PAPER

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Electrooxidative tricyclic 6–7–6 fused-system domino assembly to allocolchicines by a removable radical strategy†

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Natural allocolchicine and analogues derived thereof a tricyclic 6–7–6-system have been found as key scaffold of various biologically relevant molecules. However, the direct preparation of the allocolchicine motif remains difficult to date. Herein, we report on an electrooxidative radical cyclization of biarylynones with various carbon- and heteroatom-centered radical precursors *via* a sequential radical addition/7-*endo-trig*/radical cyclization domino reaction. This approach provides a step-economical and strategically novel disconnection for the facile assembly of a wide range of carbocyclic 6–7–6 fused ring systems. Remarkably, the sulfonyl group on the products could be easily removed by photocatalysis at room temperature with high yields.

Introduction

Seven-membered carbocycles are privileged structural motifs found in natural products and pharmaceutical compounds with important biological properties.[1] Among these, the 6–7–6 benzo-fused rings has been found as a classic scaffold, which is present in natural allocolchicine and its analogues, such as ZD6126 and *N*-acetylcolchicinol methyl ether (NSC 51046) (Fig. 1a, top).[2,3] Fortunately, in these synthetic colchicine derivatives, the 6–7–6 carbocyclic framework have promising anticancer bioactivities, but with reduced toxicity as compared to the 6–7–7 tricyclic system present in colchicine,[4] which has translated into limitations in the treatment of human neoplasm and proved ineffective for therapeutic studies.[5] Therefore, the development of modular approaches that provide a direct access to a variety of allocolchicine analogues continues to be in high demand. During the past decades, major momentum has been gained in the construction of such tricyclic frameworks, including enyne ring-closing metathesis/Diels–Alder approaches,[6,7] palladium-catalyzed direct C–H arylations,[8] intramolecular Nicholas reaction,[9] and oxidative

couplings,[10] among others.[11,12] In the meantime, the design of novel radical cascade cyclizations has emerged as an increasingly-powerful strategy to construct complex molecular scaffolds,[13] as this approach generally features mild reaction conditions, high functional group tolerance and diverse viable radical precursors. Despite these indisputable advances, almost all radical sources will unfortunately leave behind an undesired chemical footprints, which jeopardizes the resource-economy towards the desired skeleton of the target products. Consequently, we wondered whether we could devise a removable radical cascade strategy by assembling the 6–7–6
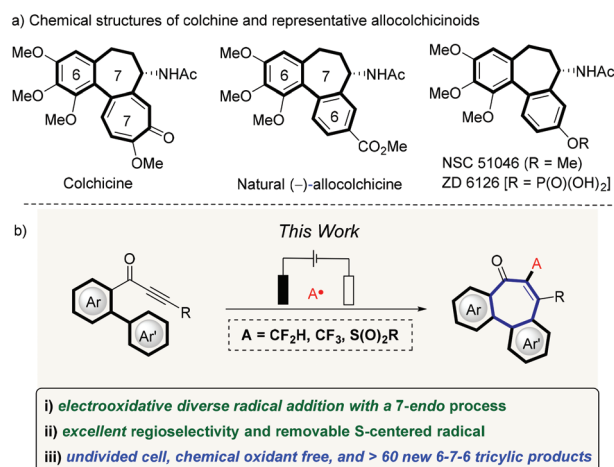
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Fig. 1 Tricyclic 6–7–6-system construction (a) selected examples of bioactive 6–7–6 tricyclic compounds, (b) reaction design.

tricyclic motif in a more straightforward manner. While we have recently reported on the construction of 6–7–6-system by a removable P-centered radical, the need for silver catalysts and stoichiometric amounts of chemical oxidants significantly limited this approach.[14]
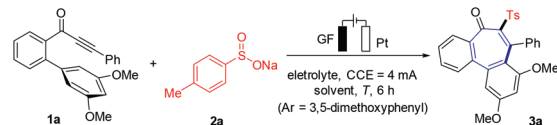
During the past few years, organic electrochemistry has been identified as an uniquely-effective and robust tool for the generation of reactive intermediates, such as radicals and radical ions, due to its inherent tunability.[15,16] Based on our continued interest in electrochemical syntheses[17] and radical formation using electricity as the sacrificial oxidant,[18] we questioned whether the efficiency noted in a electrooxidative removable radical formation could be translated into a practical strategy towards 6–7–6 scaffolds. However, there are two key challenges. First, the regioselectivity of vinyl radical cyclization needs to be well controlled by adjusting the influence of substituents on the arene moiety. Compared to five- or six-membered ring formation, the radical cyclization of the seven-*endo-trig* approach is indeed rare.[19] Second, the chemical footprints derived from various radical sources should be easily removable during the late-stage derivatization. We, herein, report on an unprecedented cascade cyclization of biaylynones under operationally-simple electrochemical conditions, which can be performed with commercially available, inexpensive radical precursors under water-tolerant radical reaction conditions (Fig. 1b, bottom). Notable features of our strategy include (a) the first Ts•, CF₂H• and CF₃• addition to internal alkynes resulting in a 7-*endo-trig* process, (b) the thus-obtained *S*-motif can be removed traceless under operationally-simple conditions, (c) the absence of catalyst and chemical oxidants, (d) simple reaction conditions, and (e) ample substrate scope.

Results and discussion

Optimization of reaction condition

We initiated our studies by probing various reaction conditions for the envisioned domino cyclization of 1-(3′,5′-dimethoxy-[1,1′-biphenyl]-2-yl)-3-phenylprop-2-yn-1-one (**1a**) as the model substrate (Table 1 and Table S-2 in the ESI†), using the inexpensive *p*-toluenesulfinate (**2a**) as the sulfonyl radical source. After considerable preliminary experimentation, we observed that the desired 6–7–6 tricyclic fused product **3a** was isolated in 73% yield with a mixed solvent system consisting of MeCN/H₂O (3:1) and Et₄NClO₄ as the electrolyte (entry 1). Different solvents and a series of supporting electrolytes were tested, but showed not to be beneficial (entries 2–6, see also Table S-2 in the ESI†). Either decreasing or increasing the reaction temperature and the current failed to improve the yield of **3a** (entries 7–9). During the optimization of the electrode material, it was found that the use of a nickel cathode, as well as a platinum anode led to a decrease in the yield or did not afford any product (entries 10 and 11). Control experiments confirmed the essential role of the electricity for the electrooxidative cyclization (entry 12). Not surprisingly, we observed a strong influence of the arene Ar′. Therefore, the substitution

Table 1 Optimization of the cascade cyclization/sulfonylation[a]

Entry	Deviation from standard conditions	Yield/%
1	no change	73
2	EtOH/H₂O (3:1)	0
3	DMF/H₂O (3:1)	0
4	1,4-Dioxane /H₂O (1:1)	39
5	DCE/MeCN/H₂O (5:5:1)	37
6	No electrolyte	36
7	Reaction at 25 °C	0
8	CCE = 3 mA	32
9	CCE = 6 mA	60
10	GF(+)|Ni(−) instead of GF(+)|Pt(−)	54
11	Pt(+)|Pt(−) instead of GF(+)|Pt(−)	0
12	No electricity	0

[a] Standard conditions: undivided cell, graphite felt (GF) anode, Pt cathode, constant current = 4 mA, **1a** (0.30 mmol), **2a** (0.60 mmol, 2.0 equiv.), Et₄NClO₄ (0.1 M), MeCN/H₂O (3:1, 4.0 mL), under air, 6 h, 3.0 F mol⁻¹. Yield of the isolated product.

effect was examined under the optimized electrooxidative conditions. Thus, the type and position of the substituents on the arene moiety determines the efficacy of the 7-*endo-trig* cyclization process, while five- or six-membered products were not observed (Fig. 2 and Scheme 1). In contrast to other substituted arenes, a substrate bearing the 2,3,4-trimethoxy phenyl moiety featured high reactivity, but in this case the reaction followed a 6-*exo-trig* process yielding the non-aromatic product **3f** (Scheme 1).
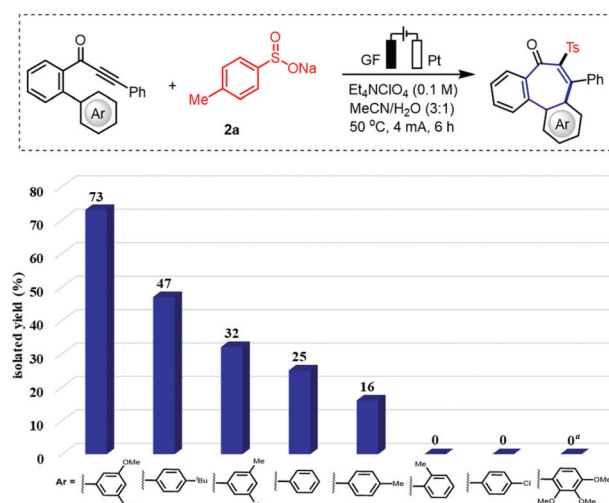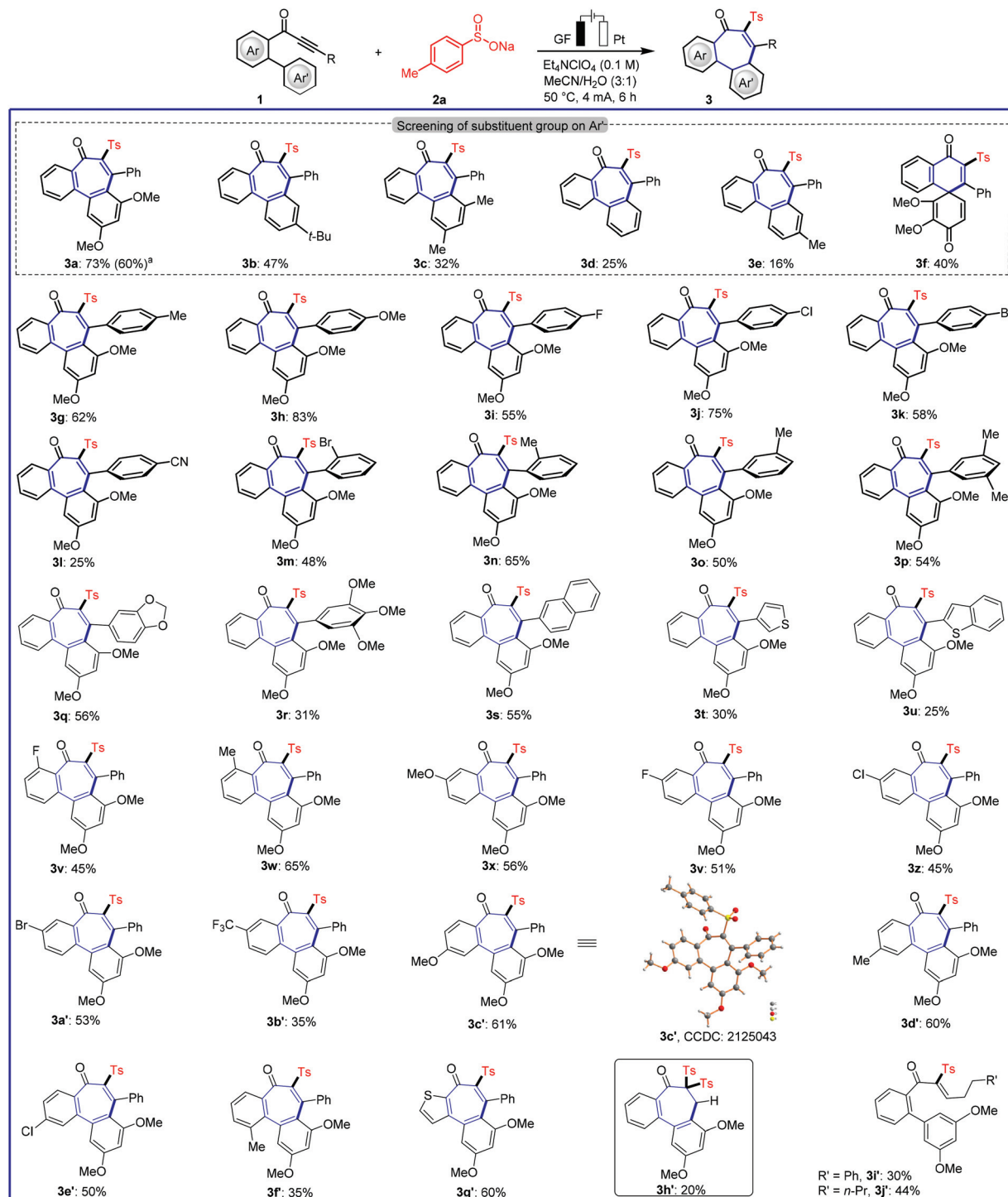

Fig. 2 Substituent impact on electrooxidative 7-*endo* radical cyclization process. Standard conditions: undivided cell, GF anode, Pt cathode, constant current (CCE) = 4 mA, **1** (0.3 mmol), **2a** (0.6 mmol), Et₄NClO₄ (0.1 M, 0.4 mmol), MeCN/H₂O (3:1, 4 mL), 50 °C, under air, 6 h. Yield of the isolated products.[a] 6-*exo* product **3f** formed in 40% yield.

Scheme 1 Robustness of electrooxidative *7-endo-trig* cyclization. Reaction conditions of Table 1, entry 1, alkynone (**1**, 0.30 mmol), 6 h. [a] 1 mmol scale (5 mL solvent).

Robustness

With the optimized reaction conditions in hand, we became interested in investigating the substrate scope of this electrooxidative radical cyclization, and we tested a diverse range of biarylyone substrates **1** with different substitution patterns
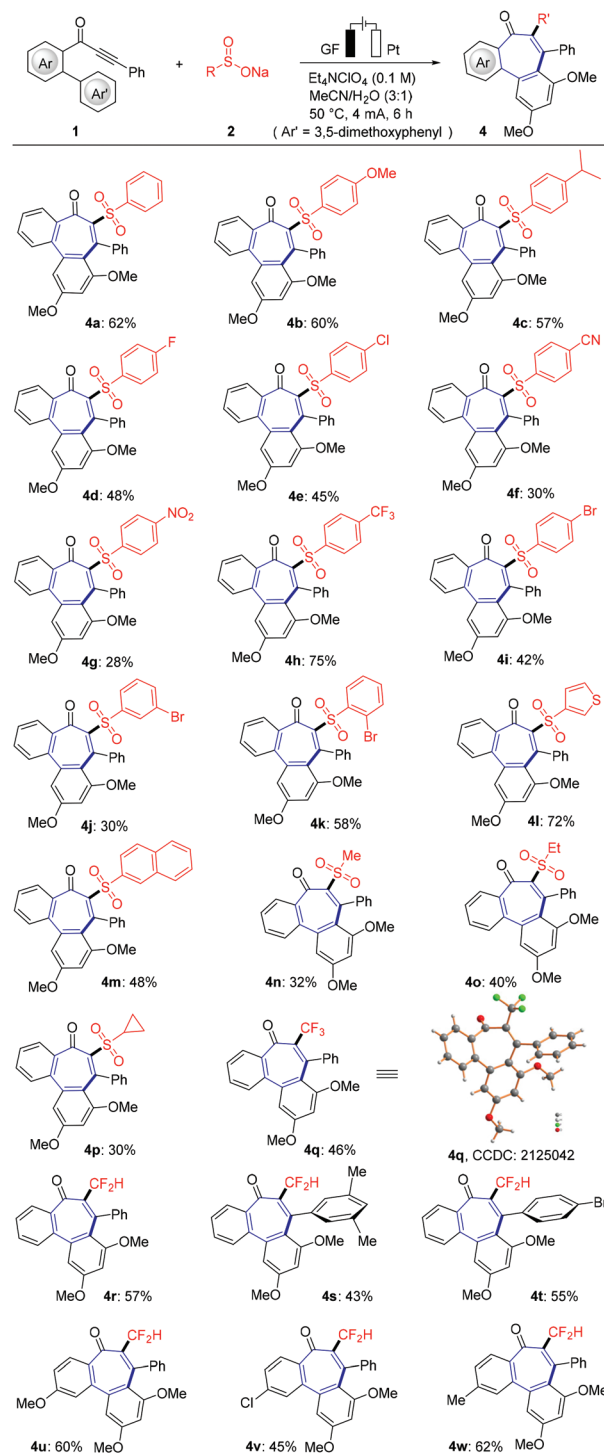
(Scheme 1). The reaction tolerated a variety of substituents with diverse electronic properties in all positions of the arene R (**3g**–**3l**). We were pleased to find that *ortho-* and *meta*-substituted arenes underwent this transformation efficiently, despite a possible steric repulsion (**3m**–**3r**), even for polysubstituted substrates. Furthermore, heterocyclic substrates bearing thio-

phene and benzothiophene as well as naphthyl substituents were also tolerated in this transformation (**3s–3u**). Having demonstrated the broad applicability with respect to the arene, substitutions on the phenone scaffold were examined. Substrates decorated with both, electron-withdrawing and electron-donating groups on aryl ring had a significant effect on the yield of the reaction. Namely, electron-withdrawing groups somewhat blocked the reaction (**3l** and **3z–3b′**). Furthermore, the reaction of substrate **1f′** was found with lower chemical yield (**3f′**), maybe due to a steric hindrance effect. A heterocyclic substrate proved also applicable in the electrooxidative transformation to selectively afford the corresponding product **3g′** in good yield. Noteworthily, also a terminal alkyne was applicable, and gave minor amounts of the products **3h′** after double radical addition. In sharp contrast, no desired product was obtained by the reaction of alkyl alkynes except for the uncyclized products (**3i'–3j'**). The connectivity of product **3c′** was unambiguously confirmed by single-crystal X-ray analysis (Scheme 1).[20a]

Next, the scope of various sodium sulfinates **2** with biaryl-none **1** was examined to probe the efficacy of the present electrochemical domino cyclization (Scheme 2). To our delight, either common electron-donating substituents or electron-withdrawing functional groups (chloro, bromo, trifluoromethyl, nitro and cyano) showed good functional group tolerance by forming the desired product. In addition, naphthalene sulfonate and thiophene sulfonate also reacted well with substrate **1a** to form tricyclic product in good yields (**4l** and **4m**). Likewise, the mild electrooxidative radical cyclization approach was found to be generally applicable for aliphatic sodium sulfinates. CF₃SO₂Na (**2r**) and CF₂HSO₂Na (**2s**) were suitable substrates, furnishing the valuable tri- and difluoromethylated tricyclic 6–7–6 fused products (**4q–4w**). The structure of trifluoromethylated product **4q** was unambiguously verified by X-ray crystallographic analysis.[20b]
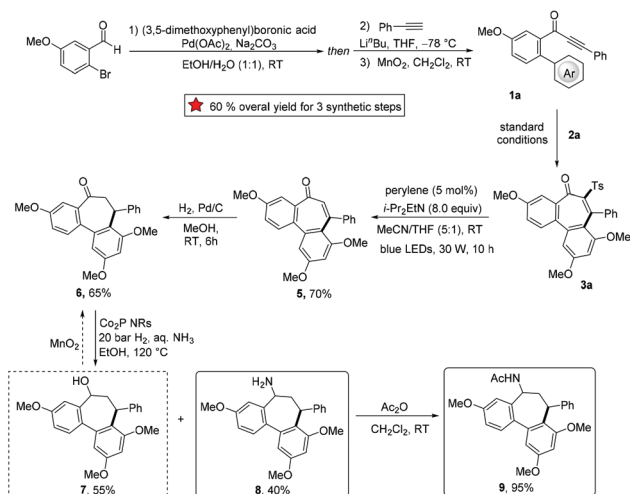
The synthetic utility of the developed domino strategy was further reflected by the efficient preparation of bioactive NSC 51046 analogues (Scheme 3). NSC 51046 is an analogue of the natural allocolchicine (Fig. 1a), which displays potent anticancer activity by inhibition of the tubulin polymerization.[21] Due to the modularity of our electrosynthesis, this approach could be beneficial for preparing diverse derivatives of NSC 51046 from 3-phenyl-1-(3′,4,5′-trimethoxy-[1,1′-biphenyl]-2-yl) prop-2-yn-1-one **1a**. Under the standard electrooxidative reaction conditions, the sulfonylation product **3a** was obtained in high yield. Subsequently, **3a** was converted to the desulfonylation product enone **5** following a perylene-catalyzed photodesulfonylation procedure.[22] Then, catalytic hydrogenation of alkene **5** led to the formation of dibenzocycloheptanone **6**, which provided the allocolchicinoid **9** after cobalt phosphide nanorods (Co₂P NRs) catalyzed reductive amination[23] followed by acetylation. Notably, though the reductive amination showed poor selectivity between amine **8** and alcohol **7** (**7** was also formed in about 50% yield), **7** could be converted into ketone **6** by simple oxidation. Hence, our strategy opened a new avenue to a versatile synthesis of allocolchicine analogues with readily available starting materials and high efficacy.

Scheme 2 Substrate scope of various sodium sulfonates **2**.

To gain mechanistic insight into this electrochemical radical addition/cyclization reaction, a radical clock reaction using (1-cyclopropylvinyl)benzene (**10**) provided the product **11** in 47% yield (Fig. 3a). In addition, when the direct addition product **12** (for detailed information, see the ESI†) was subjected to the standard electrochemical conditions, the cyclization product **3a** was not obtained. Based on these experimental

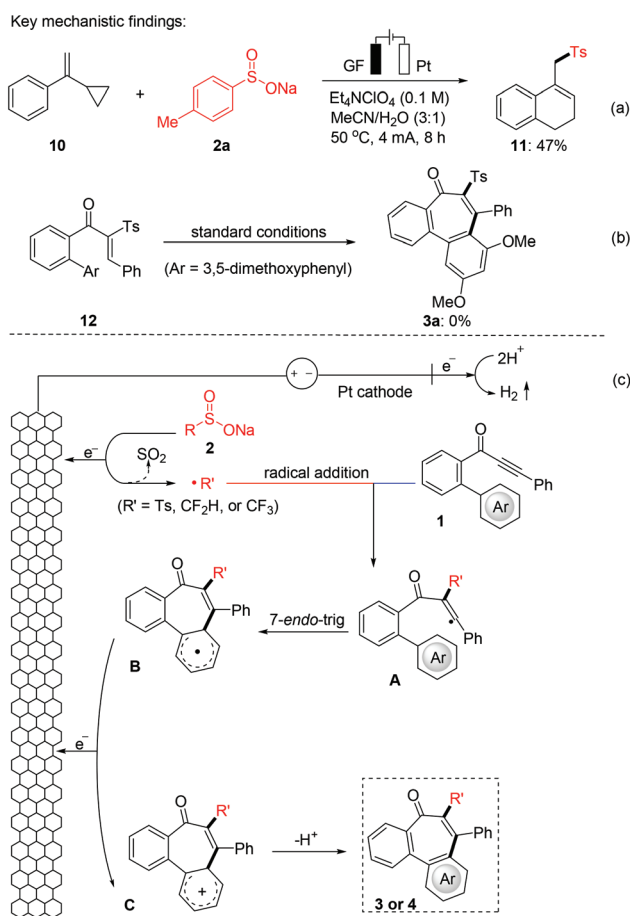**Scheme 3** NSC 51046 analogue synthesis (Ar = 3,5-dimethoxyphenyl).

Fig. 3 Mechanistic investigation on the radical annulation (a) radical trapping experiment, (b) control experiment, and (c) proposed mechanism.

results and literature,[24] a radical mechanism is proposed for this electrooxidative radical reaction as depicted in Fig. 3b. First, the S-radical, CF$_3$-radical or CF$_2$H-radical is generated
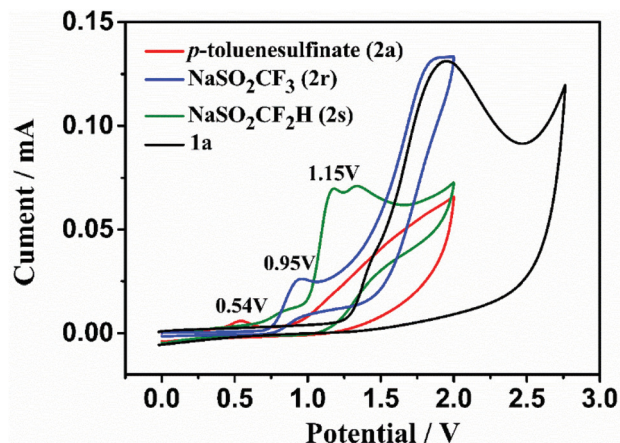

Fig. 4 Cyclic voltammetry studies. Conditions: cyclic voltammogram of target molecule (10 mM) in acetonitrile (10.0 mL containing 0.05 M n-Bu$_4$NPF$_6$) at room temperature, using a glassy carbon working electrode, a platinum wire counter electrode, and a Ag/AgCl reference electrode at a scan rate of 100 mV s^{-1}. [black line for **1a**, red line for **2a**, blue line for **2r** and green line for **2s**].

from **2** through anodic oxidation. Selective radical addition of R′ to C–C triple bonds of **1** affords a vinyl radical **A**, which undergoes 7-endo-trig cyclization to intermediate **B**. Then, intermediate **B** undergoes further SET oxidation and deprotonation to form the product **3** or **4**. In addition, we also tried to give the oxidation potential of the different radical sources in order to better understand the experimental results. Reactants **2a**, **2r** and **2s** exhibit oxidation peaks at 0.54, 0.95 and 1.15 V vs. Ag/AgCl, respectively (Fig. 4 and Fig. S1 in the ESI†). These results indicate that these radical precursors are preferentially oxidized under anodic oxidation.

Conclusions

In summary, we have developed an electrochemical strategy for the construction of tricyclic 6–7–6-system through a domino radical addition of biarylynones with various radical sources. This environmentally-friendly approach showed high regioselectivity, ample substrate scope and high functional group compatibility. It is worth mentioning that the introduced sulfonyl radical fragment of the products was easily removed in the presence of photocatalyst to give the corresponding allocolchicine analogues. The developed electrooxidative strategy represents a rare 7-endo-trig vinyl radical cyclization processes and is a useful method for the concise assembly of a variety of novel and drug-type fused molecules bearing valuable 6–7–6-scaffolds.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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