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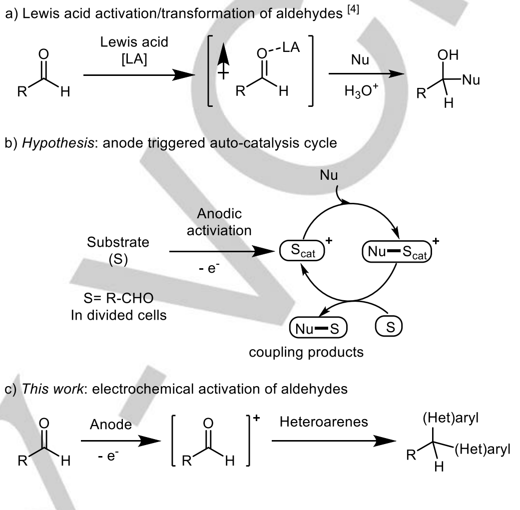
Anodically Triggered Aldehyde Cation Auto-Catalysis for Alkylation of Heteroarenes

Caiyan Liu,† Zihui Xiao,† Shuhua Wu, Yongli Shen, Kedong Yuan,* and Yi Ding

Abstract: Alkylation of heteroarenes using aldehydes is a direct approach to increase molecular complexity, which however often involves the usage of stochiometric oxidant, strong acid and high temperature. Herein, we report an energy-efficient electrochemical alkylation of heteroarenes using aldehydes under mild conditions without mediators. Interestingly, the graphite anode can trigger aldehyde cationic species, which act as the effective auto-catalysts to react with a range of heteroarene to produce the corresponding products with excellent regioselectivity and in high yields. Compared to the traditional electro-synthesis approaches, this electro-triggered reaction provides an electricity-saving and eco-friendly route to high value chemicals.

Alkyl-functionalized heteroarenes have gained increasing attentions in many applications.[1] For instance, bis/tris heteroaryl alkane derivatives have been extensively studied in drug, agrochemical discovery and functional materials.[2] Many alkyl precursors, including alkyl (pseudo)halides, aldehydes, alcohols and ethers were used as electrophiles to couple with heteroarenes by means of either transition metal catalysed reactions[3] or Lewis Acid/Bronsted acid promoted reactions,[4] while the use of expensive catalysts, stoichiometric oxidant, strong acid, high temperature conditions inevitably hampers their applications. It is thus desirable to develop an economically attractive and environmentally friendly alternative to existing approaches.

Direct electrochemical organic syntheses can utilize electrons as catalysts to activate substrates and achieve expected transformations without mediator under mild conditions, which avoid the consumption of catalysts with complicated procedures.[5] Generally, the interaction between the alkyl precursors and electrode surface would lead to the formation of alkyl radicals, wherein the control of reaction selectivity in the absence of mediators is a challenge[6] due to many alternative pathways such as radical-radical dimerization or radical over-oxidation to carbocation.[7] On the other hand, aldehydes are abundant and readily available reactants, which can be used for electrophilic alkylation reactions after the enhanced C=O polarization by Lewis acid (Scheme 1a).[4c, 4e-f] Notably, the electrochemical transformation of aldehydes through mediators (N-Heterocyclic carbene, NH_4I) would lead to the formation of esters, thioester and nitrile products.[8]



Scheme 1. Nucleophilic substitution of carbonyl compounds.

In our research, we have been seeking efficient electrochemical approaches that the substrate and electrode could interact directly to generate reactive species, which could be tamed by suitable coupling partners without extra mediators or hash conditions.[9] Interestingly, we observed the electrochemical acetalization of aldehydes and alcohols would continue even after a short period electrolysis time, indicating some active species were playing a catalytic role during the reaction. It was thus hypothesized to exist an electrochemically triggered catalytic cycle that could drive the reaction toward complete conversion. The proposed catalytic cycle depends on the anodically triggered cationic aldehyde species,[10] which make the reaction as an auto-catalysis process (Scheme 1b). Although an auto-catalysis reaction is commonly seen in the polymerization process after generation of the active species (e.g. cation, anion, radical),[11] it is scarcely reported in the fine chemical synthesis, possibly due to inhibition effect during the self-replicating active species in the reaction cycle.[12] Such an electrochemically triggered autocatalytic process would avoid the usage of expensive catalysts and simultaneously decrease energy consumption even without mediators.

Herein, we report an electrochemically triggered aldehyde cation auto-catalysis reaction, which offers a straight forward access to bis/tri(heteroaryl) substituted alkane derivatives from aldehydes and heteroarenes under mild conditions without mediators (Scheme 1c).

Initially, the electrochemical reaction of benzaldehyde **2a** with 2-methylfuran **1a** was optimized by screening different electrodes, supporting electrolytes, and the current intensity conditions (see Table S1 for more information). Interestingly, the electrochemical reaction performed in a beaker clearly demonstrated that

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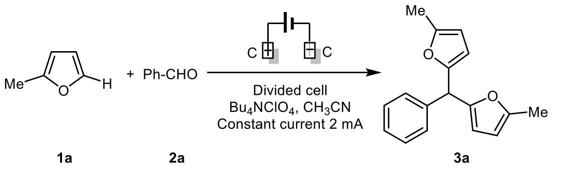
electricity could promote the reaction without extra mediators (Table 1, entries 1-2). When C(+)//C(-) were used as electrodes, the reaction carried out in 0.06 M Bu_4NClO_4/CH_3CN electrolyte under 2 mA constant current in an divided cell gave complete conversion of **2a**, producing the complete C2 alkylation product **3a** in 93% isolated yield (entry 3). Surprisingly, we found that continuous electricity supply was not essential to drive the reaction, indicating the anode triggered some active species with sufficient lifetime that played the catalytic role in the subsequent reaction cycle. Thus, the relationship between electrolysis time and the conversion of benzaldehyde **2a** was investigated in detail.

Table 1. Optimization for diheteroarylation of benzaldehyde[a].



Entry	Electro-excitation time/Reaction time	Solvent	Current (mA)	Conversion[b] (%)
1[c]	0 min/3 h	CH_3CN	0	0
2 [c]	3 h/3 h	CH_3CN	2	23
3	3 h/3 h	CH_3CN	2	100(93)
4	0 min/13 h	CH_3CN	0	0
5	5 min/13 h	CH_3CN	2	74
6	10 min/13 h	CH_3CN	2	74
7	20 min/13 h	CH_3CN	2	90
8	30 min/13 h	CH_3CN	2	100
9	5 min/2 h	CH_3CN	2	44
10	5 min/2 h	CH_3CN	1	40
11	5 min/2 h	CH_2Cl_2	2	36
12	5 min/2 h	DMF	2	11
13	5 min/2 h	DMSO	2	15
14	5 min/2 h	DCE	2	28

[a] Reaction conditions: **1a** (2.5 mmol), **2a** (1.0 mmol), Bu_4NClO_4 (0.06 mmol), CH_3CN (10 mL), graphite plates (1.0 cm^2) as anode and cathode, divided cell, electro-excitation current 2 mA, rt. under air. [b] Conversion were determined by GC using cyclohexylbenzene as the internal standard, isolated yield was given in parenthesis. [c] Reactions were performed in a beaker.

Noteworthily, no reactivity was observed without electricity passed in a divided cell (entry 4), while this reaction could be motivated by a short electrical pulse of 5 min, giving the tri(hetero)aryl methane product **3a** with complete C2 selectivity (entry 5). The reactivity was increased significantly with extending electro-excitation time (entries 5-8), which indicated that a vital intermediate was formed in the presence of current, which can autocatalyze the reaction from **1a** and **2a**. This intermediate was consumed gradually and finally depleted as current was cut off, resulting in uncompleted conversion. Control experiment showed that the constant current was not the key factors for the reaction, and no obvious reactivity difference was identified (entries 9-10). Organic solvents also affect the efficiency of auto-catalysis (entries 9, 11-14), and CH_3CN was proved to be the best solvent.

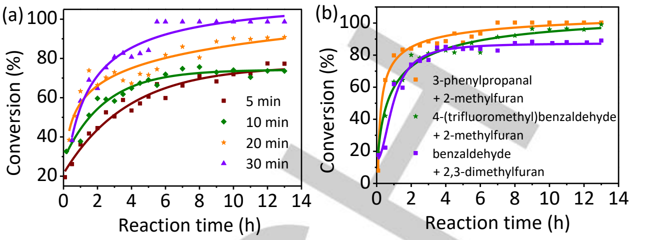
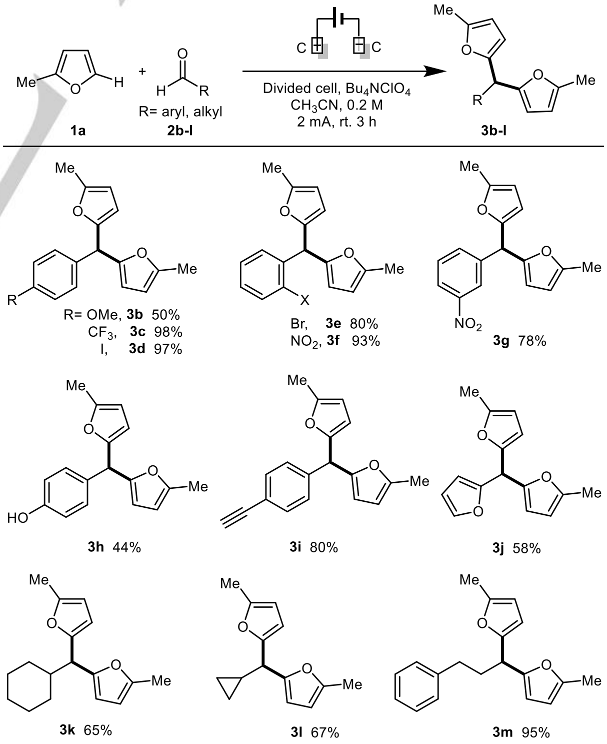


Figure 1. Influence of electrolysis time on reactivity for alkylation of **1a** with **2a** (a), profiles of reaction performance for various substrates after electrolysis of 5 min (b).

The influence of electrolysis time on reactivity for alkylation of **1a** with **2a** was further depicted in Fig. 1a, which clearly illustrated that the longer electro-excitation time was necessary to drive the complete conversion of **2a**. The same phenomenon was also observed from other aldehydes, as show in Fig. 2b. 3-phenylpropanal and 4-(trifluoromethyl)benzaldehyde were almost completely converted with **1a** after an electro-excitation of 5 min, leading to the formation of C2-alkylated furan products in high yields (>90%). The reaction between 2,3-dimethyl furan and **2a** was less reactive, while the trend toward product formation over time was not changed. These experimental results clearly demonstrated that the electrochemical reaction from aldehyde and heteroarenes was an auto-catalysis process, which was triggered by the anode and greatly reduced the electricity consumption.

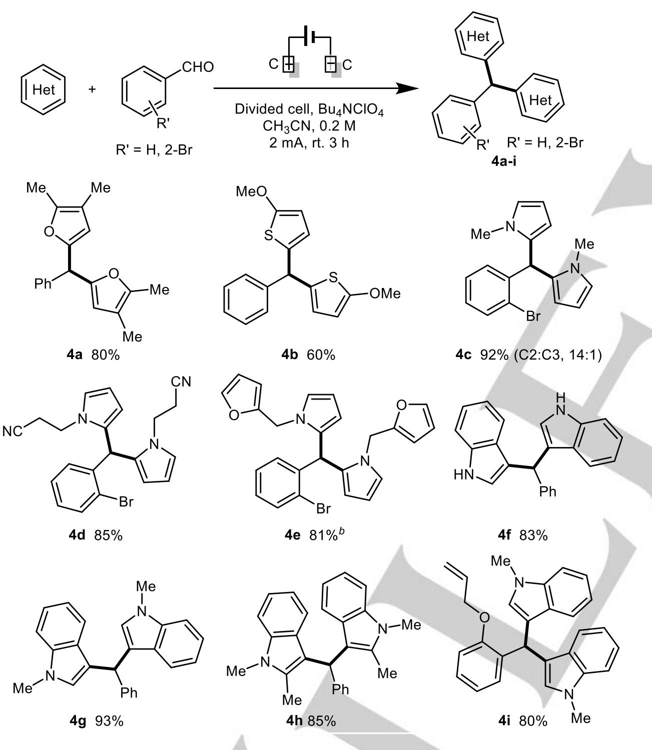
Table 2. Electrochemical benzylation of 2-methylfuran from aldehydes.[a]



[a] Reaction conditions: **1a** (2.5 mmol), aldehyde (1.0 mmol), Bu_4NClO_4 (0.06 mmol), CH_3CN (10 mL), graphite plates (1.0 cm^2) as anode and cathode, divided cell, electro-excitation current 2 mA, rt, 3 h, isolated yields.

To simplify the reaction scope study, we performed the electrochemical alkylation reaction of heteroarenes with aldehydes using continuous electrolysis time. Therefore, the electrochemical alkylation of **1a** from a variety of aldehydes (**2b-m**) were evaluated, as shown in Table 2. Both electron-rich and electron-deficient para/ortho-substituted benzaldehydes were accessed, while the electron withdrawing group substituted aldehydes exhibited higher reactivity than the electron rich ones. For example, the electrochemical reaction of 4-methoxybenzaldehyde (**2b**) with **1a** gave the corresponding product **3b** in 50% isolated yield, while trifluoromethyl or iodine substituted benzaldehyde underwent C2 selective alkylation of **1a**, giving **3c** and **3d** in high isolated yields of 98% and 97%, respectively. Ortho- and meta-substituted aldehydes were well tolerated to prepare **3e-g** in high efficiency. Sensitive but convertible functional groups, such as carbon-carbon triple bonds, -OH were also investigated, producing **3h-i** in acceptable yields with one step. A trifurylmethane (**3j**) was obtained from the reaction of 2-furylaldehyde and **1a** in moderate yield. In addition, aliphatic aldehydes were also efficiently converted under electrolysis conditions, generating 1,1-bis(heteroaryl) alkanes **3k-m** with moderate to good isolated yields.

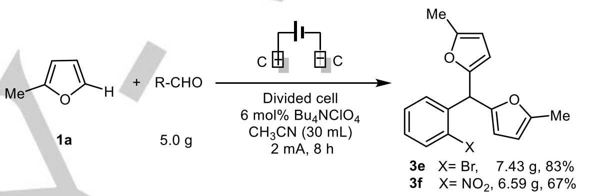
Table 3. Electrochemical alkylation of heteroarenes from aldehydes.[a]



[a] Reaction conditions: heteroarene (2.5 mmol), aldehyde (1.0 mmol), Bu_4NClO_4 (0.06 mmol), CH_3CN (10 mL), graphite plates (1 cm^2) as anode and cathode, divided cell, electro-excitation current 2 mA, rt, 3 h, isolated yields. [b] Yield of mixture of regioisomers, **4e** was isolated as a pure product.

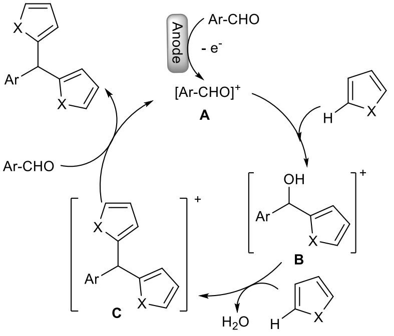
Subsequently, the reactivities between different heteroarenes and aldehydes under electrochemical conditions were investigated. As shown in Table 3, N-, O-, S-containing heteroarenes could be transformed into the corresponding alkylation products with high regioselectivity in moderate to high yields (**4a-i**) under simple electrolysis conditions. Notably, compared with N, O-containing heteroarenes, thiophene was less reactive, affording the product **4b** in moderate isolated yield, possibly due to the lower nucleophilicity of thiophene derivatives compared to the N-,O-containing heteroarenes.[13] In addition, the S-containing heteroarenes are easier to be oxidized on the surface of anode than the other N-, O-containing heteroarenes, making them less reactive under electrochemical conditions. Both C2 and C3 alkylation products were observed when the reaction was performed from 2-bromobenzaldehydes and pyrrole derivatives, and the C2 alkylation compounds **4c-e** were obtained as the major products with high regioselectivity. C3 alkylation of indoles were achieved with complete regioselectivity (**4f-i**), and even N-H free indole, allyl functional group on aldehyde were compatible with the electrochemical procedures, forming the corresponding products in 83%(**4f**), 80%(**4i**) isolated yields, respectively. Moreover, no obvious steric hindrance effect was observed when ortho-substituted benzaldehyde and indole were used as reactants, which would also be of help to obtain the pure isolated products compared to simple benzaldehyde **2a**.

To further investigate the practicality of the electrochemical reaction, two representative reactions were carried out on 5 gram-scale (from **2e**, **2f**) using a larger H-cell without redundant optimizations. As shown in Scheme 2, **3e** and **3f** were obtained in 83%, 67% isolated yield, respectively.



Scheme 2. Gram-scale electrochemical synthesis of **3e** and **3f**.

Though the exact mechanism for the electrochemical alkylation of heteroarenes is not clear, the anodic trigger cationic species clearly play a key role in the catalytic cycle, which is also verified by our previous DFT study of the interaction between aldehydes and anode.[9] Additionally, controlled linear sweep voltammetry (LSV) study of the reaction showed that the aldehydes were oxidized prior to heteroarenes, which enhanced its reactivity toward nucleophilic heteroarenes. Notably, the significant inhibition effects from radical scavengers (TEMPO, BHT, Scheme S1) for the formation of **3a** indicated that the electrochemical reaction possibly proceeded through a single electron transfer (SET) mechanism. Based on these results, an anodically triggered auto-catalysis cycle[14] was proposed to understand the bis/tri heteroaryl alkanes formation. Initially, the interaction between aldehydes and anode would lead to the formation of the aldehyde cation specie **A**, which is highly reactive towards nucleophiles due to the enhanced C=O polarization. **A** would readily reacts with heteroarenes to generate a positively charged alcohol intermediate **B** under the given conditions. The cationic alcohol intermediate will go through a dehydration process and react with another heteroarene to give a cationic tri(heteroaryl) alkane **C**,[15] accompanied by a dehydration process. The charge exchange between aldehydes and **C** leads to the formation of tri(heteroaryl) alkane product and the self-replication of **A**. Thus, the reaction would be an anodically triggered auto-catalysis process rather than a conventional electrochemical synthesis. The continuous electrical pulse would be useful to release the reactive cation species into the reaction solution, and drive the reaction toward complete conversion.



Scheme 3. Proposed auto-catalysis cycle.

In summary, we developed an electrochemically triggered auto-catalysis process for alkylation of heteroarenes under mild conditions. Aromatic, aliphatic aldehydes, bearing with some sensitive functional groups, such as alkyne, alkene, C-I, -OH, were tolerated in this method, generating the complexed bis/tri heteroaryl alkane derivatives in good yields and regioselectivity. Such a simple anode triggered auto-catalysis process decrease the synthetic cost and the energy utilization, making it an attractive approach for aldehydes transformations.

Experimental Section

Representative procedure (Table 1, entry 3): A Nafion®117 membrane separated H-type electrolysis cell (15 mL) was equipped with a pair of graphite electrodes (1.0 cm^2), which were connected to an electrochemical workstation regulated power supply. CH_3CN (10 mL) and BuN_4ClO_4 (0.06 mmol) were added to each chamber. To the anodic chamber, 2-methyl furan **1a** (2.5 mmol, 205.1 mg) and benzaldehyde **2a** (1.0 mmol, 106.1 mg) were added. The mixture was electrolyzed under constant current (2 mA) at room temperature with magnetic stirring for 3 hours under air. After the reaction completion, cyclohexylbenzene (30 μL) was added to the reaction solution as internal standard and a partial solution was filtered through a short silica gel column for GC and GC-MS analysis. The combined solution was concentrated under reduced pressure and purified by column chromatography on silica gel (petroleum ether/ethyl acetate) to afford **3a** as a pale yellow oil. **3a**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38–7.34 (m, 2H), 7.32–7.25 (m, 3H), 5.92 (dd, *J* =7.0, 3.1 Hz, 4H), 5.38 (s, 1H), 2.29 (s, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 152.8, 151.4, 139.9, 128.4, 128.3, 126.9, 108.1, 106.0, 45.1, 13.6. IR (KBr) (ν_{max}, cm^{-1}): 3117, 3069, 3036, 2923, 1619, 1562, 1501, 1453, 1388, 1218, 1027, 954, 780, 731, 707, 626.

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Keywords: Electrochemical • Cation species • Auto-catalysis • Aldehydes • Heteroarenes

[1] a) N. Koumura, Z. S. Wang, S. Mori, M. Miyashita, E. Suzuki, K. Hara, *J. Am. Chem. Soc.* **2006**, *128*, 14256-14257; b) Y. S. Won, Y. S. Yang, J. H. Kim, J. H. Ryu, K. K. Kim, S. S. Park, *Energy Fuels* **2010**, *24*, 3676-3681; c) S. Schott, E. R. McNellis, C. B. Nielsen, H. Y. Chen, S. Watanabe, H. Tanaka, L. McCulloch, K. Takimiya, J. Sinova, H. Sirringhaus, *Nature Commun.* **2017**, *8*, 15200.

[2] a) M. Shiri, M. A. Zolfigol, H. G. Kruger, Z. Tanbakouchian, *Chem. Rev.* **2009**, *110*, 2250-2293; b) R. Ragno, S. Simeoni, S. Castellano, C. Vicidomini, A. Mai, A. Caroli, A. Tramontano, C. Bonaccini, P. Trojer, I. Bauer, G. Brosch, G. Sbardella, *J. Med. Chem.* **2007**, *50*, 1241-1253; c) S. Bodendiek, C. Rubinos, M. P. Trelles, D. Jenkins, N. Coleman, H. Wulff, M. Srinivas, *Front. Pharmacol.* **2012**, *3*, 106; d) J. Jaratjaroonphong, S. Tuengpanya, R. Saeeng, S. Udompong, K. Srisook, *Eur. J. Med. Chem.* **2014**, *83*, 561-568; e) A. M. Montagut, E. Gálvez, A. Shafir, R. M. Sebastián, A. Vallribera, *Chem. Eur. J.* **2017**, *23*, 3810-3814.

[3] Transition metal catalysed alkylation of heteroarenes, see: a) K. Mertins, I. Iovel, J. Kischel, A. Zapf, M. Beller, *Angew. Chem. Int. Ed.* **2005**, *44*, 238-242; b) N. Vijay, K. G. Abhilash, N. Vidya. *Org. Lett.* **2005**, *7*, 5857-5859; c) X. Wu, J. W. T. See, K. Xu, H. Hirao, J. Roger, J. C. Hierso, J. Zhou, *Angew. Chem. Int. Ed.* **2014**, *53*, 13573-13577; d) X. Liu, C. C. Hsiao, I. Kalvet, M. Leiendecker, L. Guo, F. Schoenebeck, M. Rueping, *Angew. Chem. Int. Ed.* **2016**, *55*, 6093-6098. e) S. Podder, J. Choudhury, U. K. Roy, S. Roy, *J. Org. Chem.* **2007**, *72*, 3100-3103;

[4] Lewis/Bronsted acid promoted alkylation of heteroarenes, see: a) M. H. Zhuo, Y. J. Jiang, Y. S. Fan, Y. Gao, S. Liu, S. Zhang, *Org. Lett.* **2014**, *16*, 1096-1099. b) R. J. Tang, L. Kang, L. Yang, *Adv. Synth. Catal.* **2015**, *357*, 2055-2060; c) Z. X. Li, X. P. Liu, Y. Y. Yin, Y. J. Li, J. W. Wang, X. J. Yu, *ChemistrySelect*, **2018**, *3*, 599-601; d) M. Rueping, B. J. Nachtsheim, *Beilstein J. Org. Chem.* **2010**, *6*, 6; e) J. Chen, M. Wan, J. Hua, Y. Sun, Z. Lv, W. Li, L. Liu, *Org. Biomol. Chem.* **2015**, *13*, 11561-11566; f) S. Paul, J. Guin, *Chem. Eur. J.* **2015**, *21*, 17618-17622.

[5] a) R. Francke, R. D. Little, *Chem. Soc. Rev.* **2014**, *43*, 2492-2521; b) M. Yan, Y. Kawamata, P. S. Baran, *Chem. Rev.* **2017**, *117*, 13230-13319; c) E. J. Horn, B. R. Rosen, P. S. Baran, *ACS Cent. Sci.* **2016**, *2*, 302-308; d) Q. L. Yang, P. Fang, T. S. Mei, *Chin. J. Chem.* **2018**, *36*, 338-352; e) S. R. Waldvogel, S. Lips, M. Selt, B. Riehl, C. J. Kampf, *Chem. Rev.* **2018**, *118*, 6706-6765; f) J. Yoshida, K. Kataoka, R. Horcajada, A. Nagaki, *Chem. Rev.* **2008**, *108*, 2265-2299; g) S. Tang, Y. Liu, A. Lei, *Chem* **2018**, *4*, 27-45; h) M. D. Kärkäs, *Chem. Soc. Rev.* **2018**, *47*, 5786-5865; i) Y. Jiang, K. Xu, C. Zeng, *Chem. Rev.* **2018**, *118*, 4485-4540.

[6] a) R. P. Kreh, R. M. Spotnitz, J. T. Lundquist, *J. Org. Chem.* **1989**, *54*, 1526-1531; b) F. Barba, M. N. Elinson, J. Escudero, S. K. Feducovich, *Tetrahedron* **1997**, *53*, 4427-4436; c) Y. Kawamata, M. Yan, Z. Liu, D. H. Bao, J. Chen, J. T. Starr, P. S. Baran, *J. Am. Chem. Soc.* **2017**, *139*, 7448-7451.

[7] H. Yan, Z. W. Hou, H. C. Xu, *Angew. Chem. Int. Ed.* **2019**, *58*, 4592-4595.

[8] a) E. E. Finney, K. A. Ogawa, A. J. Boydston, *J. Am. Chem. Soc.* **2012**, *134*, 1237412377; b) R. A. Green, D. Pletcher, S. G. Leach, R. C. D. Brown, *Org. Lett.* **2015**, *17*, 3290-3293; c) K. A. Ogawa, A. J. Boydston, *Org. Lett.* **2014**, *16*, 1928-1931; d) R. A. Green, D. Pletcher, S. G. Leach, R. C. D. Brown, *Org. Lett.* **2016**, *18*, 1198-1201; e) Q. Qu, X. Gao, J. Gao, G. A. Yuan, *Sci. China: Chem.* **2015**, *58*, 747-750.

[9] C. Liu, Y. Shen, Z. Xiao, H. Yang, X. Han, K. Yuan, Y. Ding, *Green Chem.* **2019**, *21*, 4030-4034.

[10] a) R. Akaba, M. Kamata, Y. Kuriyama, H. Sakuragi, K. Tokumaru, *Chem. Lett.* **1993**, *22*, 1157-1160; b) J. C. Choe, C. J. Moon, M. Y. Choi, M. H. Kim, *RSC Adv.* **2017**, *7*, 47689-47694.

[11] a) Z. Liu, B. Wu, Y. Jiang, J. Lei, C. Zhou, J. Zhang, J. Wang, Polymer, **2018**, *143*, 129-136; b) C. G. Wang, X. Y. Oh, X. Liu, A. Goto, *Macromolecules* **2019**, *52*, 2712-2718; c) P. Scrimin, L. J. Prins, *Chem. Soc. Rev.* **2011**, *40*, 4488-4505.

[12] S. N. Semenov, L. J. Kraft, A. Ainla, M. Zhao, M. Baghbanzadeh, V. E. Campbell, K. Kang, J. M. Fox, G. M. Whitesides, *Nature*, **2016**, *537*, 656.

[13] S. Pratihar, S. Roy, *J. Org. Chem.* **2010**, *75*, 4957-4963; b) S. Pratihar, Org. Biomol. Chem. 2016, 14, 2854-2865.

[14] A. J. Bissette, S. P. Fletcher, *Angew. Chem. Int. Ed.* **2013**, *52*, 12800-12826.

[15] a) S. Dhiman, S. S. V. Ramasastry, *Org. Biomol. Chem.* **2013,** *11*, 8030-8035; b) F. Wang, Z. Liu, G. Weng, *Commun. Chem.* **2018**, *1*, 51.

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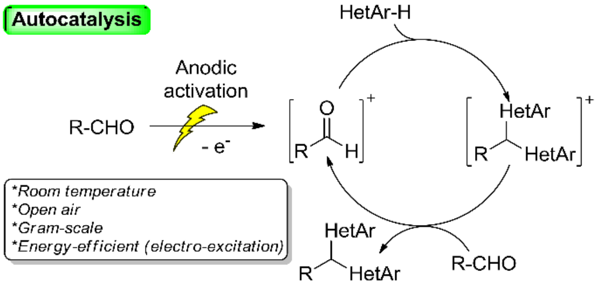

A pulse of electrical current on anode triggered aldehyde cation species can auto-catalyze the alkylation of heteroarenes to produce bis/tris heteroaryl alkane derivatives. Aromatic, aliphatic aldehydes are well compatible with the auto-catalysis process, and react with N, O, S-containing heteroarenes to form valuable products with excellent regioselectivity in high yields. The simple but efficient electrochemical reaction exhibits excellent functional-group tolerance (alkene, alkyne, -OH, -I) under the neutral and mild reaction conditions, providing a practical synthetic alternative to existing approaches.