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Electrochemical cascade migratory *versus ortho*-cyclization of 2-alkynylbenzenesulfonamides†

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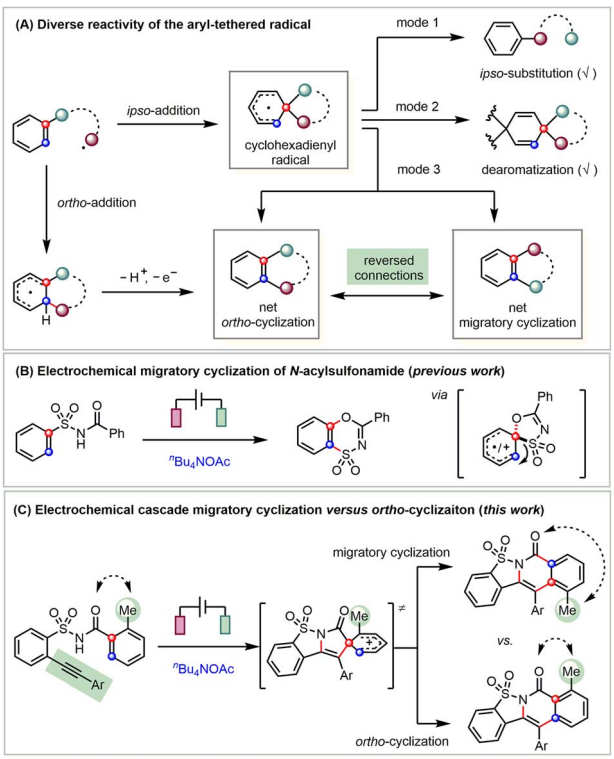
Efficient control over several possible reaction pathways of free radicals is the chemical basis of their highly selective transformations. Among various competing reaction pathways, sulfonimidyl radicals generated from the electrolysis of 2-alkynylbenzenesulfonamides undergo cascade migratory or *ortho*-cyclization cyclization selectively. It is found that the incorporation of an extra 2-methyl substituent biases the selective migration of the acyl- over vinyl-linker of the key spirocyclic cation intermediate and thus serves as an enabling handle to achieve the synthetically interesting yet under-investigated cascade migratory cyclization of spirocyclic cations.

Free radicals are typically highly reactive species yet can still form diverse products through selective transformations.[1] Key to the high selectivity of a radical reaction is the efficient control over several competing reaction pathways. For instance, a radical can add to the tethered arene *via* two pathways (Scheme 1A).[2] The straightforward *ortho*-addition generates a fused cyclohexadienyl radical that further undergoes electron and proton transfer to give the *ortho*-cyclization product.[3] Alternatively, the *ipso*-addition pathway leads to a spiro cyclohexadienyl radical.[4] While there are many studies on *ipso*-substitution reactivity, known as the Smiles rearrangement (mode 1)[5] and dearomatization (mode 2),[6] ring expansion of the spirocyclohexadienyl radical is rarely explored (mode 3).[7] Apparently, the migratory attitude of the spirocyclic linkers guides the reaction toward two products with reversed connections, *i.e.*, net *ortho*-cyclization and migratory cyclization. Though both the *ortho*-addition and *ipso*-addition can lead to net *ortho*-cyclization products, there only exist very limited studies on the selective formation of migratory cyclization products.[8]

Owing to the mild reaction conditions for generating radicals, synthetic electrochemistry[9] provides enabling handles for the fine-tuning of the diverse selectivity of radical reactions.[10] Even though there are many radical-mediated cascade reactions, very few studies have been carried out on the migratory attitude of different linkers in the *in situ* generated



Scheme 1 Contents of this study.

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spirocyclohexadienyl radicals. Understanding the innate migratory attitude of spirocyclic intermediates is not only fundamentally interesting but also potentially serves as an enabling handle for their selective transformations.

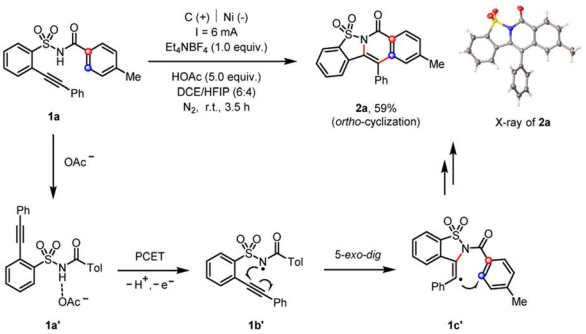
Specifically, amidyl radicals are generated either from the homolytic cleavage[11a] or photocatalysis-facilitated single-electron reduction[11b] of N–X bonds (X = halogen, O, N, *etc.*) or photochemical/electrochemical oxidation of N–H bonds.[11c] Recently, we have reported an electrochemical migratory cyclization of *N*-acylsulfonamides through an exclusive sulfone migration of the spirocyclohexadienyl intermediate (Scheme 1B).[12] This electrochemistry-enabled reactivity is in sharp contrast to an anionic Smiles *ipso*-rearrangement of the *N*-acylsulfonamide that only results in its degradation.[13]

The attachment of an *o*-alkyne[14] shifts the reactivity from the above migratory cyclization to a straightforward aza-cyclization.[15] Indeed, we found that linking the aryl acetylene to the *ortho*-position of the benzenesulfonamide results in the anticipated cascade *ortho*-cyclization (Scheme 1C).[16] More interestingly, the extra incorporation of the 2-methyl substitution favors migratory cyclization. Preliminary mechanistic investigations suggest that this 2-methyl substituent favors the selective migration of the acyl- over vinyl-linker of the key spirocyclic cation intermediate, which helps to achieve the fundamentally interesting yet rarely explored cascade migratory cyclization. Notably, the resultant sultam-fused pyridinones exhibit promising antibacterial activity and the current protocol affords a diverse array of derivatives that should be beneficial to their biological studies.[17]

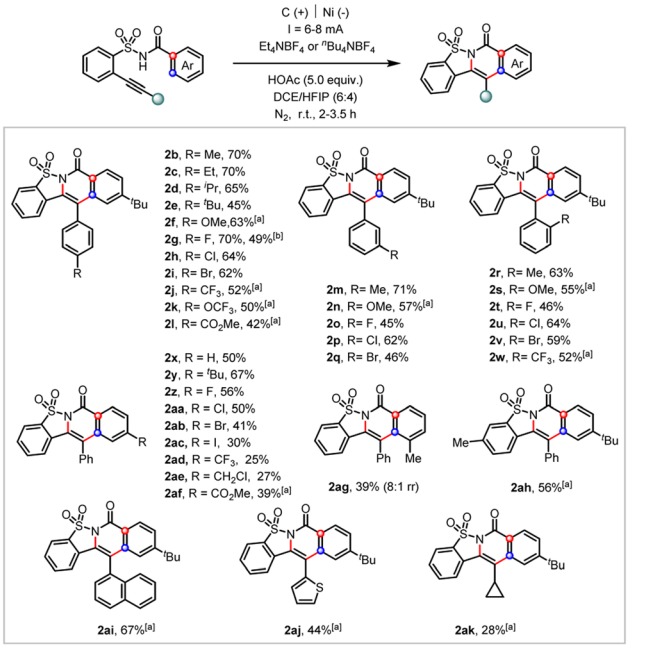
Initially, our extensive optimization of reaction conditions (see ESI†) disclosed that the 2-alkynylbenzenesulfonamide (**1a**) underwent an electrochemical cascade *ortho*-cyclization[18] to afford the corresponding heterocycle (**2a**) in 59% yield, whose chemical structure was confirmed by the X-ray diffraction analysis (Scheme 2).[19] Among several solvents tested, the combination of dichloroethane (DCE) and 1,1,1,3,3,3-hexafluoro-2-propanol (HFIP) mixed solvents afforded the cleanest reaction system that facilitated the purification of products. The use of HOAc was crucial to the observed reactivity since HOAc served as the sacrificial oxidant and the resultant acetate acted as a base in the following proton-coupled electron transfer (PCET) process, which was further substantiated both by the cyclic-voltammetry and nuclear-magnetic-resonance studies (see ESI†).[11c,20] We proposed that the acid–base complex (**1a′**) underwent electrochemical oxidation toward the formation of an amidyl radical (**1b′**). The subsequent 5-*exo*-*dig* radical cyclization gave rise to a vinyl radical (**1c′**), which readily attacked the pendant phenyl moiety to release the *ortho*-cyclization product (**2a**).

The substrate scope of this electrochemical cascade *ortho*-cyclization was investigated (Scheme 3). A broad spectrum of substrates with varying electron-donating and electron-withdrawing substituents located at either the arylethynyl (**2b–2w**), benzoate side (**2x–2af**), or arylsulfonamide (**2ah**) moiety were tolerated. The scalability of this transformation was demonstrated by a 4 mmol scale preparation of the desired cascade cyclization heterocycle (**2g**, 49%). Aromatic iodide (**2ac**), $-CF_3$ (**2ad**), and aliphatic halide (**2ae**) were all tolerated under these electrochemical reaction conditions. Notably, the *meta*-methyl derivative underwent the cascade *ortho*-cyclization at the sterically more hindered site in good regioselectivity (**2ag**, 8 : 1 rr). While 1-naphthylene- and 2-thiophene-tethered alkynes (**2ai** and **2aj**) were compatible substrates, the cyclopropyl one (**2ak**) only afforded the desired product in 28% yield. Unfortunately, aliphatic alkyne and terminal alkene derivatives were not applicable under the current electrolytic conditions (see more unsuccessful substrates in ESI†).

When a methyl group was introduced at the *ortho*-position (**3a**), we observed not only the anticipated cascade *ortho*-cyclization (**4a**) but also the unexpected migratory cyclization (**5a**)

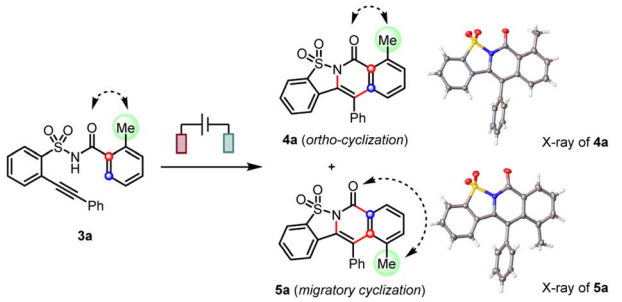


Scheme 2 Electrochemical cascade *ortho*-cyclization.



Scheme 3 Substrate scope of the electrochemical cascade *ortho*-cyclization. Reaction conditions: undivided cell, C(+)/Ni(−), substrate (0.2 mmol), Et_4NBF_4 or $^nBu_4NBF_4$ (1.0 equiv.), HOAc (5.0 equiv.), $CHCl_3$/HFIP = 6 : 4, room temperature, I = 6–8 mA, under a N_2 atmosphere, 2–3.5 h; [a] C(+)/Pt(−), $^nBu_4NOAc$ (1.0 equiv.), Cp_2Fe (20 mol%), I = 6–8 mA, 5–7 h, MeCN; [b] 4 mmol scale reaction.

Table 1 Cascade *ortho*-cyclization *versus* migratory cyclization



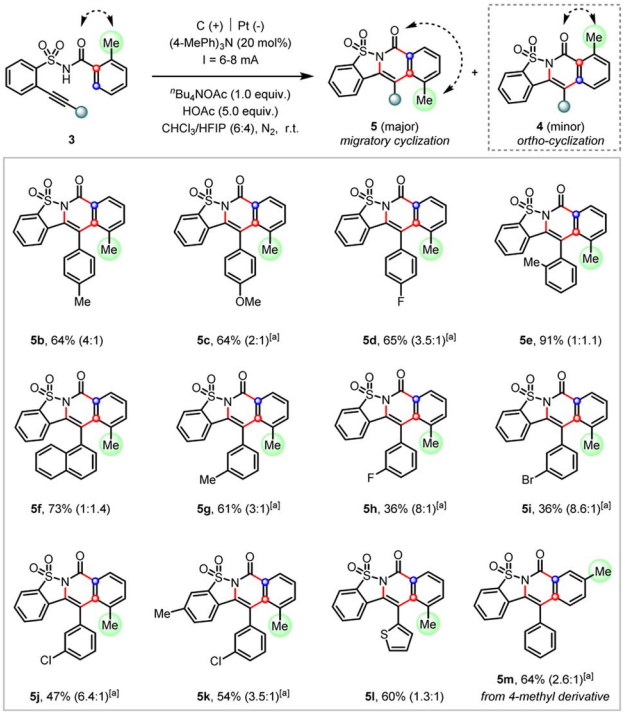
Entry	Electrolytic conditions	Yield[a] (**4a** + **5a**, %)	Ratio[b] (**4a** : **5a**)
1	C(+)|Ni(−) I = 6 mA, Et_4NBF_4 (1.0 equiv.) HOAc (5.0 equiv.), DCE/HFIP (6 : 4) N_2, r.t., 3.5 h	54	1 : 1.6
2	C(+)|Pt(−) $(4\text{-MePh})_3N$ (20 mol%) I = 8 mA, $^nBu_4NOAc$ (1.0 equiv.) HOAc (5.0 equiv.), $CHCl_3$/HFIP (6 : 4) N_2, r.t., 4.5 h	58	1 : 3.5

[a] Isolated yield. [b] The regioisomeric ratio was determined by ^{1}H NMR analysis of the crude mixture.

product (Table 1, entry 1). According to the X-ray diffraction analysis, the migratory product (**5a**) featured a translocation of the original *ortho*-methyl to the *meta*-position. After thorough optimizations (see ESI†), the electrolytic conditions in entry 2 afforded the migratory cyclization (**5a**) as the major product in the optimal 3.5 : 1 ratio. While similar results can be obtained without a redox mediator, the incorporation of a catalytic amount of trimethyltriphenylamine as the redox mediator[9a,21] in $CHCl_3$/HFIP mixed solvents provided a very clean reaction and thus generally afforded a higher yield.

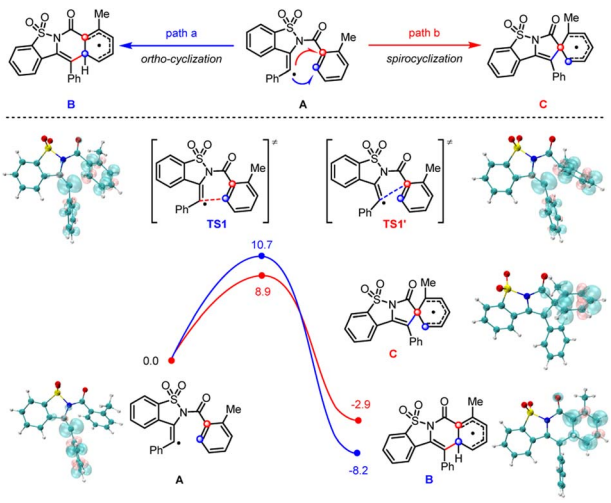
This migratory cyclization reactivity was further examined with a variety of substituted arylethynyl derivatives (Scheme 4). These reactions generally afforded the cascade cyclization products smoothly favoring the migratory product in moderate to good selectivity. It was found that the increase of steric hindrance at the *ortho*-position of arylethynyls (**5e** and **5f**) or the replacement of the aryl by thiophene (**5l**) was deleterious to the selectivity. Interestingly, the *meta*-halo substituent of arylethynyls (**5h–5j**) afforded the highest preference for the migratory cyclization products (up to 8.6 : 1) despite moderate yields. Finally, such an electrochemical migratory cyclization was also applicable to the 4-methyl derivative (**5m**). Unfortunately, attempts to further improve the migratory selectivity *via* the replacement of the methyl group by other *ortho* substituents, such as phenyl, ethyl, halide (F or Br), or acetyl were not successful yet (see ESI† for details).

While the nitrogen-radical-initiated cascade cyclizations have been heavily investigated, the corresponding migratory cyclization through a spirocyclic intermediate is much less

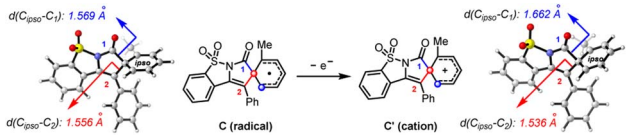


Scheme 4 Substrate scope of the electrochemical cascade migratory cyclization. Reaction conditions: undivided cell, C(+)/Pt(−), substrate (0.2 mmol), $^nBu_4NOAc$ (1.0 equiv.), $(4\text{-MePh})_3N$ (20 mol%), HOAc (5.0 equiv.), $CHCl_3$/HFIP = 6 : 4, room temperature, I = 8 mA, under a N_2 atmosphere, 4.5 h. The regioisomeric ratio was determined by ^{1}H NMR analysis of the crude mixture; [a] I = 6 mA.

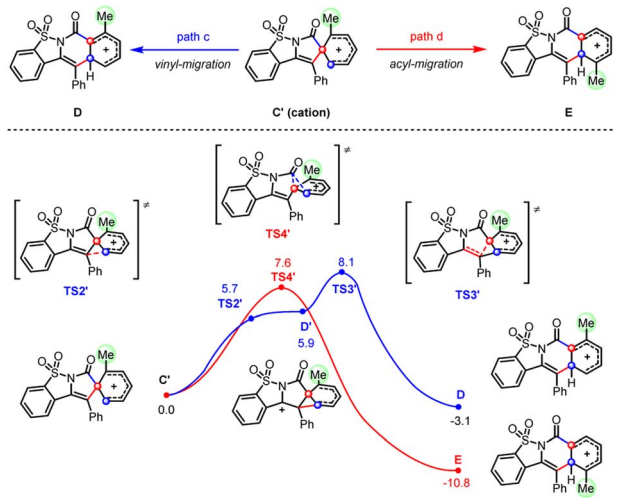
explored. Density-functional-theory calculations (DFT) provided more mechanistic insights into the origin of this selectivity (Scheme 5). We calculated two radical addition pathways for the 2-methyl substituted vinyl radical (**A**) and found while both pathways were thermodynamically and kinetically favorable,



Scheme 5 A proposed mechanism and potential energy surface of the addition process for the 2-methyl substituted vinyl radical (**A**). The Gibbs free energies are given in kcal mol^{-1}. The spin density plots of each species are given (isovalue = 0.005 a.u.).



Scheme 6 DFT calculations on the spirocyclic radical (**C**) and cation (**C′**).



Scheme 7 DFT calculations on vinyl- and acyl-migration of spirocation (**C′**).

the reaction barrier of *ipso*-addition is 1.8 kcal mol^{-1} lower than that of *ortho*-addition (**TS1** *versus* **TS1′** is 10.7 *versus* 8.9 kcal mol^{-1}). By contrast, the energy difference of *ipso*-addition *versus* *ortho*-addition for the analog 4-methyl substituted vinyl radical (**A1**) is only 0.2 kcal mol^{-1} (see Fig. S9.3†). Those results suggest the incorporation of a 2-methyl substituent is indeed beneficial to the *ipso*-addition of the vinyl radical.

The spirocyclic radical (**C**) is known to be readily oxidized into its corresponding spirocyclic cation (**C′**)[22] *via* a radical-polar-crossover process,[23] which is supposed to be the key intermediate in migratory cyclization. According to our calculations (Scheme 6), the spirocyclic cation (**C′**) displayed an elongated C_{ipso}–C_1 bond (1.662 Å *versus* 1.569 Å) and a shortened C_{ipso}–C_2 bond (1.536 Å *versus* 1.556 Å) compared to those of the radical intermediate (**C**), suggesting that the acyl migration (toward the migratory cyclization) should be more accessible than the vinyl migration (toward net *ortho*-cyclization) through a spirocyclic cation intermediate.

Consistent with the above hypothesis, the cationic acyl migration (path d) was both kinetically and thermodynamically more favorable than the vinyl migration (path c, Scheme 7). However, the small difference between the reaction barriers of these two transition states (7.6 *versus* 8.1 kcal mol^{-1}) suggested only a moderate preference for migratory cyclization (**E**) over *ortho*-cyclization (**D**) could be achieved, which is also consistent with our experimental observations. By contrast, calculations

Scheme 8 Electrochemical cascade dearomative spirocyclization.

on the migratory attitudes of the spirocyclic radical intermediate (**C**) revealed no such preference for acyl migration (see Fig. S9.5†). The proposed migratory mechanism could be further substantiated by a couple of methyl-substituted products, *i.e.*, **4a**/**5a** and **4m**/**5m**, derived from *ortho*- and *para*-Me substrates, respectively. Their structures have been unambiguously confirmed by the X-ray diffraction analyses (see ESI†).

Finally, the existence of a spirocyclic cation intermediate was further substantiated by the facile dearomative spirocyclization of a *p*-methoxyl 2-alkynylbenzenesulfonamide derivative (Scheme 8).[6c,24]

In summary, we have developed an electrochemical cascade *ortho*-cyclization of 2-alkynylbenzenesulfonamides to afford the corresponding polycyclic heterocycles of promising antibacterial activity. Remarkably, the incorporation of an extra 2-methyl substituent facilitates the formation of a spirocyclic dienyl radical and also favors the cationic migration of the acyl- over vinyl-linker of the key spirocyclic cation, leading to the selective formation of the rarely explored migratory cyclization products. These findings bring new insights into the fine-tuning of the migratory attitude of the linkers of spirocyclic intermediates for selective transformation of radical chemistry.

Data availability

Detailed synthetic procedures and complete characterization data for all new compounds can be found in the ESI.†

Author contributions

K. Y. conceived the concept and directed the investigations. Z. S. and T. L. conducted the majority of the experimental work. W. W. and N. L. contributed to the preparation of substrates. J. Z. and S. D. designed and carried out all DFT calculations. K. Y., J. Z., and Y. Y. wrote the manuscript with input from all the authors.

Conflicts of interest

There are no conflicts to declare.

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