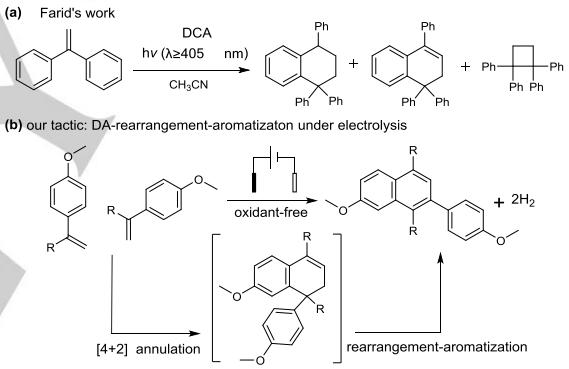
# Electrochemical [4+2] Annulation-Rearrangement-Aromatization of Styrenes: Synthesis of Naphthalene Derivatives

Yueyue Ma, Jufeng Lv, Chengyu Liu, Xiantong Yao, Guoming Yan, Wei Yu, and Jinxing Ye*

***Abstract:*** *We report the first electrochemical strategy to synthesize functionalized naphthalene derivatives via [4+2] annulation-rearrangement-aromatization from styrenes under mild conditions. The electrolysis does not require metals, oxidants and high valence substrates, indicating the atom and step-economy ideals. The dehydrodimer produced through [4+2] cycloaddition of 4-methoxy α-methyl styrene is isolated and proved to be the key intermediate for the following oxydehydrogenation to form carbon cation, which undergoes rearrangement-aromatization to afford the final products. This reaction represents a powerful access to construct multi-substituted naphthalene blocks in a single step.*

Functionalized naphthalenes and its derivatives are valuable structural skeletons among functional materials, pharmaceuticals, and natural products.[1-3] To regioselectively access this structures is always the targets in organic synthesis. The most prevalent and synthetically useful method is Diels-Alder (DA) reactions, followed by the sequenced oxidative aromatization.[4] Furthermore, due to the absence of stoichiometric oxidants, dehydro or dehydrogenative Diels-Alder reactions (DDA), in which the diene or alkene are replaced by high-valence substrates, reveals its remarkable advantages in the synthesis of sophisticated aromatics.[5,6] But, its applications are also limited by its pre-dehydrogenative highly saturated substrates and thermal conditions, where the heat, microwaves, and transition metals are indispensable to initiate DA reactions. Therefore, developing a green and mild method to access multi-substituted aromatics from easily obtained reactants is an appealing and challenging task for chemists.

There is no doubt that the radical-cation cycloaddition has enormously enriched the scope of thermal DA reaction. It not only proceeds at more rapid reaction rates than the thermal pericyclic reaction with excellent regio- and chemo-selectivity, but also occurs between two electron-rich dienes.[7] Particularly, photo- and electro-initiated radical cation DA reactions of electron-rich olefins have been extensively reported.[8,9] For instance, Yoon et al. developed a visible light mediated radical cation DA reaction of two electron-rich olefins using low loadings of Ruthenium (II) polypyridyl complexes.[8c] Chiba et al. established an electrocatalytic DA reaction assisted by aromatic redox tag between styrene and diene.[9b] Most of these works only involved the [4+2] annulation to afford non-conjugated products. Lei et al. developed an oxidative [4+2] cycloaddition between styrenes and alkynes under photoredox/cobaloxime dual catalytic system to construct naphthalene motifs.[8d] Especially, Farid et al. reported a photo-induced cycloaddition reaction of 1, 1-diarylethylenes and yielded [4+2] cyclodimers, dehydrodimers and [2+2] cyclodimers (Scheme 1, a).[8a] Inspired by this work, we hypothesized that the aromatic motifs might be constructed through further rearrangement-aromatization of dehydrodimer employing electrochemical method (Scheme 1, b)[10]. In this work, electrochemical [4+2] annulation-rearrangement-aromatization of styrenes is reported to access naphthalene derivatives under mild conditions in absence of the high valence substrates, metals and oxidants are required.




**Scheme 1.** Radical cation triggered DA reactions

In view of the relatively low oxidation potential ($E_{p/2}$ = 1.35 V) and high nucleophilicity,[11] 4-methoxy α-methyl styrene (**1**) was chosen as a model substrate to optimize the electrolysis conditions. After screening a wide range of reaction systems, in an undivided cell equipped a carbon felt (CF) anode and Ni plate cathode, the desired product **2** was prepared in 67% yield using $CH_3CN$ as the solvent, hexafluoroisopropanol (HFIP) as the co-solvent, tris(4-bromophenyl)amine (**I**, TBPA) [12] as mediator and 0.02 M $Et_4NOTs$ as electrolyte under a constant current of 10 mA (details see SI, Table s1). It is worth to note that the concentration of $Et_4NOTs$ was much less than 0.1 M, which is the normal concentration used in practice. In the absence of TBPA, the yield dropped to 41%. The electrode material is pivotal to achieve the desired product. And the carbon felt was irreplaceable as the anode and Ni was the best as the cathode, even similar result obtained using Pt plate (65% yield). Replacing CF with other carbon material as anode, such as reticulated vitreous carbon (RVC) and graphite, only a trace of **2** was produced. Furthermore, the electrolysis failed when HFIP was replaced by AcOH or MeOH as co-solvent, which involved the cathodic reduction to generate $H_2$ and base in situ and may also stabilize the intermediate radical cation [13].

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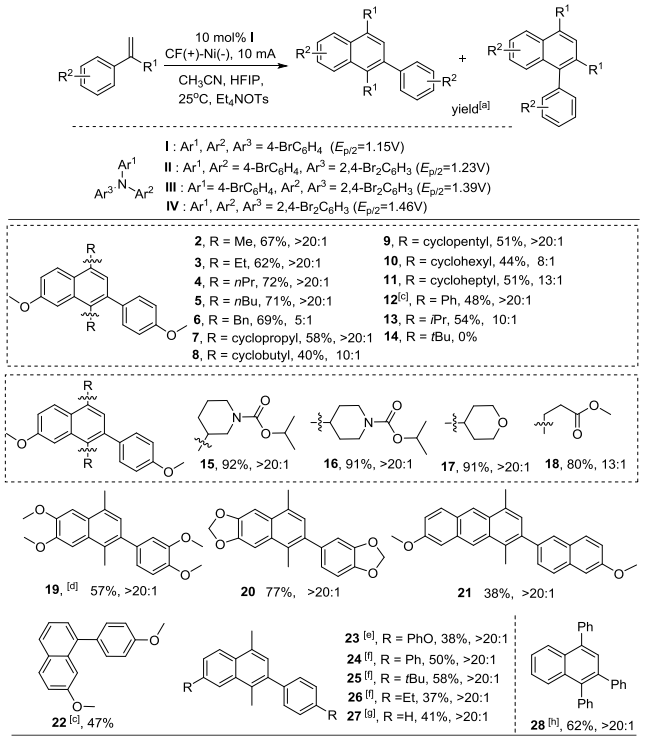
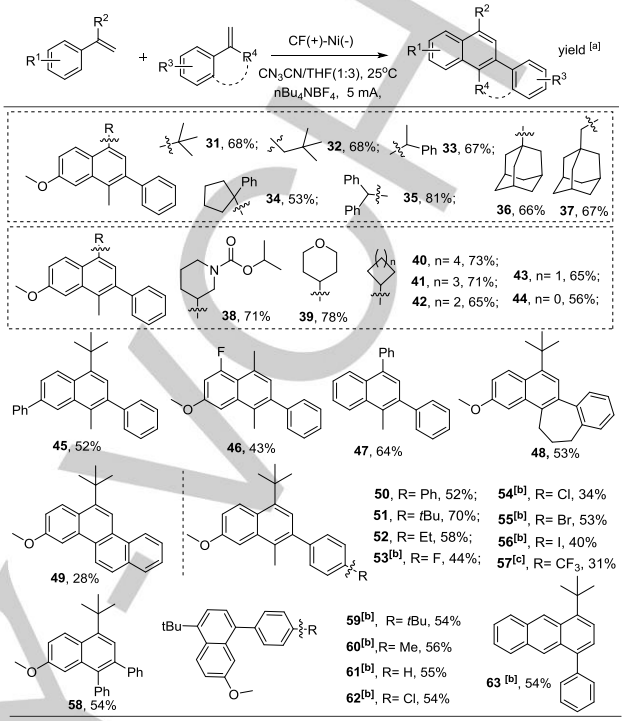



**Scheme 2.** Substrate scope for the homo-cycloaddition. Reaction conditions: Carbon felt anode, Ni plate cathode, constant current =10 mA, **1** (0.4 mmol), **I** (0.04 mmol), $Et_4NOTs$ (0.16 mmol), HFIP (100 μL) and 8 mL $CH_3CN$. [a] Yield of isolated two isomers. [b]: Ratio of the two isomers, determined by $^1$HNMR. [c]: Catalyzed by **III**. [d] Reaction performed under $N_2$ atmosphere. [e]: Catalyzed by **II**, constant potential = 5 mA. [f]: 8 mL acetone, 0.05M *t*$Bu_4NBF_4$. [g]: 8 mL acetone, 0.05M t$Bu_4NBF_4$, 56 °C. [h] 8 mL THF/$CH_3CN$ (3:1), 0.05 M *t*$Bu_4NBF_4$.

With the optimal condition in hand, the scope of the homo-cycloaddition was investigated. A variety of primary alkyl groups were tested and smoothly produced the desired products with synthetically useful yields (Scheme 2, **2**-**6**). Secondary alkyl groups, including chain, cyclic, and aromatic groups, also underwent this conversion with moderate yields (Scheme 2, **7**-**13**). However, when it was replaced by tertiary alkyl, the product of interest was not discovered. Perhaps its steric bulk restrained the formation of the crowded dehydrodimer (Scheme 2, **14**). With respect to the migration groups containing heteroatoms, such as tetrahydropyran, carbamates and ester, the electrolysis demonstrated excellent yields and current efficiency (Scheme 2, **15**-**18**). For *para*, *meta* disubstituted, 3, 4-methylenedioxy substituted styrenes and vinylnaphthalene, the process exhibited single regioselectivity (Scheme 2, **19**-**21**). In the synthesis of **21**, the formed insoluble substances caused the passivation of the electrodes and decreased the yield. For non-α-substituted 4-MeO styrene, it was catalyzed by **III** to yield the expected unmigrated product **22**. Because the oxidation potential of **23** ($E_{p/2}$ = 1.45 V) is lower than its substrate ($E_{p/2}$ = 1.57 V), **23** is more prone to oxidation than its reactants even under indirect electro-catalysis, leading to the decreasing yields.

For some weak electron-donating groups, such as phenyl, tertiary butyl, and ethyl, poor yields were obtained even under the catalysis of **IV**. But, the direct electrolysis provided relatively high yields (Scheme 2, **24**-**26**). α-Methyl styrene and 1,1-diphenylene also gave the desired products in moderate yields (Scheme 2, **27**-**28**). As the process was affected by the electron-donating ability of phenyl substituents, the electron-deficient styrenes were not tolerated in the homo-cycloaddition. Due to the selectivity of migrating groups, chemoselectivity was found in individual examples, such as **6**, **8**, **10**, **11** and **13**. Its ratios were dependent to the substrates and had no explicit relation with its structure.




**Scheme 3.** Substrate scope for the cross-cycloaddition. Reaction conditions: Carbon felt anode, Ni plate cathode, constant current =5 mA, **31** (0.2 mmol), **30** (0.6 mmol), *n*$Bu_4NBF_4$ (0.2 mmol), HFIP (50 μL), 4 mL $CH_3CN$/THF (1:3). [a] Yield of isolated products. [b]: Electrolysis performed at 45°C. [c]: Electrolysis performed at reflux.

Our following task was to explore the hetero-cycloaddition between different styrenes. After a series of tests using **1** and α-methyl styrene (**29**) as substrates, we found that the cross [4+2] annulation suffered from the production of **2**, due to the lower oxidation potential and stronger nucleophilicity of **1** than those of **29**. To avoid the homo-cycloaddition and nonselective oxidation, the styrene as cation radical precusor must be oxidized first and not proceed homo-cycloaddition. Therefore, 4-methoxy α-*tert*-butyl styrene (**30**) and **29** were chosen as the model substrates. Thus, **31** was formed in 68% yield under the direct electrolysis with an electrolyte solution of *n*$Bu_4NBF_4$ in $CH_3CN$/THF(1:3) (details see SI, Table s1).

Next, the substrates scope of the cross-cycloaddition was explored with respect to the 4π compounds. The electrolysis exhibited well tolerance with a host of steric substitutes at α position, such as neopentyl, diphenylmethyl, and adamantyl (Scheme 3, **31**-**37**). When it was replaced by the cyclic secondary alkyl groups, the selectivity for homo-dimerization was gradually surpassed over cross-cycloaddition with the decreasing of ring member. By slowly adding 4π compounds and using 4 equiv **29**, the selectivity was significantly improved and **38**-**44** were obtained in moderate to good yields with trace of homodimers produced. Other less electron-rich diene were also suitable substrates for this protocol (Scheme 3, **45**-**47**). It is worth to note that **46**-**47** without large steric group were also formed in 43% and 64% yields under the standard conditions. Furthermore, exocyclic double bonds also underwent smooth cycloaddition with **30** and provided the ring expansion product **48** in 53% yield and chrysene

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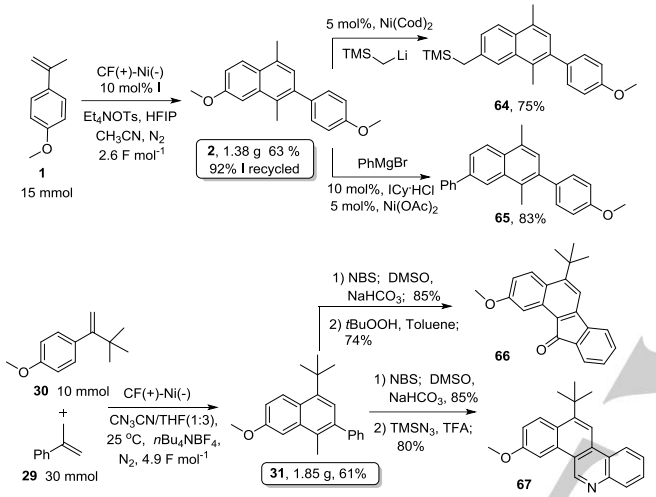
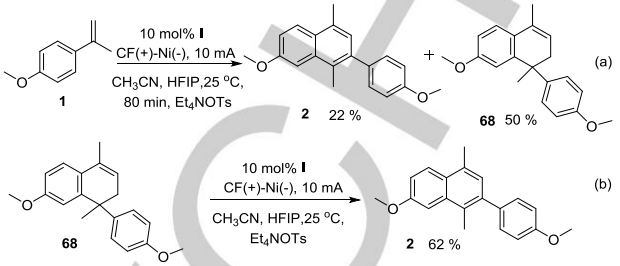
**49** in 26% yield, which derived from further dehydro-aromatization. A variety of dienophiles bearing various electronic properties were investigated and broad compatibility was demonstrated. In general, the reactivity of dienophiles depends on the electron-donating ability of the substituents. In the presence of electron-donating groups, **50**-**52** were prepared in moderate to good yields. Due to the lower nucleophilicity of electron-deficient stryrenes, its electrolysis was performed at 45 ℃ to provide the desired products in lower yields (Scheme 3, **53**-**57**). Besides serving as 4π compound, 1,1-diphenylethylene also can function as 2π compound in the reaction with **30** (Scheme 3, **47**, **58**). For non-α-substituted styrenes with much lower nucleophilicity than α-methyl styrene,[14] the transformation was also proceeded smoothly and gave 1-aryl-substituted naphthalenes in moderate yields (Scheme 3, **59**-**63**).




**Scheme 4.** Gram-scale synthesis and product transformations

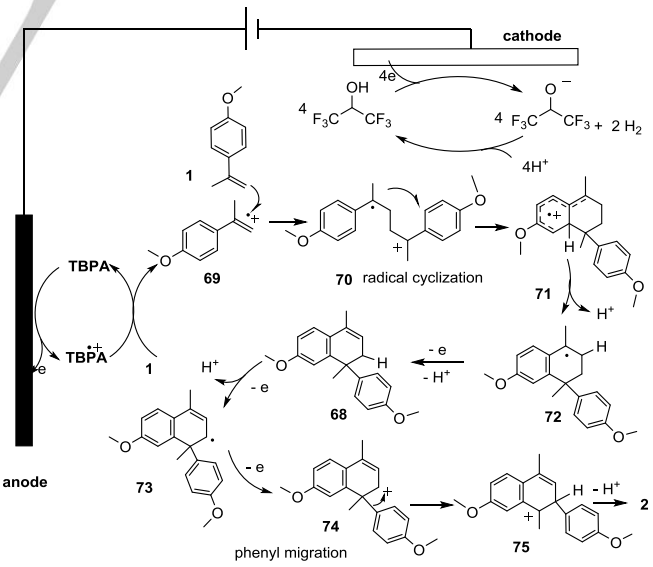
We also explored the synthetic utility of our method through scale-up experiment and product transformations (Scheme 4). For instance, we electrolyzed 15 mmol of **1** and obtained **2** in 63% yield, with little decrease in yield and current efficiency in comparison to the smaller scale. Meanwhile, 92% of **I** was also recovered. Based on the previous works [15] in the Ni-catalyzed C-O bond activation, **2** was converted to **64** and **65** in 75% and 83% yield.[15c,15g] The cross-cycloaddition is also scalable and demonstrates great synthetic value in constructing polycyclic aromatic compounds, such as benzophenanthridines[16] and benzofluorenones[17]. Compared with the 68% of yield and 4.7 F $mol^{-1}$ of current efficiency in 0.2 mmol scale, 1.85 g **2** was also furnished in 61% yield and 4.9 F $mol^{-1}$ under the electrolysis of 10 mmol of **30**. The transformation of methyl group to formyl group was achieved via the subsequent bromination and hydrolysis of **31**. This important intermediate underwent TBHP-promoted intramolecular carbonylation to provide **66** in 74% yield and transformed into **67** in 80% yield via intermolecular nitrogenation. It provides a metal-free protocol to synthesize benzophenanthridine derivatives and benzofluorenones from simple styrenes by three steps.

Monitored by GC, the compound **68** was detected under the homo-cycloaddition and its concentration increased first and then descended (details see SI, G). So, **68**, which is isolated in 50% yield (Scheme 5, a), might be the intermediate of the reaction. Using **68** as starting material, **2** was afforded in 62% yield (Scheme 5, b), which further proved our hypothesis. The electrochemical behavior of **68** was studied by CV, and two anodic peaks were detected at 1.45 V and 1.90 V respectively, representing the loss of two electrons in sequence. The CV curve of 0.1 M $Et_4NOTs/CH_3CN$ containing **I** and **68** indicated the oxidation of **68** could also be mediated by **I**, just like the interaction of **I** and **1** (details see SI, E3).




**Scheme 5.** The synthesis of intermediate and its transformation

Based on these, a proposed mechanism for the electrochemical [4+2] annulation-rearrangement-aromatization was outlined in Scheme 6 using **1** as model substrate. The reaction is initiated by the anodic oxidation of TBPA to form a stable radical-cation TBPA ($TBPA^{\bullet+}$). Then it oxidizes the electron-rich styrene **1** through SET to give styrene radical cation **69** and TBPA (details see SI, E1). As a nucleophilic agent, **1** attacks radical cation **69** to yield **70** through radical cyclization [8b], which is deprotonated to generate radical **72**. Subsequent electron and proton loss afford dehydrodimer **68**. Similarly, oxidized by $TBPA^{\bullet+}$, **6** losses one electron and proton to afford carbon radical **73**, which further oxidized to **74**. By rearrangement, the secondary carbon cation transforms into more stable tertiary carbon cation **75**. Compared with methyl, para-anisole migration is favored due to its electron-rich property. Finally, the oxydehydrogenation aromatization of **75** affords the desired product **2**.




**Scheme 6.** Proposed mechanism

In summary, we have developed a straightforward protocol to synthesis multi-substituted naphthalenes via electro-induced [4+2] annulation-rearrangement-aromatization of styrenes. The typical features of the reaction are its scalability, absence of high valence substrates, oxidants and metals, and significant synthetic value in constructing polycyclic aromatic compounds. Mechanism

studies imply that the dehydrodimer **68** is the key intermediate of this process.

**Keywords:** metal- and oxidant-free • [4+2] annulation • styrenes • rearrangement-aromatization • naphthalene derivatives

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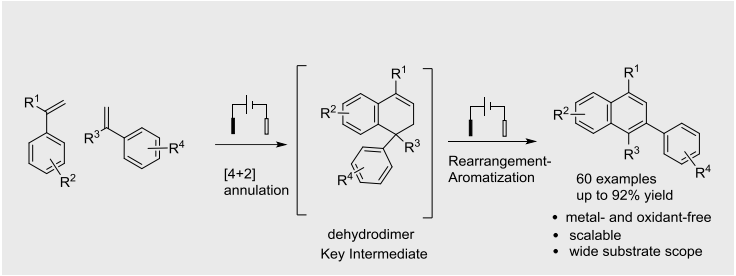


*Yueyue Ma, Jufeng Lv, Chengyu Liu, Xiantong Yao, Guoming Yan, Wei Yu, and Jinxing Ye**

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**Electrochemical [4+2] Annulation Rearrangement Aromatization of Styrenes: Synthesis of Naphthalene Derivativese**

A novel electrochemical protocol to construct multi-instituted naphthalenes without oxidants, metals and high valence reactants is reported. The dehydrodimer produced by electro-induced [4+2] annulation is the key intermediate, which undergoes oxydehydrogenation and rearrangement-aromatization to yield final product.