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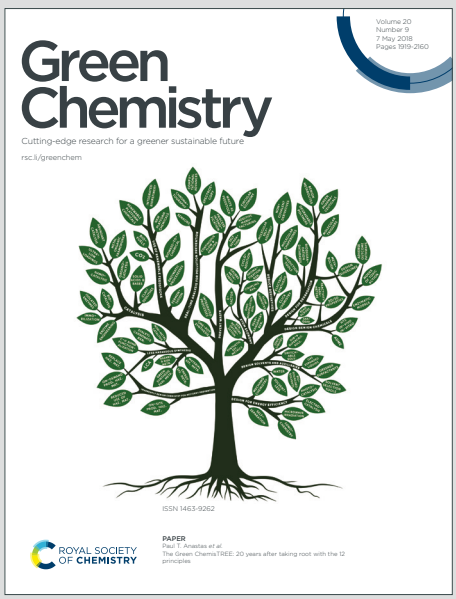

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COMMUNICATION

Electrochemical Oxidative C(sp³)-H Azolation of Lactams Under Mild Conditions

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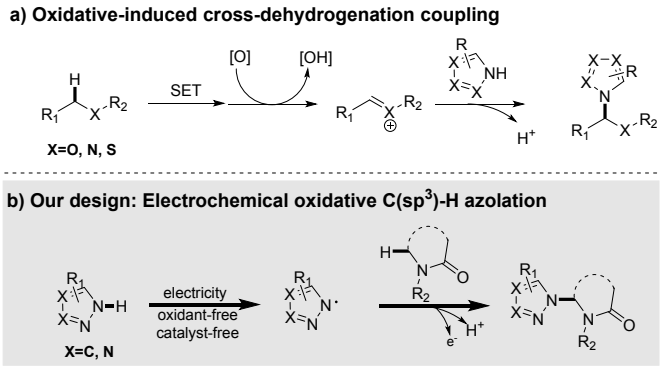
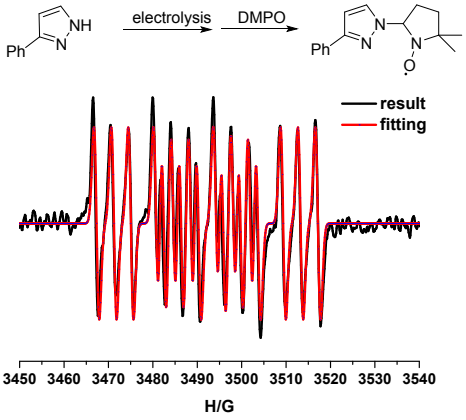
Lactam-containing structural compounds are ubiquitous in drugs and biomolecules. An electrochemical oxidative direct C(sp³)-H azolation of lactams has been reported under metal catalyst free and external oxidant free conditions. This electrochemical C(sp³)-H/N-H coupling is characterized by its broad substrate scope of azoles and lactams, mild conditions at room temperature. Mechanistic studies suggested that the reaction possibly involves a radical process. Moreover, the site selectivity can be explained by DFT calculations. More meaningfully, a gram-scale synthesis method of flow electrochemistry was performed to demonstrate the scaled-up applicability of this transformation.

Lactam compounds have proven to be used in medical and biological science,[1] being used antibiotic and drug. Among them, γ-lactam with a variety of biological activities have been utilized in a large number of drugs.[2] Not surprisingly, the C–H functionalization of lactam is of great significance to bio-pharmaceuticals. Azoles are an important class of heterocyclic structures, which are rich in electrons with strong, π-π stacking interaction, easy to form hydrogen bonds.[3] The presence of azole group provides a number of bio-chemicals that function effectively, such as ligands, ionic liquids, and azole affinity drugs[4]. Based on these, direct C-H azolation of lactams with azoles shows potential applications for seeking novel drugs. In recent years, the C(sp³)-H azolation method has been reported using transition metal catalysis,[5] photochemistry[6] and other methods. Particularly under metal-free reaction, these research advances have greatly promoted the development of C(sp³)-N bond formation and many chemicals have been created. However, stoichiometric oxidants need be used to achieve this transform, including *tert*-butyl hydroperoxide (TBHP),[7] $PhI(OAc)_2$,[8] $K_2S_2O_8$,[9] etc.[10] Therefore, developing an efficient and environmentally friendly C(sp³)-H azolation might be highly desirable.



Scheme 1. Methods for C(sp³)-H azolation with azoles.



Scheme 2. The electron paramagnetic resonance experiment of 3-phenyl-1*H*-pyrazole.

Oxidative-induced cross-dehydrogenation coupling is undoubtedly a powerful strategy for C(sp³)-H azolation (Scheme 1, a). During the course of the reaction, the C(sp³)-H bond adjacent to the heteroatom gives a carbenium ion by single-electron transfer (SET) and deprotonation, which is trapped by azole to give the azolated product. It is worth noting that the method of oxidative induction is azolation by

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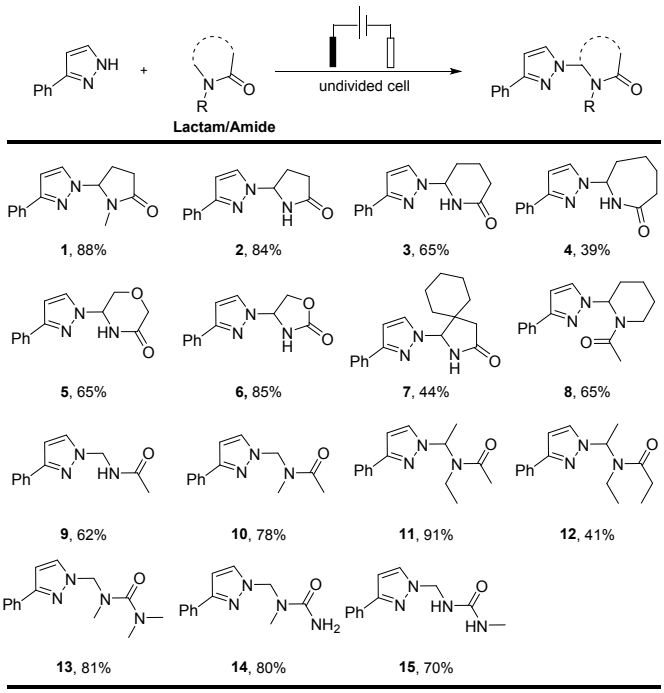
direct oxidation of the sp^3 C-H bond. We envisage whether the azole can be anodized in the electrolytic cell to obtain a nitrogen radical, which is then used directly to formation of C-N bond with lactam (Scheme 1, b). Actually, the method for achieving C-H/N-H cross coupling by anodizing strategies has been reported, and C(sp^2)-N bond formation is becoming more and more mature.[11] However, the activation of C(sp^3)-H is still challenging with only a few reported cases,[12] which may be due to the poor chemical activation energy of the sp^3 C-H bond.

Electrochemical oxidation has emerged one of the most promising organic synthesis.[13] Our group has long been to the development of green organic synthesis methods while interest in mechanism studies. We have demonstrated through experiment of electron paramagnetic resonance (EPR) that azole can be oxidized to give a nitrogen radical during electrolysis (Scheme 2). Encouraged by this result, we sought to develop an azolation reaction of organic compounds. Herein, we report a direct electrochemical oxidation reaction to achieve C(sp^3)-H azolation, using a broad range of azole and lactams substrates under mild reaction conditions.

Initially, 3-phenyl-1*H*-pyrazole and 1-methyl-2-pyrrolidinone were used to identify the optimal condition for the C-N coupling product. After painstaking efforts, we discovered that using a carbon cloth anode and a platinum plate cathode, under the constant-current electrolysis at 10 mA for 4 h at room temperature, the product **1** was obtained in 88% yield (SI, Entry 1). While keeping the electric quantity constant (4.97 F), properly increasing or decreasing the constant current, lower reaction yields were obtained (SI, Entries 2 and 3). The electrosynthesis of **1** could also beconducted with cheaper nickel plate as cathode, the nickel plate was slightly less effective than the platinum plate (SI, Entry 4). Further screening of the electrolyte showed that ^{n}Bu$_4$NBF$_4$ was the best one (SI, Entries 6-8). To understand effect of solvent on the reaction, several solvents were examined (SI, Entry 9-11), attempts using MeOH or *N,N*-dimethylformamide (DMF) was not successful, and when dichloroethane (DCE) was used instead of MeCN, just 29% of yield was obtained. In addition, 52% yield was obtained when conducted under air, and some *N*-methylsuccinimide are detected by GC-MS (SI, Entry 12). Finally, this conversion cannot occur without current (SI, Entry 13).

Scheme 3. Electrochemical oxidative C(sp^3)-H azolation with different amides.



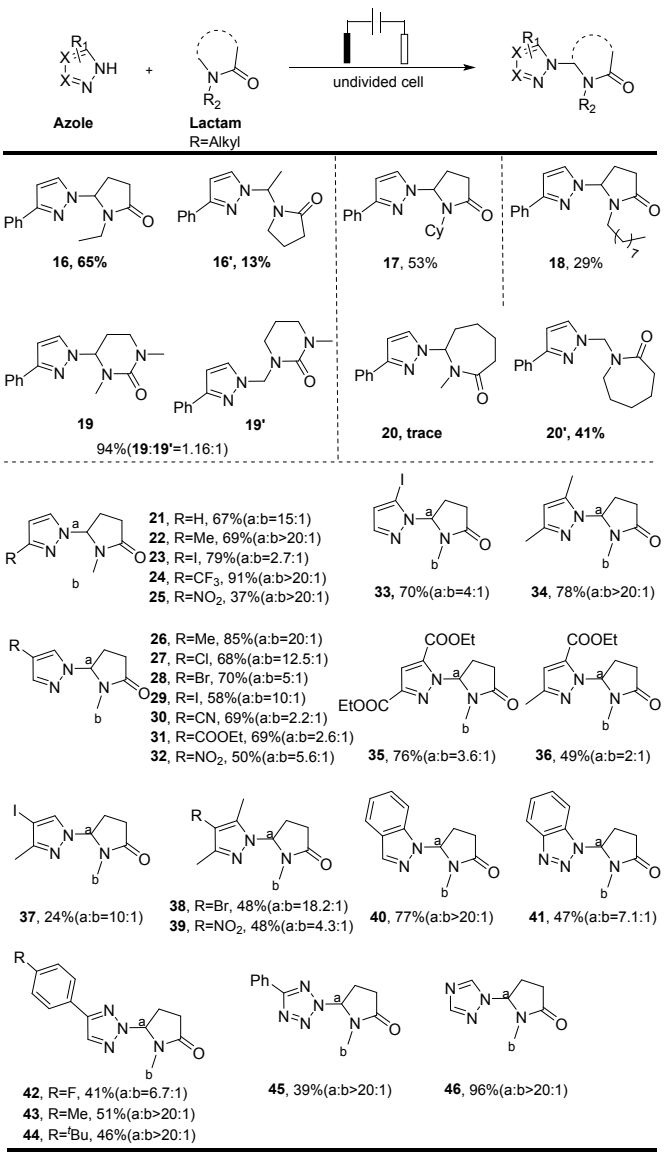
[a]Reaction conditions: **1a** (0.3 mmol), **2a** (0.6 mmol), carbon cloth anode (15 mm*15 mm*0.36 mm), Pt plate cathode (15 mm*15 mm*0.3 mm), constant current=10 mA, ^{n}Bu$_4$NBF$_4$ (0.5 mmol), MeCN (10 mL), room temperature, 4 h, undivided cell (4.97 F).

With the optimal reaction conditions in hand, to verify the universality of lactam azolation, pyrrolidin-2-one was first used for investigation (Scheme 3), gave corresponding the product in 84% yield (**2**). The six- and seven-membered lactams provide the products in moderate to good yields (**3**, **4**). The reaction can also tolerate lactams with oxygen atom, gave corresponding products in 65% and 85% yields (**5**, **6**). The substrate with a large steric effect, gabapentin-lactam provided the product in 44% yield (**7**). Next, we started using amides as a coupling partner with azole, *N*-acetylpiperazine gave the corresponding azolation product **8**. We also investigated the chain amides, *N*-methylacetamide, DMF, *N,N*-dimethylacetamide, *N,N*-diethylpropionamide to provide the products in yields of 41%-91% (**9**-**12**). A variety of ureas, including 1,1,3,3-tetramethylurea, 1,1-dimethylurea, *N,N'*-dimethylurea were also compatible with the reaction (**13**-**15**).

We next explored the regioselectivity by using 1-ethyl-2-pyrrolidone (NEP) (Scheme 4). 3-Phenyl-1*H*-pyrazole coupling with NEP regio-isomers **16** and **16'** in a ratio of 5:1 with an overall overall yield of 78%. The nitrogen atom of pyrrolidone could be substituted with cyclohexyl (**17**) and octyl (**18**), in which case delivering predominantly the specific selection products, and the steric hindrance reduced the overall yield. When *N,N'*-dimethyl- *N,N'*-trimethyleneurea was used in the reaction as cyclic amide substrate, the ratio of the *N*-methyl regioselective is close to half of the total yield. Interestingly, the reaction of *N*-methylcaprolactam was the *N*-methyl regioselective, provide product in 41% yield. The regioselectivity seem to be affected by the number of ring atoms. The C-H azolation of 1-methyl-2-pyrrolidinone with various types of azoles shown that more *N*-CH_2 explored the regioselectivity by changing the substituents of azoles. As summarized in Scheme 4, the pyrazole ring could be substituted with phenyl (**1**), methyl (**22**), Trifluoromethyl (**24**), and Nitro (**25**) at position 3, and *N*-CH_2 regioselective coupling is the main product (ratio>20:1). Importantly, we have found that when pyrazole ring at position 4 with a high electron withdrawing group, the proportion of *N*-methyl regioselective coupling products

increases (**30**-**32**). Further, the 3, 5 position of pyrazole was substituted by an iodine atom, the proportion of the *N*-methyl coupling product was increased, 3-iodopyrazole, 5-iodopyrazole, afforded products consisting of regioisomers in the ratio of 2.7:1(**23**) and 4:1 (**33**). The azolation of lactams is also effectively using substrates with a multisubstituted pyrazole ring, when the 3, 5 position of pyrazole was substituted with the electron-rich Me group, the reaction proceeded with good to excellent regioselectivity (**34**, **37**, **38**). The directing effect of the *N*-methyl regioselective was enhanced when the electron withdrawing CO_2Et (**35**, **36**), NO_2 (**39**) was introduced. Finally,

Scheme 4. The regioselectivity of electrochemical oxidative C(sp³)-H azolation between lactams and azoles.

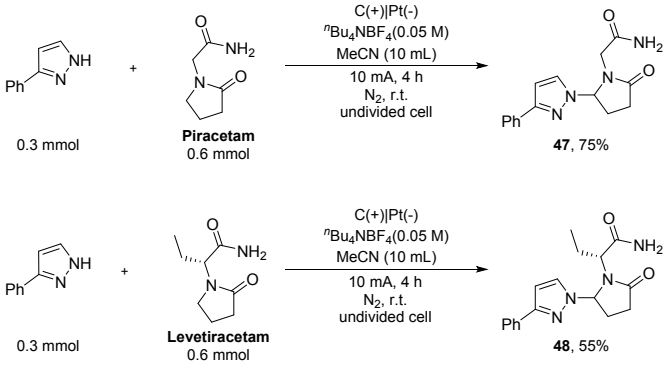


[a]Reaction conditions: **1a** (0.3 mmol), **2a** (0.6 mmol), carbon cloth anode (15 mm*15 mm*0.36 mm), Pt plate cathode (15 mm*15 mm*0.3 mm), constant current=10 mA, $^nBu_4NBF_4$ (0.5 mmol), MeCN (10 mL), room temperature, 4 h, undivided cell (4.97 F).

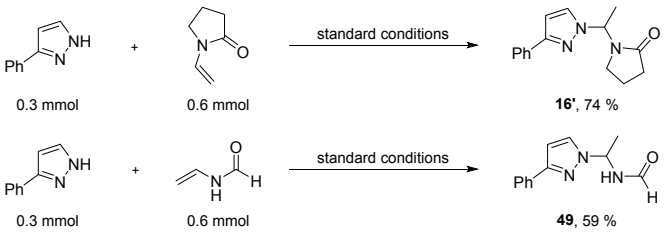
various azoles, such as indazole (**40**), 1*H*-benzotriazole (**41**), triazole (**42**-**44**, **46**), and tetrazole (**45**) were also compatible with the process, producing the corresponding products in 39%-96% yields.

To further demonstrate the applicability of this reaction protocol, clinical drugs have been explored, like Piracetam and Levetiracetam, and the drug bearing electron-withdrawing amide group was compatible with corresponding azolation products obtained in 75% and 55% yields (Scheme 5).

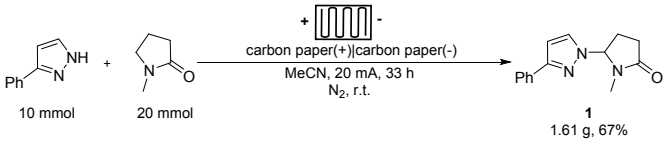
Furthermore, we attempted *N*-vinyl amides (Scheme 6). It is worth noting that C(sp³) of *N*-vinyl-2-pyrrolidinone carbon was unreactive in this transformation. Under our standard



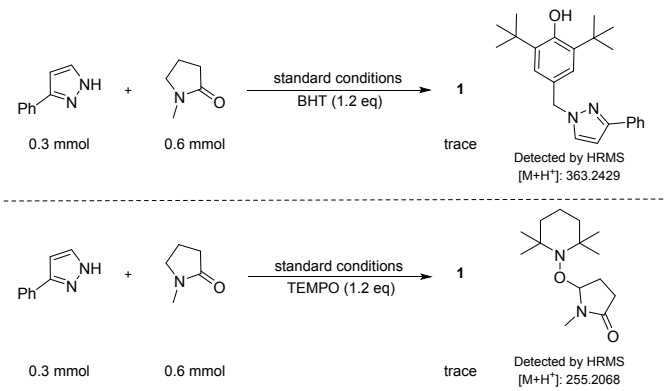
Scheme 5. Electrochemical oxidative C(sp³)-H azolation with drugs.



Scheme 6. Electrochemical oxidative 3-phenyl-1*H*-pyrazole with *N*-vinyl amide.



Scheme 7. Gram-scale synthesis in flow cell.



Scheme 8. Control experiments.

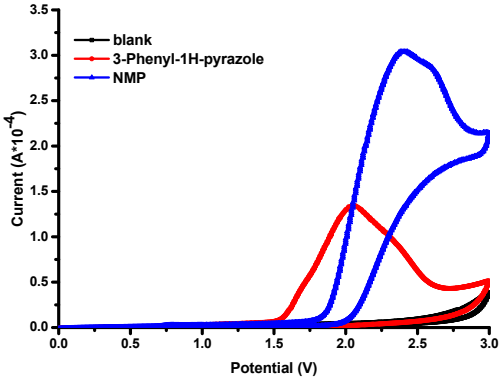
conditions, *N*-vinylpyrrolidone undergoes an addition reaction with 3-phenylpyrazole. A similar reaction occurs in *N*-vinylformamide and obtain a carbon-carbon double bond addition product, which indicates that coupling products may involve a nucleophilic attack process.[14]

To further explore the practicality of our approach, we expanded synthesis of **1** in gram scale (Scheme 7).[15] When the reaction was carried out under 20 mA constant current for 33 hours using carbon paper anode and carbon paper cathode in a flow cell, the desired product (**1**) could be obtained in 67% yield in the presence of 10 mmol 3-phenyl-1*H*-pyrazole and 20 mmol 1-methyl-2-pyrrolidinone in 60 mL CH_3CN.

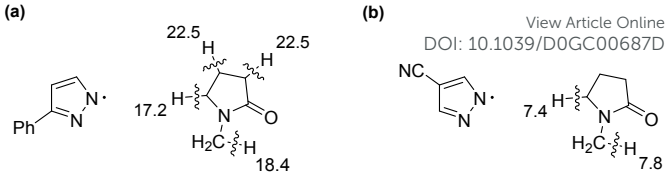
To ascertain the mechanism involved, we carried out several control experiments (Scheme 8). 2,2,6,6-Tetramethylpiperidin-1-oxyl (TEMPO) and 2,6-di-tert-butylphenol (BHT) were added to the electrochemical oxidative reaction respectively, which can inhibit the formation of coupled product **1** significantly. At the same time, two capture products were detected by HRMS. These results demonstrate that there may be a mechanism of radical processes in the transformation.

In order to further the details of the mechanism, we studied the electrochemical oxidation step of substrates by performing cyclic voltammetry (CV) experiments (Scheme 9). The oxidation peak of the substrate 3-phenyl-1*H*-pyrazole (2.04 V, red line) was observed to be smaller than the oxidation potential of the substrate 1-methyl-2-pyrrolidinone (2.39 V, blue line) Therefore, we conjecture that 3-phenyl-1*H*-pyrazole is the first substrate to be oxidized during the reaction. To confirm the oxidation of the two coupling substrates of the reaction, electron paramagnetic resonance (EPR) experiments were carried out to determine the radical intermediates (see Supporting Information). No radical signal was detected in the presence of 1-methyl-2-pyrrolidinone. These results proved that 3-phenyl-1*H*-pyrazole is the first substrate to be oxidized by the carbon anode under the electrolytic conditions.

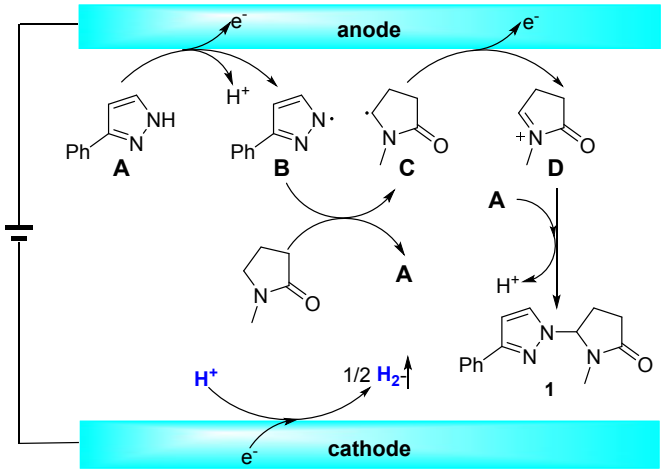
The selectivity of the reaction can be rationalized using DFT calculations.[16] As show in Scheme 10, the free energy barrier of hydrogen atom abstraction process between 3-



Scheme 9. Cyclic voltammetry of 3-phenyl-1*H*-pyrazole and 1-methyl-2-pyrrolidinone in MeCN (10 mL).



Scheme 10. Free energy barrier of the hydrogen atom abstraction at different site of 1-methylpyrrolidin-2-one using (a) 3-phenyl-1*H*-pyrazole N radical; (b) 1*H*-pyrazole-4-carbonitrile N radical. The energies are in kcal/mol.



Scheme 11. Possible mechanism.

phenyl-1*H*-pyrazole N radical, 1*H*-pyrazole-4-carbonitrile N radical and 1-methyl-2-pyrrolidinone were calculated. When 3-phenyl-1*H*-pyrazole was employed as substrate, the lowest two energy barrier occurred at the sites of C3-H and N-CH_2-H, which fitted well with the observed selectivity (Scheme 3, **1**). The same trend could be observed for the selectivity when 1*H*-pyrazole-4-carbonitrile was used as substrate (Scheme 4, **30**).

On the basis the above results and literature reports,[17] a possible mechanism was proposed as show in Scheme 11. First, 3-phenyl-1*H*-pyrazole with relatively low oxidation potential was oxidized at anode, followed by hydrogen transfer to form nitrogen radical B. Then, radical B and the 1-methyl-2-pyrrolidinone undergo an intermolecular hydrogen atom transfer to obtain radical C and 3-phenyl-1*H*-pyrazole. Next, radical B was oxidized on the anode and the iminium cation D generated, D was trapped by 3-phenyl-1*H*-pyrazole to give the product **1**. Meanwhile, concomitant cathodic reduction of proton-hydrogen would generate H_2 during the reaction process.

Conclusions

In summary, we have developed a method to activate azoles and lactams to corresponding C(sp^3)-H/N-H coupling products under mild electrochemistry conditions. This transformation accommodates pyrazoles with various substituents and other types of azoles. Various types of amides can be used in this process. Utilizing the flow cell, gram scale product with a good conversion yield provide the possibility of industrial application. Control experiments, cyclic voltammetry experiments, DFT

calculations and EPR experiments were conducted and a reasonable reaction mechanism were proposed. Further studies on the C(sp^3)-H compound electrochemistry synthetic applications is currently ongoing in our group.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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