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Catalyst-free, direct electrochemical synthesis of annulated medium-sized lactams through C–C bond cleavage†

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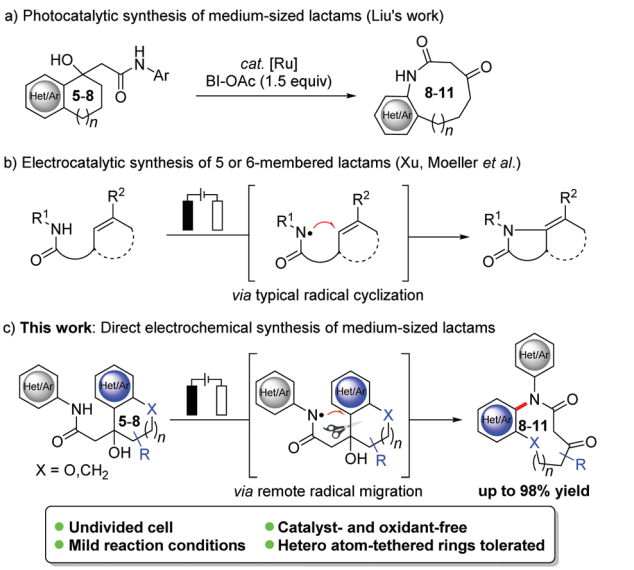
A catalyst-free, direct electrochemical synthesis of synthetically challenging medium-sized lactams through C–C bond cleavage has been developed. In contrast to previous typical amidyl radical cyclization, this electrosynthetic approach enabled step-economical ring expansion through a unique remote amidyl migration under mild, metal- and external-oxidant-free conditions in a simple undivided cell. The strategy features unparalleled broad substrate scope with all ring sizes of (hetero)aryl-fused 8–11-membered rings and hetero atom-tethered rings, high yields, and good functional group tolerance. Our experimental and computational findings provided strong support for a SET-based reaction manifold.

Medium-sized lactams (8–11-membered rings)[1] are important structural motifs as they are featured in numerous natural products and bioactive molecules, such as *inter alia* decursivine, rhazinilam, balasubramide, and dibenzepin.[2] These scaffolds can generally be accessed by only a few limited methods, mostly by intramolecular carbonylation,[3] ring-closing metathesis (RCM),[4] Claisen-type rearrangement[5] and among others.[6] More recently, Liu and coworkers reported a photocatalytic synthesis of medium-sized lactams by employing ruthenium based redox catalyst and equivalent acetoxybenziodoxole (BI-OAc) as oxidant (Scheme 1a).[7] However, these intramolecular cyclization reactions have thus far largely been limited to high-dilution solvent, transition-metal catalysts or stoichiometric chemical oxidants,[8] which badly violate the green chemistry postulates.[9] Thus, it is highly desirable, yet challenging, to develop catalyst- and reagent-free radical cyclizations in a green and sustainable manner.

In the meantime, organic electrochemistry,[10] employing protons and electrons as redox reagents, has been established as an eco-friendly, atom-economic and increasingly powerful green tool[11] for molecular synthesis.[12] In this context, amidyl radical generated by electro-oxidation of the amide N–H bond *via* direct or indirect electrolysis was applied by the groups of Moeller,[13] Waldvogel,[14] Zeng[15] and Xu[12n–s] in various C–N bond-forming cyclization reactions to construct N-containing heterocycles (Scheme 1b). Despite these major advances, the reported electrochemical methods involving amidyl radicals are limited to produce 5 or 6-membered rings through typical amidyl radical cyclizations, the electrochemical oxidative C–N bond formation to afford 8–11-membered lactams has proven to be elusive.

With our continuing efforts in developing efficient electrochemical syntheses of heterocycles,[12g,l,16] we herein report a



Scheme 1 Electrochemical synthesis of lactams by C–C cleavage.

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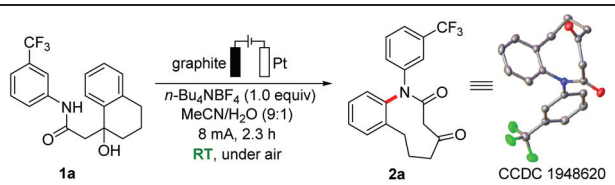
first electrochemical synthesis of medium-sized lactams *via* a rare amidyl radical migration by C–C bond cleavage (Scheme 1c). Notable features of our general strategy include (1) exceedingly mild and environmental-friendly reaction conditions in a transition metal-[17] and chemical oxidant-free[18] fashion, and (2) an unparalleled broad substrate scope highlighting all ring sizes of (hetero)aryl-fused medium-sized rings and hetero atom-tethered rings with high functional group tolerance. In contrast to previous typical amidyl radical cyclization, this electrosynthetic approach set the stage for atom- and step-economical ring expansion through a unique remote amidyl (hetero)aryl migration from carbon to nitrogen.

At the outset of our studies, we probed a variety of different electrolysis conditions employing an undivided cell equipped with a graphite anode and a platinum cathode towards the envisioned C–N bond formation of substrate **1a**, which is readily prepared from commercially available 1-tetralone in a single step (Table 1, and Tables S1 in the ESI†).[19] The optimal results were obtained when substrate **1a** was directly electrolyzed at a constant current in a mixed electrolyte solution of *n*-Bu_4NBF_4 in MeCN/H_2O (9 : 1) at room temperature under atmospheric conditions without additional catalysts or bases. Under these conditions, the desired 9-membered lactam **2a** was isolated in 98% yield (Table 1, entry 1). The structure of **2a** was unambiguously confirmed by single-crystal X-ray diffraction studies. The electrolyte and current were both found to be essential for the reaction to achieve the optimal yield (entries 2 and 3). Thus, among a variety of electrolytes, Et_4NBF_4 and *n*-Bu_4NPF_6 showed good efficacy (entries 4 and 5), while Et_4NClO_4 displayed poor performance (entry 6). Further control experiments verified the essential role of H_2O as the proton source, since performing the electrolysis in the methanol solvent also produced the desired **1a** in moderate yield (entries 7–10). The choice of electrode material proved critical because a dramatically reduced product yield was obtained when using a Pt anode (entry 11).

With the optimized electrooxidation in hand, we explored the viable substrate scope first testing the effect exerted by substituents on the arene of the aniline moiety (Scheme 2). The electrolysis reaction exhibited excellent compatibility with a variety of electron-withdrawing and electron-donating groups at either the *meta*- or *para*-position[20] of the aniline to afford desired products (**2a–2g**). Thereafter, we investigated the effect of substituents on the aryl ring of the tetrahydronaphthalene motif. Thus, the robust nature of the electrooxidative ring-expansion transformation was reflected by fully tolerating a wealth of valuable functionalities, including sensitive chloro, bromo and fluoro groups, which could serve as a handle for future late-stage modifications. Subsequently, we explored the scope with respect to viable annulated ring size scaffolds. To our delight, the strategy for the direct electrochemical synthesis of medium-sized lactams hence provided 8- to 11-membered medium-sized lactams **2–5** in good yields.

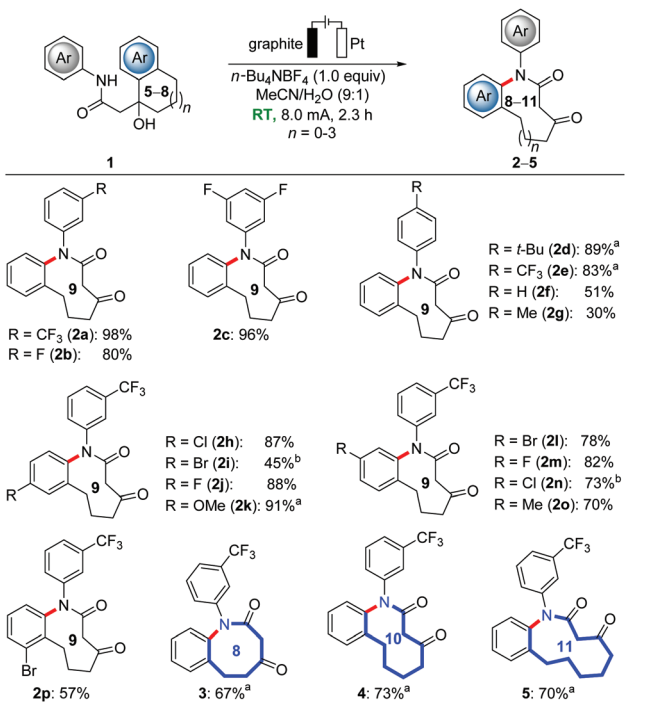
Furthermore, encouraged by these exciting results, we next investigated the compatibility with various substituted ketones in the electrochemical ring-expansion approach (Scheme 3). A wealth of alkyl and aryl substituents on the different position of rings, including methyl (**6**, **7**), 2-fluorophenyl (**8**) and 3,4-dichlorophenyl (**9**), were found to be fully tolerated by the optimized electrooxidation. The practical utility of our approach was further illustrated by successfully performing the desired

Table 1 Optimization of reaction conditions[a]

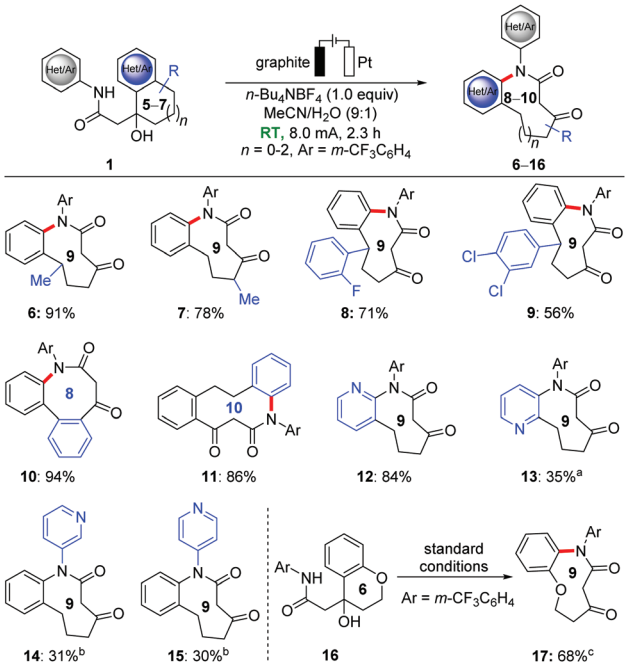


Entry	Deviation from standard conditions	Yield[b] [%]
1	**None**	**98**
2	No *n*-Bu_4NBF_4	0
3	No current	0
4	Et_4NBF_4 instead of *n*-Bu_4NBF_4	81
5	*n*-Bu_4NPF_6 instead of *n*-Bu_4NBF_4	96
6	Et_4NClO_4 instead of *n*-Bu_4NBF_4	48
7	No H_2O	Trace
8	MeOH instead of MeCN/H_2O (9 : 1)	51
9	MeCN/H_2O (3 : 1) instead of MeCN/H_2O (9 : 1)	90
10	MeCN/H_2O (1 : 1) instead of MeCN/H_2O (9 : 1)	84
11	Pt as anode	20

[a] Reaction conditions: Undivided cell, graphite anode, Pt cathode, **1a** (0.2 mmol), *n*-Bu_4NBF_4 (0.2 mmol), MeCN/H_2O (9 : 1, 5.0 mL), constant current = 8.0 mA, 2.3 h (3.4 F mol^{-1}), 23 °C, under air. [b] Yields of isolated product.



Scheme 2 Scope of medium-sized annulated lactams fused with aryl rings. [a] 4.5 h. [b] 3.0 h.

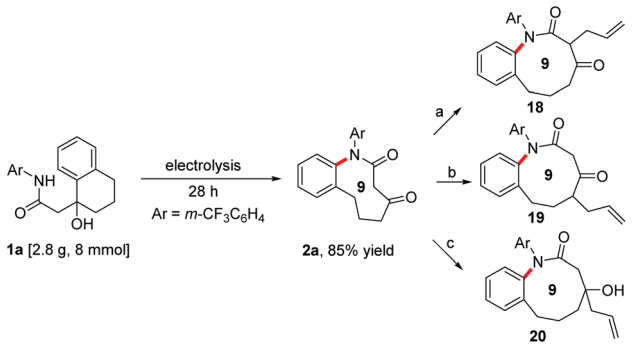


Scheme 3 Scope of medium-sized lactams with substituted rings or fused with (hetero)aryl rings. [a] 6.7 h. [b] 3.0 h. [c] 50 °C, 4.5 h.

expansion with substrates bearing additional fused arenes within the backbones of the expanding rings, to effectively deliver 8-membered lactam **10** and 10-membered lactam **11** in excellent yields, respectively. Gratifyingly, the 2-pyridine-containing substrate was smoothly transformed to the pyridine-annulated medium-sized lactam **12** in 84% yield under the optimized conditions. In addition, other azacycle-possessing substrates also survived our electrooxidative reaction conditions with extended time to give the desired lactams **13–15**, albeit in somewhat lower yields. It is particularly noteworthy that the substrate **16** featuring oxygen-tethered ring was well accepted by the robust metal-free electrooxidation regime to generate the corresponding product **17** at 50 °C. These observations mirror the unique potential for applications in the assembly of diversity decorated medium-sized scaffolds.

The outstanding potential of our ring-expansion approach was further demonstrated by its easy scalability and versatile transformations of the generated medium-sized β-keto lactams (Scheme 4). For instance, we electrolyzed 2.8 g (8 mmol) of alcohol **1a** to deliver the corresponding 9-membered product **2a** in 85% yield, without appreciable loss in efficacy.

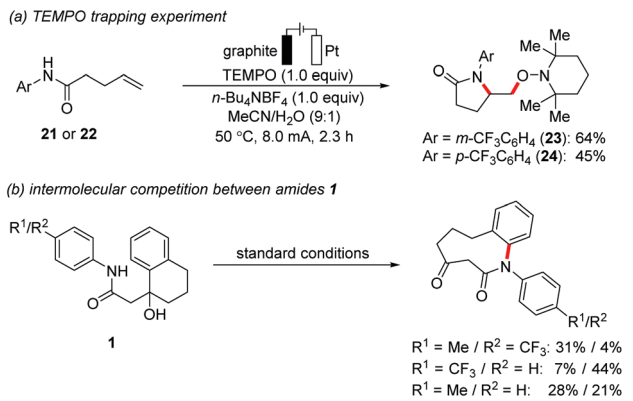
Furthermore, products **18–20** featuring an allyl tag on varied site positions, could be obtained by the nucleophilic substitution of lactam **2a** with allyl bromide and nucleophilic addition to ketone with an allyl Grignard reagent in 50–62% yields. Besides, other common and useful manipulations, such as Suzuki–Miyaura coupling of aryl bromide with an aryl boronic acid, of our prepared medium-sized lactams were also readily amenable.[19]



Scheme 4 Gram-scale synthesis and product transformations. Reaction conditions: (a) Allyl bromide, NaH, THF, 0 °C → rt, 50%. (b) Allyl bromide, LDA, THF, −78 °C → rt, 56%. (c) Allylmagnesium chloride, THF, rt, 62%.

In light of the outstanding versatility of the electrocatalytic ring-expansion methodology we became intrigued by delineating its mode of action. To this end, the possible involvement of an amidyl radical was strongly supported by the formation of oxyamination products **23** and **24** from corresponding amides **21** and **22**, with TEMPO as radical terminator, respectively, bearing an anilide moiety the same with that in substrates **1a** and **1e**, under the otherwise optimized conditions except that temperature was changed to 50 °C (Scheme 5a). According to the reported radical hydroamination mediated by amidyl radical,[13,21] the reaction was likely *via* a pathway involving 5-*exo*-*trig* intramolecular cyclization followed by TEMPO addition.[21a] The formation of amidyl radical was further supported by intermolecular competition experiments between electronically discriminated substrates **1**, revealing electron-rich substrates being inherently more reactive (Scheme 5b), which is in good agreement with previous findings reported in the literature.[21d]

Likewise, cyclic voltammetric analysis revealed key mechanistic insights into the electrochemical transformation (Fig. 1).[22] The voltammogram disclosed that anodic oxidation of the substrate **1a**, generating amidyl radical species **A**, occurred at a potential of *ca.* 2.2 V (*vs.* Ag/AgCl), followed by an



Scheme 5 Summary of key mechanistic findings.

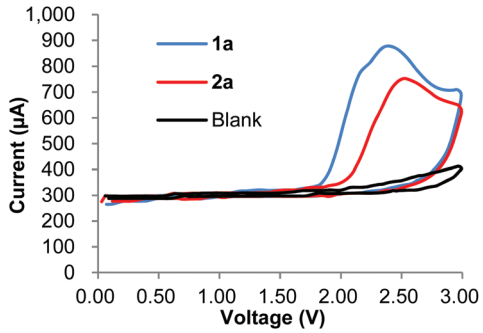


Fig. 1 Cyclic voltammograms of 0.1 M n-Bu_4NBF_4 in acetonitrile (blank, black line), substrate **1a** (blue line) and product **2a** (red line). Reference electrode: Ag/AgCl in 3 M KCl in H_2O. Scan rate = 200 mV s^{-1}.

irreversible oxidation of the intermediate **C**, affording the desired product **2a** at a potential of *ca.* 2.3 V, well below the oxidation potential of the medium-sized lactam **2** (*ca.* 2.5 V *vs.* Ag/AgCl), protecting the product from oxidative decomposition partly.[12d]

The possible reaction mechanism was next examined by computational density functional theory (DFT) calculations (Fig. 2). The first pathway commences with a cyclization *via* a 5-membered ring transition state, followed by a favorable β-scission step. Cyclisation *via* 6-membered ring transition state was also considered, but is energetically unfavorable. The second rationale initiates with a hydrogen atom transfer from the hydroxyl group to the amidyl radical, followed by β-scission (see Fig. S4†).[19] However, the first pathway was found to be energetically favorable.

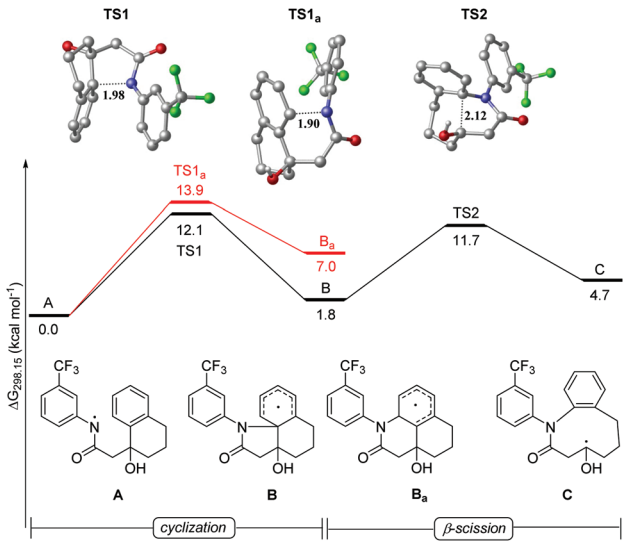
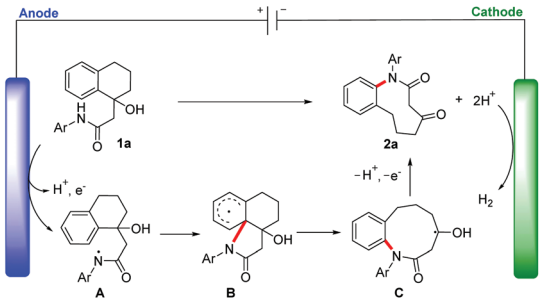


Fig. 2 Computed relative Gibbs free energy profile for the cyclization and β-scission elementary steps in kcal mol^{-1} starting from intermediate **A** at the B3LYP-D3(BJ)/6-311++G(d,p) + SMD(Acetonitrile)//B3LYP-D3(BJ)/6-31+G(d) level of theory. The cyclization *via* both 5-membered ring transition state (black) and 6-membered ring transition state (red) were analysed. Non-relevant hydrogen atoms were omitted for clarity.



Scheme 6 A plausible mechanistic pathway.

Based on our mechanistic studies, a plausible mechanism is proposed using **1a** as a model substrate (Scheme 6). The reaction is first initiated by the anodic oxidation of the amidyl N–H bond in **1a**, leading to the generation of an amidyl radical intermediate **A**, which could then readily undergo intramolecular cyclization with the aryl ring to form a new C–N bond in delocalized radical **B**, followed by selective C–C bond cleavage to furnish the neutral ketyl radical **C**. Finally, single-electron oxidation of this ketyl radical **C** followed by the loss of a proton would afford the medium-sized lactam **2a**. However, due to the two close oxidative waves of **1a** in cyclic voltammogram, the cationic pathway cannot be excluded.[23]

Conclusions

In summary, we have reported on the first electrochemical ring-expansion protocol for the direct synthesis of a variety of synthetically challenging medium-sized lactams by means of C–C bond cleavage. The strategy provides expedient access to a diverse range of 8–11-membered (hetero)arene-annulated lactams with ample scope, high yield, and broad functional group tolerance. Thus, exceedingly mild electrolysis of amide substrates under catalyst- and external-oxidant-free conditions occurred efficiently in an undivided cell. Detailed mechanistic studies revealed a remote radical migration pathway *via* a SET-type fashion.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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