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Coupling of α-bromoamides and unactivated alkenes to form γ-lactams through EDA and photocatalysis†

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γ-Lactams are prevalent in small-molecule pharmaceuticals and provide useful precursors to highly substituted pyrrolidines. Despite numerous methods for the synthesis of this valuable motif, previous redox approaches to γ-lactam synthesis from α-haloamides and olefins require additional electron withdrawing functionality as well as *N*-aryl substitution to promote electrophilicity of the intermediate radical and prevent competitive O-nucleophilicity about the amide. Using α-bromo imides and α-olefins, our strategy enables the synthesis of monosubstituted protected γ-lactams in a formal [3 + 2] fashion. These species are poised for further derivatization into more complex heterocyclic scaffolds, complementing existing methods. C–Br bond scission occurs through two complementary approaches, the formation of an electron donor–acceptor complex between the bromoimide and a nitrogenous base which undergoes photoinduced electron transfer, or triplet sensitization with photocatalyst, to furnish an electrophilic carbon-centered radical. The addition of Lewis acids allows for further increased electrophilicity of the intermediate carbon-centered radical, enabling tertiary substituted α-Br-imides to be used as coupling partners as well as internal olefins.

N-heterocycles provide essential cores to a number of biologically active molecules. As a privileged heterocyclic scaffold, γ-lactams are found not only in natural products and pharmaceuticals, but are also valuable intermediates in the synthesis of highly functionalized amines as well as other saturated N-heterocycles.[1–3] Despite numerous conventional methods for the construction of γ-lactams, current technologies often limit the synthetic versatility of their products due to requisite substitution in starting materials to enable reactivity.[4–8] Synthesizing γ-lactams in an intermolecular fashion from widely available precursors therefore provides a significant opportunity in organic methods development.

Atom-transfer radical addition (ATRA) reactions through both photoredox and Cu catalysis have been well studied for a variety of haloalkanes, especially α-Br-carbonyl compounds.[9–11] In the case of α-Br-amide derivatives, efficient addition to unactivated olefins require electron withdrawing groups such as *gem*-difluoro substitution to increase the electrophilicity of the intermediate radical.[12–15] This limitation thus mandates that γ-lactam syntheses from α-Br-amides require α,α substitution, eliminating valuable synthetic derivatization of the protected lactam products[16–18] (Fig. 1A).

Electron donor–acceptor (EDA) complexes have gained prominence due to the useful reactive species that can be generated simply *via* photoirradiation.[19,20] Excitation of these intermediates with an exogenous photosensitizer may likewise proceed *via* triplet energy transfer (EnT). EDA complexation has been utilized towards the activation of various C–halogen bonds to form corresponding C-centered radicals.[21–23] Whereas many strategies have leveraged the bathochromic shift of complex formation to enable electron transfer under visible light,[24–29] only recently have groups demonstrated using the donor or acceptor component in a catalytic fashion.[30–37] (Fig. 1B).

We envisioned that EDA complexation could enable activation of α-halo-amides through donor catalysis with sufficient energy irradiation or *via* EnT with an appropriate photocatalyst. Whereas α-halo-amides require additional electron withdrawing functionality at carbon to enable electrophilic radical formation *via* single electron transfer, energy transfer strategies offer an orthogonal activation mechanism. EnT from excited state photosensitizers has been leveraged through both substrate modification as well as Lewis acid activation in previous studies.[38–48] (Fig. 1C) The formation of a Brønsted acid-base adduct should promote complexation between a donor base and an acceptor acid in the case of sufficiently acidic amides, poising it for photoinduced electron transfer or

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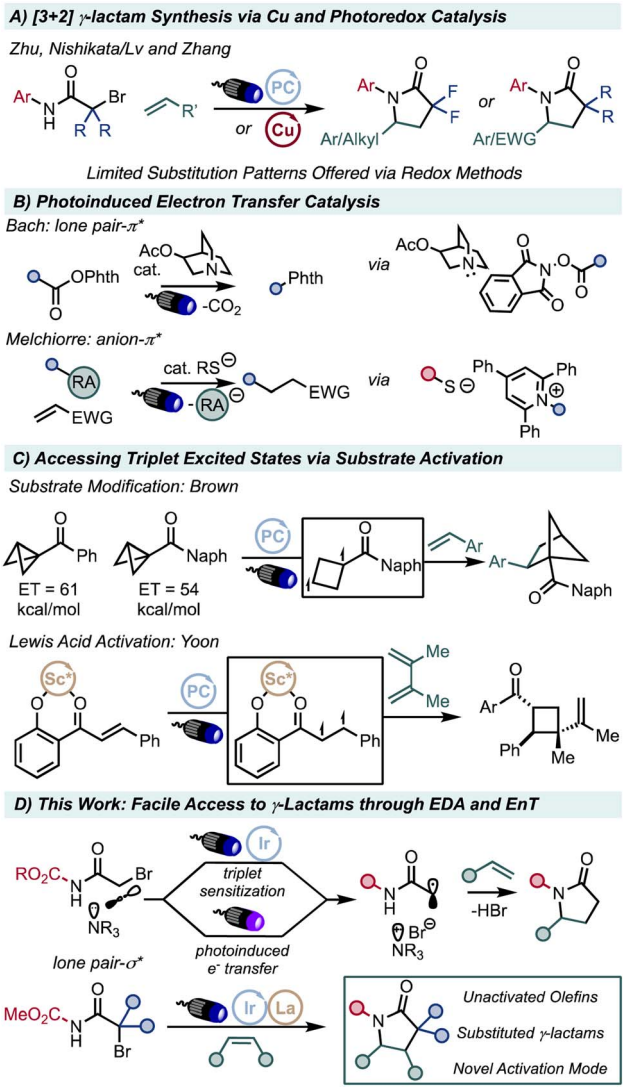
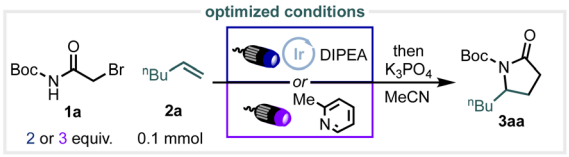


Fig. 1 EDA complexation and Lewis acid activation permits access to highly electrophilic α-amido radicals.



Entry	Deviation from Standard Conditions	Yield 3aa (%)
1	none	88
2	no light	0
3	no PC	33
4	no base	20
5	2 equiv. olefin, 1 equiv. imide	50
6	1 equiv. olefin, 1 equiv. imide	29
7	no PC, 390 nm irradiation	48
8	none	68
9	no light	0
10	no base	10

Fig. 2 Selected optimization trials (see ESI† for complete details). All reactions were conducted on 0.1 mmol scale. Yields were determined by ^{1}H NMR integration relative to 0.5 equiv. dibromomethane as an internal standard. Standard conditions A: 1% Ir = (Ir[dF(CF$_3$)ppy]$_2$(dtbpy))PF$_6$, 20% DIPEA = *N*,*N*-diisopropylethylamine, 440 nm irradiation in 0.4 M DCE. Standard Conditions B: 20% 2-Me-pyridine, 390 nm irradiation in 0.4 M DCE. Both conditions are followed by the addition of K$_3$PO$_4$ in MeCN (0.1 M).

photocatalytic EnT. We designed our reagent with a traceless electron-withdrawing substituent at N, *tert*-butoxy carbonyl, to both facilitate ATRA with unactivated olefins and promote intramolecular N-cyclization of the intermediate alkyl halide *via* facile deprotonation of the acidic N–H bond (Fig. 1D).[49,50]

We began our studies by reacting *tert*-butyl (2-bromoacetyl) carbamate **1a** with 1-hexene (**2a**) *via* photocatalysis with catalytic loading of N,N,-diisopropylethylamine (DIPEA). Subjecting 2-bromoacetamide and *N*-phenyl-2-bromoacetamide under identical conditions resulted in complete recovery of starting material (see Table ESI 1†). Having achieved high conversion of the ATRA product we found that basic workup with excess K$_3$PO$_4$ in wet MeCN furnishes our desired Boc-protected γ-lactam **3aa** in good yield (88%, Fig. 2). Evaluation of the reaction controls revealed the necessity of visible light, Ir photocatalyst, and the tertiary amine base for high yields (Fig. 2, entries 2–4). Likewise, an excess of the α-Br-acyl carbamate **1a** was found to be essential for efficient reactivity (Fig. 2, entries 5–6).

Interestingly, the reaction proceeds modestly in the absence of photocatalyst (Fig. 2, entry 3) suggesting an alternative activation mode enabled solely by irradiation. The use of higher energy light (390 nm) leads to a more efficient transformation to deliver synthetically useful yields of the ATRA product. Screening of amine bases (Table ESI 6†) showed 2-methylpyridine to be the optimal donor catalyst in the absence of exogenous photosensitizer (Fig. 2, entry 8). A larger excess of **1a** (3 equiv. *vs.* 2 equiv.) is required to achieve comparable yields of the ATRA product without the addition of photocatalyst.

With optimized conditions in hand, we set to explore the scope of olefin coupling partners under both sets of conditions (Fig. 3). We found α-olefins to be effective coupling partners with various alkyl and aryl substituents (**3aa–3ag**, **3an**) undergoing coupling in high yield. Of note, olefin substrates **2c** and **2d** undergo the ATRA reaction with comparable yields to other substrates, but the α-tertiary and α-quaternary positions of the intermediate alkyl bromide impart steric hindrance on the subsequent intramolecular alkylation, lowering the yield of the desired γ-lactam. In exploring functional group tolerance, we found that alkenes bearing esters (**3ah**, **3ai**), ketones (**3am**), and protected alcohols (**3ai**, **3al**) tolerate the reaction conditions. Pleasingly, the incorporation of polar electrophiles in the substrate such as alkyl halides (**3aj**) and alkyl tosylates (**3ak**) also deliver the desired lactam in good yields. Finally, imides (**3ao**) and various amides (**3ap–3as**) all undergo efficient coupling using our protocol. In many cases, the direct sensitization of the EDA complex was shown to be competitive with the photocatalytic reaction. We posited that the direct irradiation protocol would be amenable to larger scale reactions due to the low cost and availability of 2-Me-pyridine as a catalyst. Indeed,

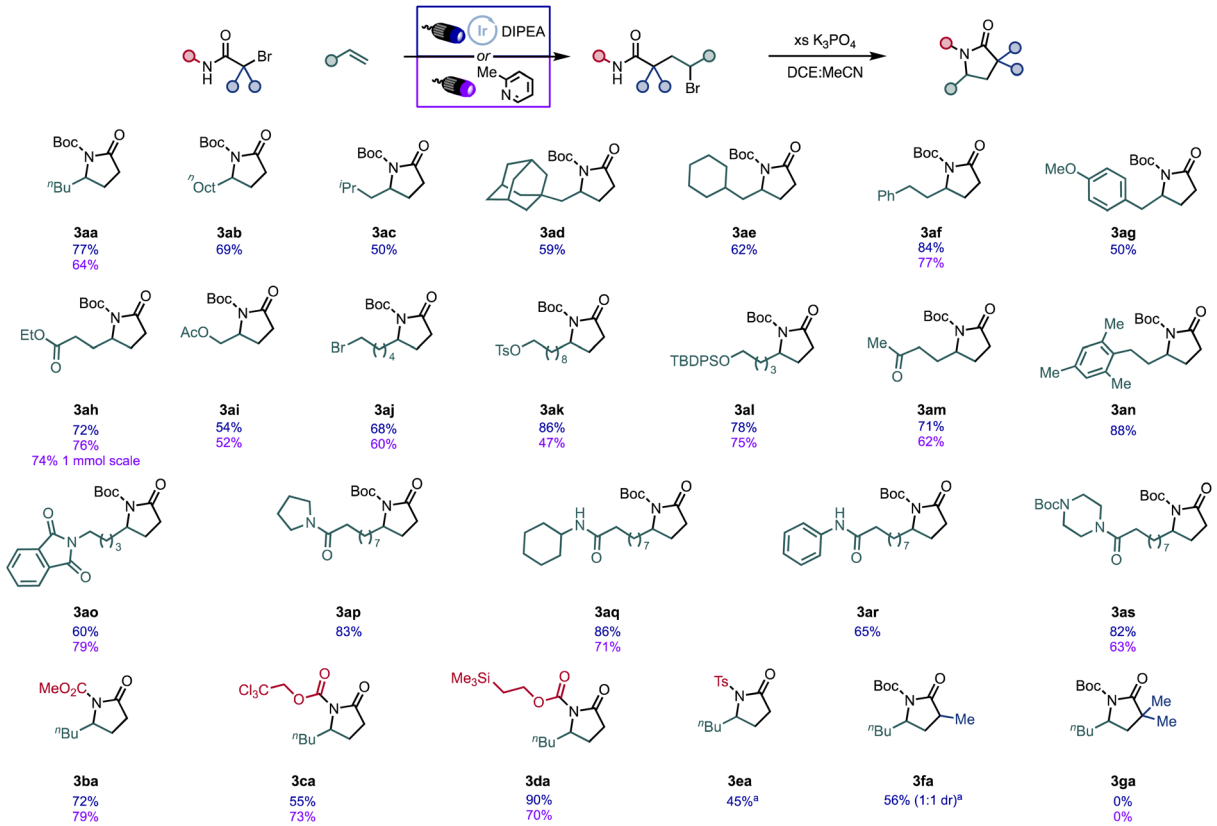


Fig. 3 Scope of γ-lactam synthesis. All reactions performed on 0.3 mmol scale. All yields are from isolation. [a]See ESI† for reation details.

the procedure scales up to 1 mmol with similar efficiency (76% *vs.* 74% for **3ah**), demonstrating the additional synthetic utility of this method.

In order to augment the derivatization available to our lactam products, we explored the possibility that other carbamate protecting groups could be utilized in the formal [3 + 2] coupling with high efficiency. This protocol proves to be general in this regard, with methoxycarbonyl (**3ba**), 2,2,2-trichloroethoxycarbonyl (Troc) (**3ca**), and 2-(trimethylsilyl)ethoxycarbonyl (Teoc) (**3da**) all furnishing the desired protected γ-lactam products in high yields. Likewise, a tosyl imide results in product **3ea** albeit with a modified protocol (see ESI†). These protecting groups offer opportunities for orthogonal deprotection strategies and may be carried through as intermediates towards further valuable N-containing complex products.

Focusing our attention on expanding the scope of α-Br-imide coupling partners, we found that additional alkyl substitution at the site of electrophilic radical generation was detrimental to the ATRA step. We attribute this attenuated reactivity to the reduced electrophilicity of the intermediate radical, which should react more slowly with α-olefins leading to slightly diminished yields of the desired γ-lactam product and in undesirable 1 : 1 diastereoselectivity (**3fa**). Furthermore, tertiary alkyl bromides lead to quantitative recovery of unreacted starting material under identical conditions (**1g**), indicating that activation of the substate is also inhibited by insufficient electrophilicity. We hypothesized that the formation of a Lewis acid adduct with the substrate could enable single electron transfer (SET) to the substrate, enhance the electrophilicity of the intermediate radical, and further enable the substrate to act

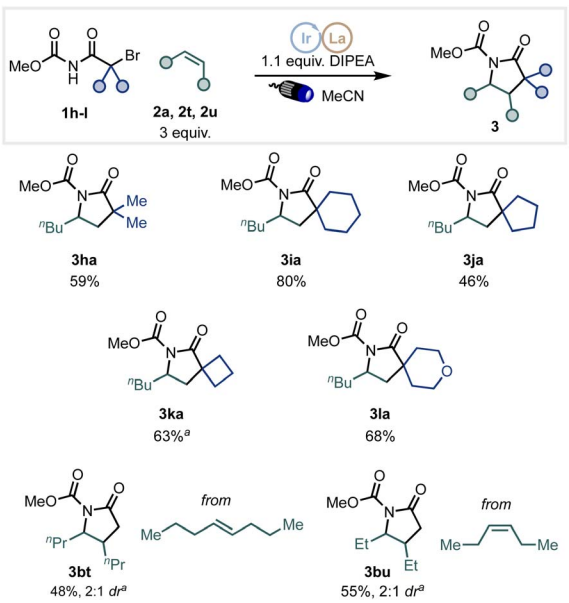


Fig. 4 Scope of γ-lactam synthesis through Lewis acid activation. All reactions performed on 0.3 mmol scale. All yields are from isolation. [a]See ESI† for experimental details.

as a halogen atom donor under a radical chain paradigm. The combination of photoredox catalysis and Lewis acid activation has become a powerful tool in organic synthesis in recent years.[43,45–47,51,52] Due to the instability of imide **1g** in the presence of various Lewis acids, we shifted to imide **1h**. Screening and optimization (Table ESI 7–9†) showed $La(OTf)_3$ to be the most effective Lewis acid, improving the yield of the desired product **3ha** from 0% to 59% in a single step with slight excess of DIPEA (Fig. 4). Evaluation of this protocol on the corresponding primary α-Br-imide **1b** showed limited cyclization (<15%) after the first step under identical conditions, suggesting that a Thorpe–Ingold effect likely facilitates the formation of the desired final product without the need for additional inorganic base. Evaluation of the scope of tertiary alkyl halides proved fruitful, as fused ring systems are readily furnished *via* this protocol, including cyclohexyl (**3ia**), cyclopentyl (**3ja**), and cyclobutyl (**3ka**) substituents. Additionally, heterocycles such as tetrahydropyran (**3la**) prove to be well tolerated. Furthermore, the addition of $La(OTf)_3$ enables ATRA with internal olefins such that symmetric internal olefins could be added to the protocol albeit with modest diastereoselectivity (**3bt** and **3bu**). The successful reaction of these substrates supports the role of the Lewis acid in enhancing the electrophilicity of the intermediate radical to promote addition to hindered olefins (Fig S8†).

In order to understand the mechanism of initial radical formation, as well as radical propagation, we conducted a number of electrochemical and photochemical studies. Cyclic voltammetry was conducted on **1h**, to reveal an irreversible 1-electron wave corresponding to the reductive cleavage of the C–Br bond occurring at $E_{1/2} = -1.47$ V *vs.* SCE (Fig S2†), meaning that reduction by the reduced state of the photocatalyst ($E^{red} = -1.37$ V *vs.* SCE[53]) would be endothermic and therefore unfavorable at room temperature. Similarly, the employment of photocatalysts with greater reduction potentials in their excited state do not furnish high yields of the ATRA product (Table ESI 2†). Further cyclic voltammetry studies demonstrated that SET to **1h** could be made even more facile through addition of $La(OTf)_3$, to shift the reduction potential as low as at $E_{1/2} = -1.32$ V *vs.* SCE with an irreversible 2-electron wave (Fig S2†) indicating that the addition of Lewis acid may indeed change the mechanism of activation of the C–Br bond in the starting material from EnT to SET. Higher yields are achieved with excess DIPEA relative to starting material **1h**, indicating that the concentration of reduced photocatalyst may additionally enable this change in mechanism as there may be a higher concentration of the more reducing reduced state photocatalyst. Lewis acids have been shown to promote EnT as well as produce complexes more amenable to SET.[47,48]

UV-vis spectroscopy of the starting material **1a** reveals a significant absorption in the UV region with $\lambda_{max} = 288$ nm (Fig S1†). UV-vis characterization of mixtures of DIPEA and starting material **1a** reveal a growing shoulder absorption tailing into the visible range with $\lambda_{max} = 344$ nm (Fig. 5C). We ascribe this absorption to an EDA complex of the tertiary amine base with the α-Br-imide, which enables direct photoinduced

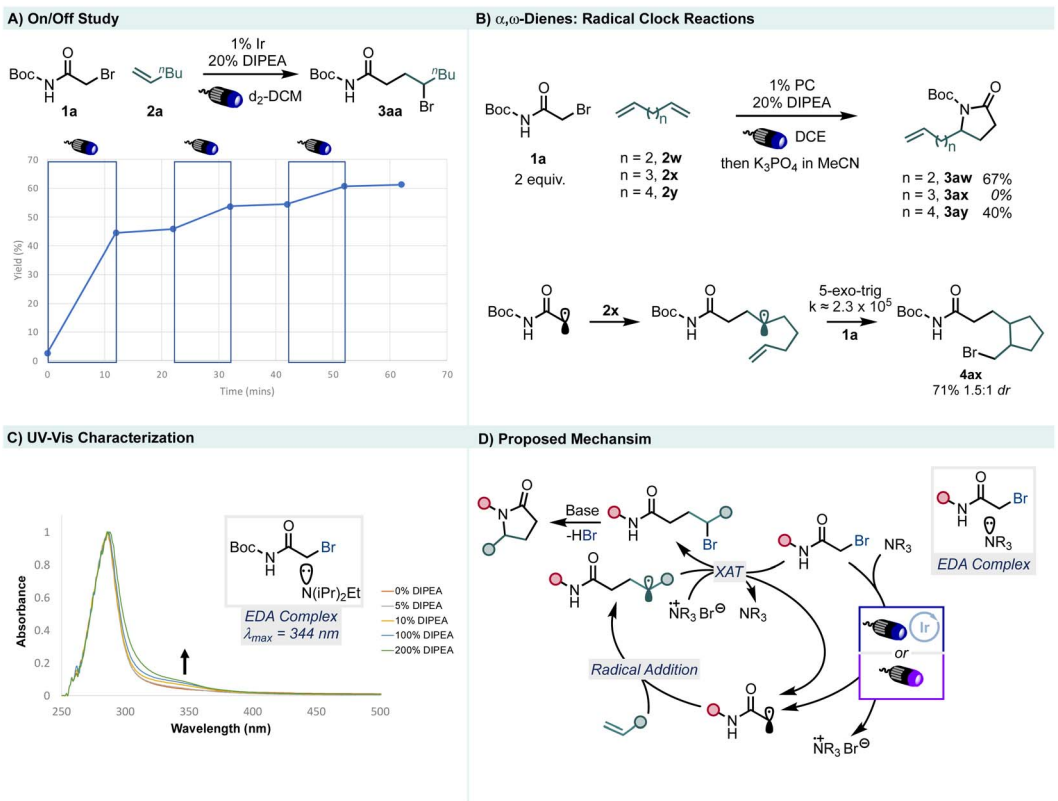


Fig. 5 Mechanistic investigations.

electron transfer without the need for photocatalyst under sufficiently high energy irradiation. When present, the photocatalyst sensitizes the EDA complex under visible light irradiation to enable initial radical formation *via* an EnT mechanism (E_T = 61.7 kcal mol^{-1}).[53] Similar studies were undertaken with 2-Me-pyridine as the donor to find a similar red shift in the UV-vis absorption (Fig S3†).

When α-ω-dienes **2w**, **2x**, and **2y** are used as coupling partners, we note radical cyclization only in the case of 1,6-heptadiene (**2x**), which permits a rough estimate of the rate of alkyl radical halogenation when compared to the analogous known radical cyclization rate constants[54] (Fig. 5B). This shows that halogen atom transfer must occur at a rate roughly between 5.5×10^3 and 2.3×10^5 s^{-1} under the reaction conditions, as the 5-*exo*-trig cyclization is the only cyclization fast enough to cyclize prior to intermolecular halogen atom transfer. Since the 6-*exo*-trig cyclization product is not detected, the rate of intermolecular halogen transfer under our conditions must exceed the rate constant of the cyclization which is 5.5×10^3 s^{-1}.[54] To test whether the reaction is merely initiated, proceeding primarily through a radical chain, we conducted an on-off study which revealed that the reaction is photocontrolled (Fig, 5A). However, experimental determination of the quantum yield (Φ = 14, see ESI†) showed that radical chains are indeed operative, although they are relatively short lived and likely attenuate as the reaction progresses.

Therefore, we propose the following mechanism (Fig. 5D). First, formation of an EDA complex between α-Br-imide **1a** and a nitrogenous base is sensitized by the triplet excited state of the Ir photocatalyst through an EnT mechanism or through direct EDA complex absorption. The resulting electrophilic radical reacts with an olefin to form a C-centered electron rich radical. This intermediate is then poised to undergo XAT with another equivalent of **1a** or an *in situ* formed N–Br$^+$ species to form the ATRA product. This readily forms the desired lactam product upon treatment with excess base in acetonitrile in a single pot.

We have demonstrated a valuable method for the formal [3 + 2] synthesis of γ-lactams, enabled by complementary approaches using EDA complexation or photoredox catalysis. This strategy permits the facile synthesis of highly substituted γ-lactams from readily synthesized α-Br-imide starting materials and abundant olefins, enabling novel bond disconnections. Such opportunities will streamline synthetic routes as well as provide novel biologically active compounds for use in small-molecule pharmaceuticals.

Data availability

The datasets supporting this article have been uploaded as part of the ESI.†

Author contributions

S. M. T., D. V., and T. R. conceived the study. S. M. T. and D. V. designed and executed the experiments. S. N., S. M. T., and C. T. conducted electrochemical investigations. All authors contributed to writing the manuscript, and given it final approval.

Conflicts of interest

The authors declare no competing financial interest.

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