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Late-stage azolation of benzylic C–H bonds enabled by electrooxidation

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The installation of azoles *via* C–H/N–H cross-coupling is significantly underdeveloped, particularly in benzylic C–H azolation due to the requirement for external chemical oxidants and the challenge in controlling the site- and chemo-selectivity. Herein, a late-stage azolation of benzylic C–H bonds enabled by electrooxidation is described, which proceeds in an undivided cell under mild, catalyst- and chemical-oxidant-free reaction conditions. The strategy empowers the C–H azolation on primary, secondary, and even challenging tertiary benzylic positions selectively. The remarkable synthetic utility of our approach is highlighted by its easy scalability without overoxidation of products and ample scope with valuable functional groups. The approach can be directly used to install benzyl and azole motifs on highly functionalized drug molecules.

electrooxidation, azolation, external oxidant-free, cross-dehydrogenative coupling, late-stage functionalization

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1 Introduction

Azoles are important structural motifs that are featured in numerous natural products and pharmaceutical agents, such as astemizole, letrozole, clotrimazole, sartan as well as triptan analogues [1]. Thus, facile installation of azole skeleton remains critical goal for organic synthesis. In this context, the benzyl azolation for C–N bond formation has attracted intensive interest and various elegant methodologies have been established. For example, the transition metal-catalyzed decarboxylative benzylic amination was reported by using oxidative Cu catalysis with excess MnO_2 (Scheme 1(a)) [2]. In recent years, light-promoted benzyl azolation has also been developed, however, involving dissociation of C–LG (LG=leaving group) [3], N–H insertion with metal or base catalysts [4], and hydrogen atom transfer (HAT) promoted by dual metal and photoredox catalysis (Scheme 1(b)) [5]. Although some advances have been achieved by atom and step-economical ways through benzylic C(sp^3)–H/N–H cross-coupling with protected amines [6], the azoles, especially tetrazolium, are seldom explored by these strategies [7]. In addition, some critical common limitations still exist for the present benzylic amination, such as poor site-selectivity, the use of metal catalysts and excess external oxidants [8]. Thus, it is highly desirable and challenging, to develop a catalyst-, and oxidant-free direct selective benzyl C–H azolation in a user- and en-

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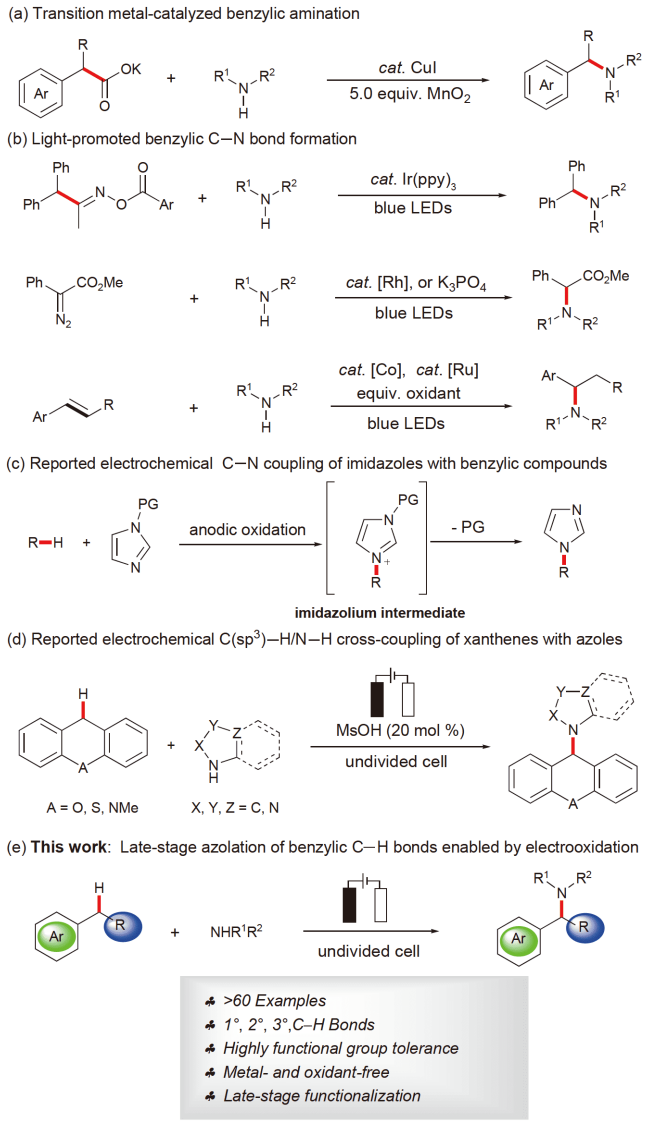


Scheme 1 Traditional and electrochemical azolation of benzylic C–H bonds (color online).

vironmentally-friendly manner features.

Organic electrosynthesis [9], employing protons and electrons as redox reagents, has been established as an increasingly powerful and attractive tool for dehydrogenative cross-coupling [10]. Despite the recent advances by electrochemical C(sp^2)–H aminations [11], the azolation of C(sp^3)–H bonds is still rare [12]. However, electrochemical benzylic C(sp^3)–H functionalization has been suggested to be challenging as the crucial choice of solution due to its easy overoxidation to ketone by the attack of protic solvent [13]. Moreover, the electrooxidative benzylic C–H amination is also deemed to be difficult, because the close potentials between the substrate and product result in overoxidation of the amine product. Yoshida and coworkers [14] developed a method by the formation of electrochemically inactive imidazolium ions as initial products, avoiding overoxidation (Scheme 1(c)). Meanwhile, the benzylic amination has been proven to be much less successful than the similar alkoxylation of benzylic C–H bonds by photochemical oxidatively dehydrogenative reactions [15]. In addition, oxidative C–H functionalizations *via* electron transfer mechanisms were commonly limited to the secondary benzylic positions other than the primary and tertiary sites due to the unstable carbocation or stereoelectronic effects [15a,16]. Recently, a highly efficient electrochemical C(sp^3)–H/N–H cross-coupling of xanthenes with azoles under acidic condition was reported by Li and coworkers [12d], accessing xanthen-9-azoles (Scheme 1(d)).

With our program on electrochemical functionalization [11a,17], we herein report an unprecedented late-stage azolation of benzylic C–H bonds *via* electrooxidative C–H/N–H cross-coupling (Scheme 1(e)) [18]. Notable features of our general strategy include (1) exceedingly mild and environmental-friendly reaction conditions in a metal- and chemical oxidant-free fashion [19], (2) robust C–H azolation on primary, secondary, as well as more challenging tertiary benzylic positions, (3) an unparalleled broad substrate scope with significant functional group tolerance, and (4) setting the stage for versatile syntheses and modifications of complex bioactive compounds and marketed drugs.

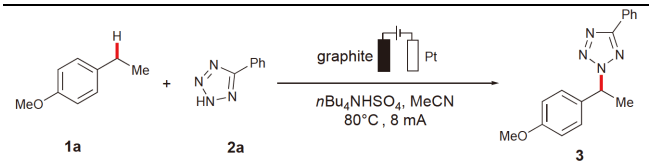
2 Experimental

General procedure for electrochemical reactions. In an undivided cell (15 mL) equipped with a stirring bar, a mixture of substrates **1** (1.5 mmol), **2** (0.5 mmol), nBu$_4$NHSO$_4$ (0.5 mmol, 170 mg) and MeCN (5.0 mL) were added. The cell was equipped with graphite plate (1.0 cm×1.0 cm×0.2 cm) as the anode and platinum plate (1.0 cm×1.0 cm×0.01 cm) as the cathode connected to an AXIOMET AX-3003P DC regulated power supply. The reaction mixture was stirred and electrolyzed at a constant current of 8 mA at 80 °C by heating mantle for 12 h. Upon completion, the solvent was removed directly under reduced pressure to afford the crude product, which was further purified by flash column chromatography to afford the desired products **3–51** and **55–64**.

3 Results and discussion

To start our investigations, we probed a variety of different electrolysis conditions employing an undivided cell equipped with a graphite anode and a platinum cathode towards the envisioned benzylic C–H amination of azoles (Table 1 and Table S1, Supporting Information online). The optimal results afforded the desired product **3** in 83% yield when substrate **1a** and **2a** were directly electrolyzed by using a

Table 1 Optimization of reaction conditions[a)]



Entry	Deviation from standard conditions	Yield (%)[b)]
1	none	83
2	nBu$_4$NBF$_4$ instead of nBu$_4$NHSO$_4$	61
3	Et$_4$NClO$_4$ instead of nBu$_4$NHSO$_4$	75
4	MeCN/H$_2$O (9:1) instead of MeCN	56
5	MeOH instead of MeCN	0[c)]
6	23 °C instead of 80 °C	60
7	10 mol% of Cp$_2$Fe was added	39
8	10 mol% of 1,4-benzoquinone was added	0
9	Pt as anode	70
10	no electricity	0

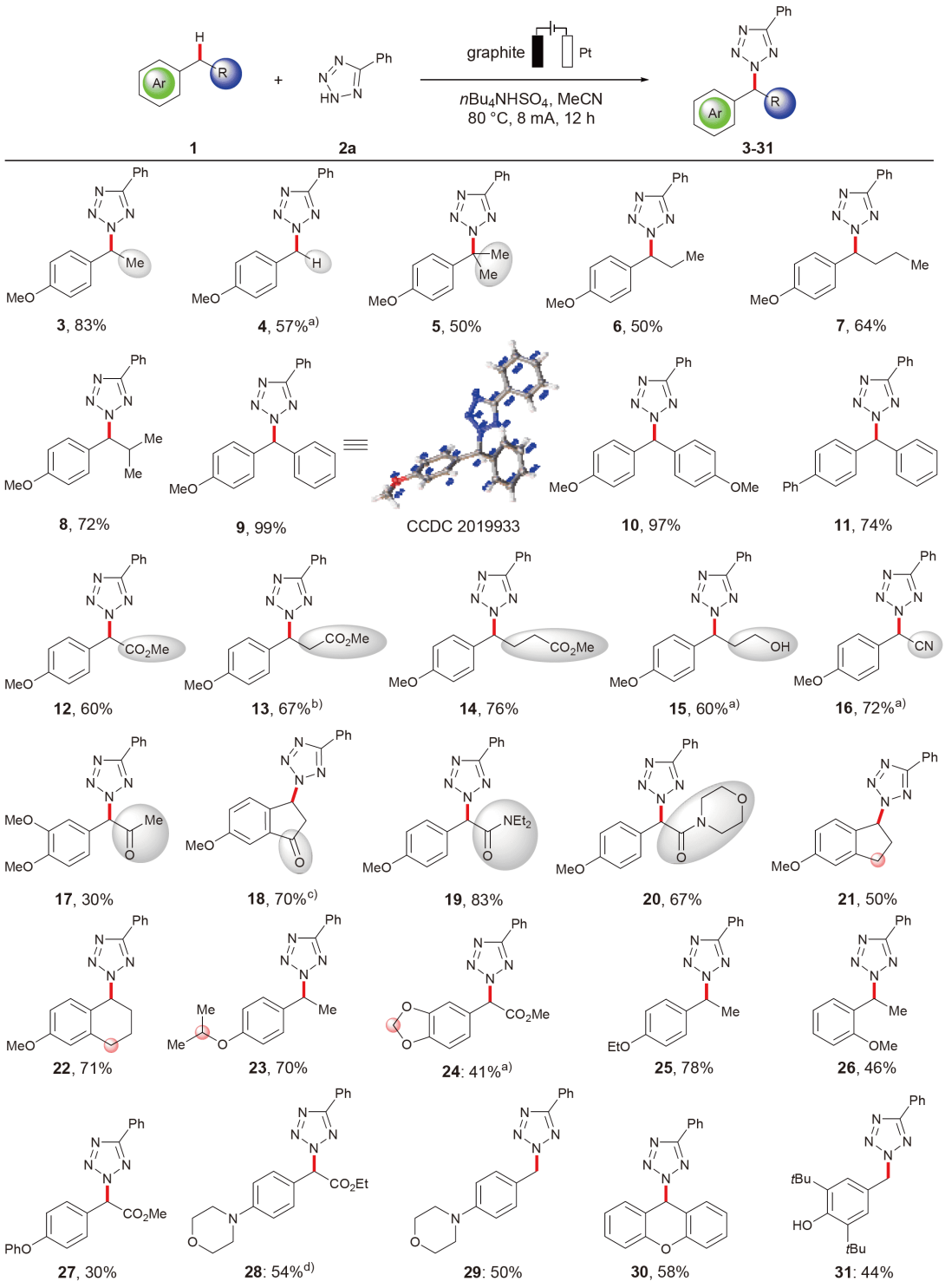
a) Reaction conditions: undivided cell, graphite anode (1.0 cm×1.0 cm×0.2 cm), Pt cathode (1.0 cm×1.0 cm×0.01 cm), **1a** (1.5 mmol), **2a** (0.5 mmol), nBu$_4$NHSO$_4$ (0.5 mmol), MeCN (5.0 mL), constant current= 8 mA, 12 h (7.2 F mol^{-1}), 80 °C. b) Yields of isolated products. c) 4′-methoxyacetophenone was isolated.

constant current of 8 mA in an electrolyte solution of nBu$_4$NHSO$_4$ in MeCN, at 80 °C, under atmospheric conditions for 12 h without additional catalysts or bases (Table 1, entry 1). The use of an alternative electrolyte, such as nBu$_4$NPF$_6$ and Et$_4$NClO$_4$, showed a moderate to good efficacy (entries 2–3). The choice of solvent was found to be essential for the reaction to achieve the optimal yield. The use of a mixed solvent of MeCN/H$_2$O (9:1) resulted in a decreased yield of 56% (entry 4), as well as the solvent system of DCE/HFIP developed by Xu (Table S1) [18]. Moreover, the replacement of MeCN with MeOH completely shut down the azolation reaction, occurring with the side-product formation of 4′-methoxyacetophenone (entry 5). Reducing the temperature to 23 °C exhibited less effective (entry 6). In addition, performing the transformation *via* indirect electrolysis manner by the addition of redox mediators, such as Cp$_2$Fe or 1,4-benzoquinone, resulted in an extremely low conversion (entries 7–8). Notably, a 70% yield of **3** was still obtained when using a Pt anode (entry 9). Further control experiments verified the essential role of the external electricity (entry 10).

After establishing the optimal reaction conditions for the electrooxidative azolation, we next explored its versatility of a set of representive benzylic substrate **1** with tetrazole **2a** (Scheme 2). The electrolysis reaction exhibited good compatibility with secondary benzylic positions, primary C–H bonds as well as tertiary sites to afford desired products (**3**–**5**), overcoming competitive overoxidation problems in the photoredox catalytic system. This result allows chemists to reliably and selectively perform the late-stage functionalization of specific benzylic C–H bonds in more complicated compounds. The reaction also exhibited acceptable tolerance of alkylbenzenes carrying a longer side chain (**6**–**8**). Gratifyingly, the azolation of different electronic diphenylmethanes gave corresponding products in excellent yields (**9**–**11**). The structure of product **9**, benzylated on N2-site of tetrazole, was unambiguously confirmed by single-crystal X-ray diffraction studies. Thereafter, we investigated the effect of substituents on alkylbenzene. Thus, the robust nature of the electrooxidative azolation was reflected by fully tolerating a wealth of valuable functionalities, including sensitive alcohols (**15**), esters (**12**–**14**), aliphatic nitriles (**16**), ketones (**17** and **18**), amides (**19** and **20**), and acetals (**24**), which could serve as a handle for future late-stage modifications. It is noteworthy that the reaction displayed a highly site selectivity on *p*-alkoxy-activated benzylic positions (**21**–**24**). To our delight, the strategy for the direct electrochemical benzylic C–H amination of azoles proved to be suitable for the substrates with various alkoxyl (**23**–**25**), *ortho*-methoxyl (**26**), phenoxyl (**27**) and morpholine- (**28** and **29**) substituted benzenes as well as xanthenes (**30**). However, the electron poor aromatics were not suitable substrates for the transformation. Notably, the desired product was obtained by directly employing a radical scavenger BHT (2,4-di-*tert*-butyl-4-methylphenol) as a benzylic reactant (**31**).

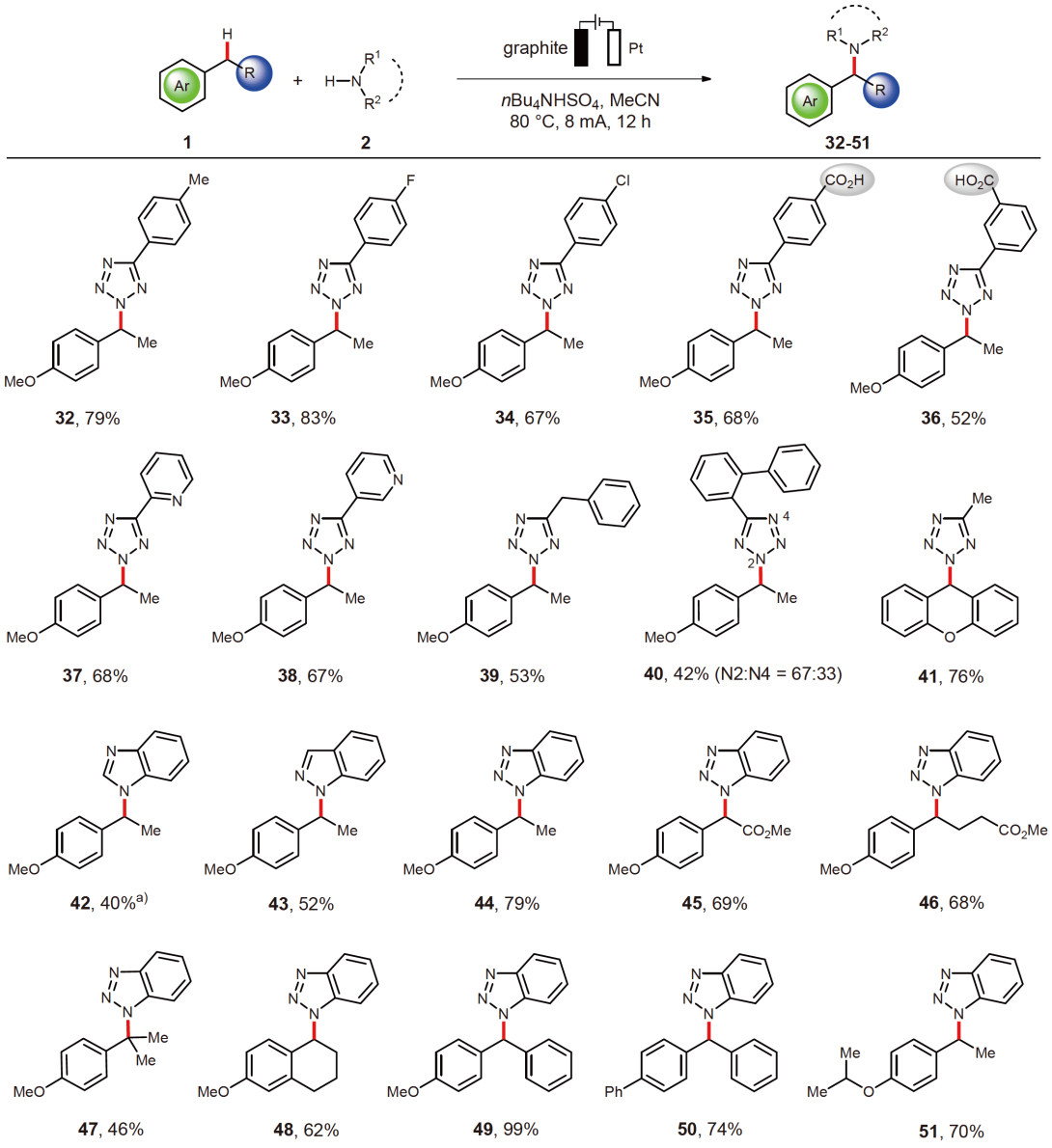
Furthermore, encouraged by these exciting results, the scope of the reaction with respect to azole nucleophiles in the electrochemical amination approach was also investigated (Scheme 3). Various substitutents on the 5-phenyl-tetrazoles, including methyl (**32**), fluoro (**33**), chloro (**34**), carboxyl (**35** and **36**) at the *para*- or *meta*-position of the phenyl ring, were found to be fully tolerated by the optimized electrooxidation. The practical utility of our approach was further illustrated by successfully performing the desired azolation with *N*-heterocycle and benzyl substituted tetrazoles in good yields (**37**–**39**). Remarkably, the biphenyl substituted tetrazoles resulted in a mixture product of benzylation on N2 and N4 positions, which could be isolated by column chromatography, probably due to the steric hinderance or electronic properties (**40**). In addition, it is particularly noteworthy that other nucleophiles such as simple tetrazoles (**41**), imidazoles (**42**), indazoles (**43**) and triazoles (**44**–**51**), were well suited to the robust metal- and oxidant-free electrooxidation protocol to generate a series of products of benzylic C–H amination. These observations mirror the unique potential for applications in the late-stage azolation in the building of diversity decorated bioactive compounds.

The practical utility of our benzylic C–H azolation approach was further demonstrated by the gram-scale synthesis of **3**, in which larger electrodes and higher constant current (160 mA) were employed to ensure the conversion in 12 h (Scheme 4).

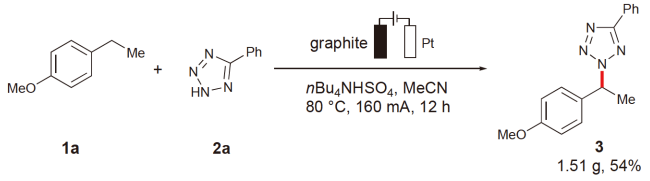


Scheme 2 Scope of benzyl substrates. Reaction conditions: undivided cell, graphite anode, Pt cathode, **1** (1.5 mmol), **2a** (0.5 mmol), nBu$_4$NHSO$_4$ (0.5 mmol), MeCN (5.0 mL), constant current = 8 mA, 12 h, 80 °C. Isolated yields were given. a) **1** (2.0 mmol), 13 h. b) **1** (2.0 mmol), 15 h. c) **1** (2.0 mmol), 17 h. d) **1** (2.0 mmol), 19 h (color online).

In light of the outstanding versatility of the electrochemically benzylic C–H azolation methodology, we were intrigued to delineate its mode of action. To this end, the intermolecular competition experiment between **1a** and BHT led to a solo product of azolated BHT adduct in 44% yield (Scheme 5(a)), which is consistent with the observation in latter cyclic voltammetric analysis (Scheme 5(d)). In addition, 4-allyl-1,2-dimethoxybenzene (**52**) was employed for the electrooxidative C–H azolation under standard conditions, contributing to the rearrangement of allyl with **53** and



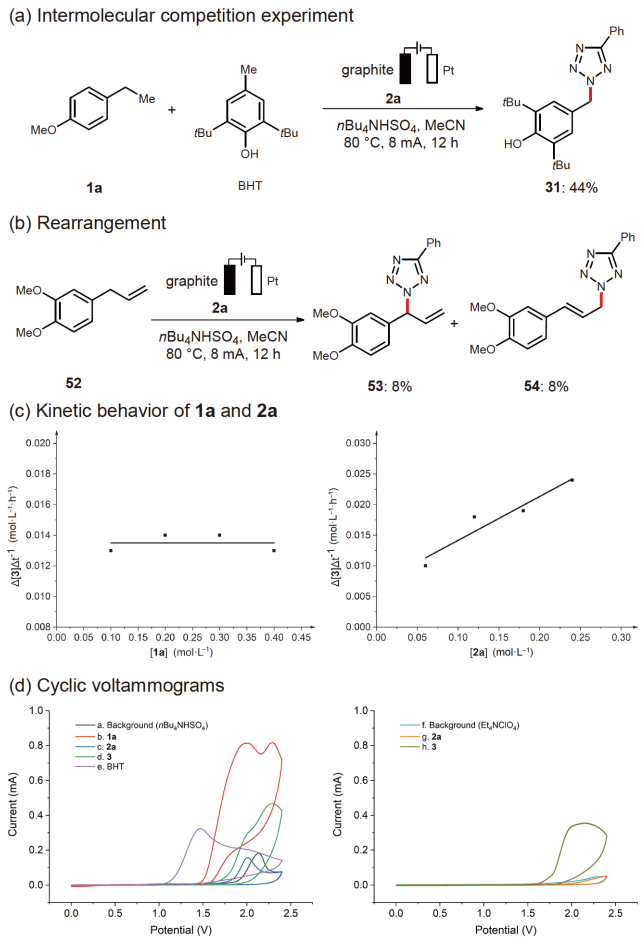
Scheme 3 Scope of azoles. Reaction conditions: undivided cell, graphite anode, Pt cathode, **1** (1.5 mmol), **2** (0.5 mmol), nBu$_4$NHSO$_4$ (0.5 mmol), MeCN (5.0 mL), constant current = 8 mA, 12 h, 80 °C. Isolated yields were given. a) DCE (4 mL), HFIP (2 mL), 50 °C (color online).



Scheme 4 Gram-scale reaction. Reaction conditions: graphite anode (3.0 cm×3.0 cm×0.6 cm), Pt cathode (3.0 cm×3.0 cm×0.01 cm), **1a** (30.0 mmol), **2a** (10.0 mmol), nBu$_4$NHSO$_4$ (10.0 mmol), MeCN (100 mL), constant current = 160 mA, 12 h (color online).

54 formation (Scheme 5(b)). These mechanistic observations indicated that the reaction probably involved a radical or carbocation process. Besides, preliminary kinetic studies were also carried out to determine the order of reaction components for the electrochemical C–H azolation. As depicted in Scheme 5(c), the initial reaction rate was independent of the concentration of **1a**, demonstrating a zero-order dependence on benzylic substrate **1a**, which indicated the reaction rate was limited by specific electrode area and mass transport [20]. Conversely, a first-order on **2a** was confirmed, elucidating the concentration of tetrazole was critical for this transformation.

To further explore the mechanism, cyclic voltammetric analysis revealed key mechanistic insights into the electrochemical amination (Scheme 5(d)). The voltammograms disclosed that the anodic oxidation of benzylic substrate **1a** occurred at a potential of ca. 1.98 V (*vs.* Ag/AgCl), well below the oxidation potential of **2a** (>2.00 V *vs.* Ag/AgCl, Scheme 5(d), right) [21] and **3** (2.14 V *vs.* Ag/AgCl), suggesting that **1a** was more easily oxidized at the anode than **2a**

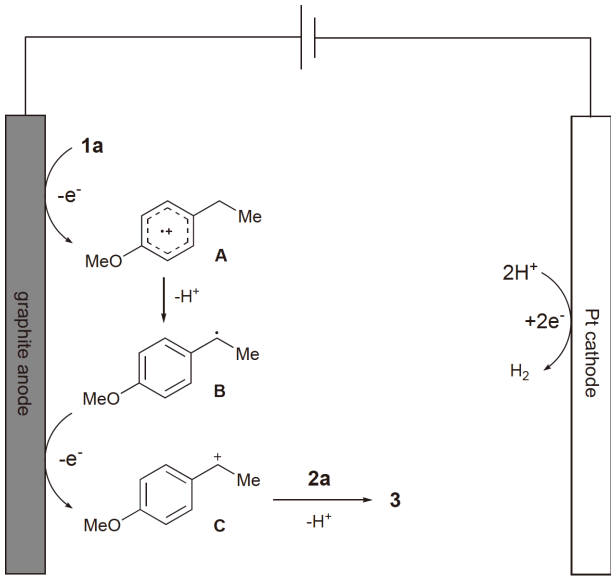


Scheme 5 (a) Intermolecular competition experiment. (b) Rearrangement. (c) Kinetic behavior of **1a** and **2a**. (d) Cyclic voltammograms. Conditions: a glassy carbon working electrode, a Ag/AgCl (3 M KCl) reference electrode, and a platinum wire counter electrode, 0.01 M analyte in 0.1 M nBu$_4$NHSO$_4$ (left) or Et$_4$NClO$_4$ (right) dissolved in MeCN, 100 mV/s scan rate (color online).

and **3**.

Based on our mechanistic studies, a plausible mechanism for the electrochemical C–H functionalization is proposed using **1a** as a model substrate asdepicted in Scheme 6. The reaction is first initiated by the anodic oxidation of **1a**, leading to the generation of radical cation **A**, which loses a benzylic proton to furnish carbon radical **B**. Further single-electron oxidation of **B** to carbocation **C**, followed by nucleophilic trapping, affords the final azolation product **3**. Meanwhile, protons undergo cathodic reduction to generate H_2, which obviates the demand for sacrificial chemical oxidants.

Considering the remarkable advantage of high site selectivity and significant functional group compatibility, the versatile electrochemical benzylic C–H azolation finally set the stage for the efficient late-stage diversification of highly complex bioactive molecules (Scheme 7). The electrooxidative aminations were performed smoothly on the benzylic C–H bonds of hydrocarbon substrates derived from

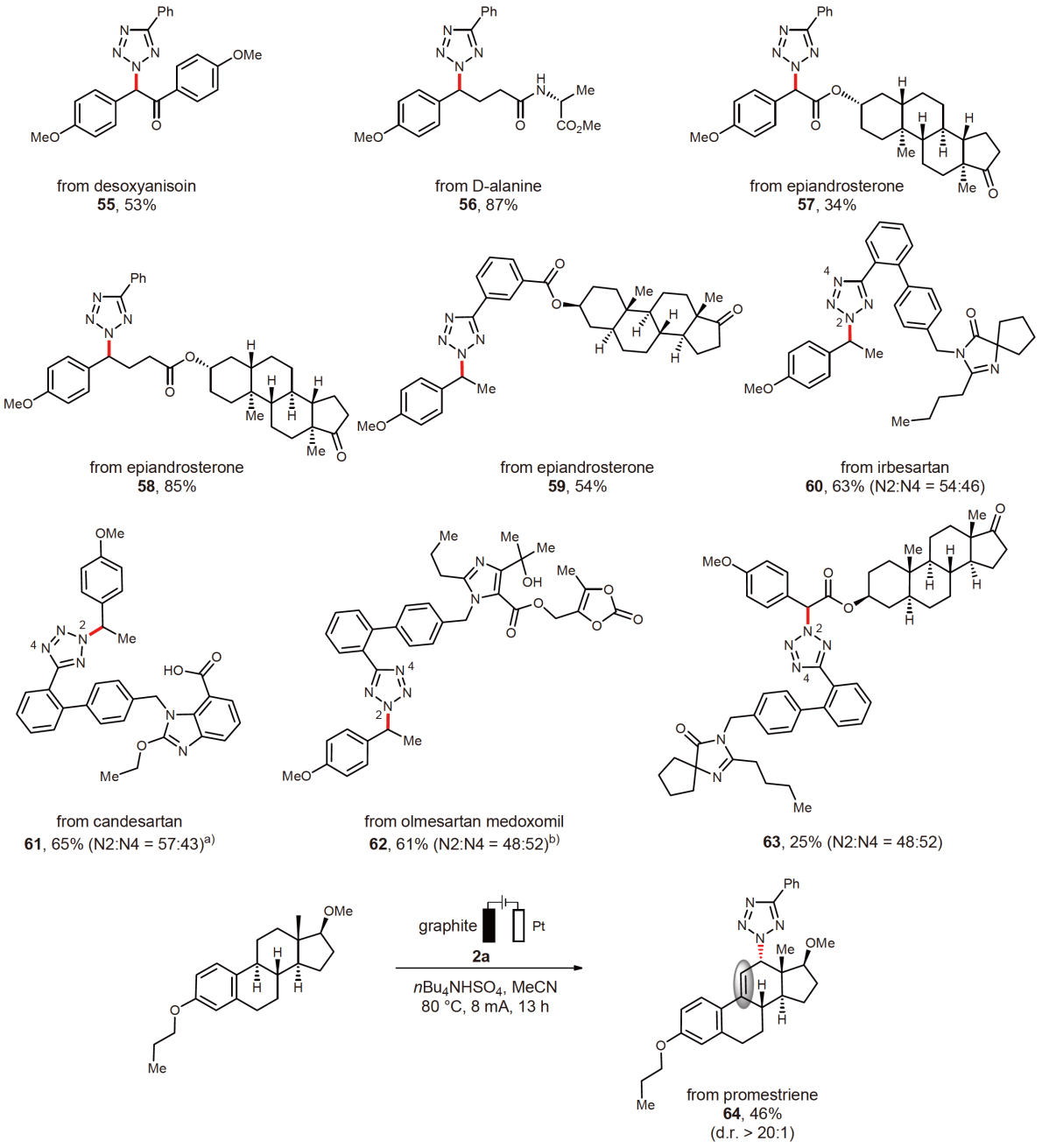


Scheme 6 A plausible mechanistic pathway.

biologically relevant compounds, such as desoxyanisoin (**55**) amino acid (**56**) and epiandrosterone (**57** and **58**) in moderate to good yields. Moreover, it is particularly noteworthy that a range of commercially available drugs and derivatives, carrying tetrazole tail, such as sartan pharmaceuticals, were fully accepted by the robust electrochemical functionalization using as amination reagents, providing novel, undisclosed alkylation analogs (**59**–**62**). The ratios of regioselectivity of tetrazoles were determined by the isolation on column chromatography. In addition, the electrochemical azolation selectively occurred at the *p*-alkoxy-activated benzylic position of promestriene, which contains a complex structure with tertiary and secondary reacted sites, affording remote amination product in single chair conformation preference *via* hydrogen elimination (**64**). Obviously, our method can be used for coupling two high-value complex reaction partners, albeit with decreased yields (**63**).

4 Conclusions

In summary, we have developed an electrochemical benzylic C–H amination of azoles, which proceeds in an undivided cell under mild, catalyst- and chemical-oxidant-free reaction conditions. The strategy enables selective C–H azolation on primary, secondary, as well as more challenging tertiary benzylic positions. The remarkable synthetic utility of our approach is highlighted by its easy scalability and compatibility with a wide range of highly functional groups and azoles. Thus, the unique power of the versatile electrooxidative C–H azolation approach set the stage for the efficient modification and assembly of complex bioactive compounds, providing a promising new platform to design new bond formation,



Scheme 7 Late-stage functionalization *via* electrooxidative C–H azolation. Reaction conditions: undivided cell, graphite anode, Pt cathode, **1** (1.5 mmol), **2** (0.5 mmol), nBu$_4$NHSO$_4$ (0.5 mmol), MeCN (5.0 mL), constant current = 8 mA, 12 h, 80 °C. Isolated yields were given. a) **1** (2.0 mmol), 15 h. b) **1** (2.0 mmol), 13 h (color online).

sustainable oxidative functionalization reactions with broad practicality in synthetic and medicinal chemistry.

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Conflict of interest The authors declare no conflict of interest.

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1 (a) Schmidt B, Schieffer B. *J Med Chem*, 2003, 46: 2261–2270; (b) Breschi MC, Calderone V, Digiacomo M, Martelli A, Martinotti E, Minutolo F, Rapposelli S, Balsamo A. *J Med Chem*, 2004, 47: 5597–5600; (c) Zhang HZ, Gan LL, Wang H, Zhou CH. *Mini-Rev Med Chem*, 2017, 17: 122–166; (d) Das P, Delost MD, Qureshi MH, Smith DT, Njardarson JT. *J Med Chem*, 2019, 62: 4265–4311; (e) Al-Azmi

A, George P, El-Dusouqui OME. *J Heterocycl Chem*, 2007, 44: 515–520; (f) Vitaku E, Smith DT, Njardarson JT. *J Med Chem*, 2014, 57: 10257–10274
2 Kong D, Moon PJ, Bsharat O, Lundgren RJ. *Angew Chem Int Ed*, 2020, 59: 1313–1319
3 Fan X, Lei T, Liu Z, Yang XL, Cheng YY, Liang G, Chen B, Tung CH, Wu LZ. *Eur J Org Chem*, 2020, 2020: 1551–1558
4 (a) Stivanin ML, Fernandes AAG, Silva AF, Okada Jr CY, Jurberg ID. *Adv Synth Catal*, 2020, 362: 1106–1111; (b) Wang K, Chen P, Ji D, Zhang X, Xu G, Sun J. *Angew Chem Int Ed*, 2018, 57: 12489–12493
5 Sun HL, Yang F, Ye WT, Wang JJ, Zhu R. *ACS Catal*, 2020, 10: 4983–4989
6 (a) Yang Y, Yu Y, Wang Y, Zhang Q, Li D. *Tetrahedron*, 2018, 74: 1085–1091; (b) Yamamoto C, Takamatsu K, Hirano K, Miura M. *J Org Chem*, 2016, 81: 7675–7684; (c) Ye L, Tian Y, Meng X, Gu Q, Liu X. *Angew Chem Int Ed*, 2020, 59: 1129–1133; (d) Prier CK, Zhang RK, Buller AR, Brinkmann-Chen S, Arnold FH. *Nat Chem*, 2017, 9: 629–634; (e) Clark JR, Feng K, Sookezian A, White MC. *Nat Chem*, 2018, 10: 583–591
7 (a) Song C, Dong X, Yi H, Chiang CW, Lei A. *ACS Catal*, 2018, 8: 2195–2199; (b) Wang X, Li C, Zhang Y, Zhang B, Sun K. *Org Biomol Chem*, 2019, 17: 8364–8368; (c) Pandey G, Laha R, Singh D. *J Org Chem*, 2016, 81: 7161–7171
8 (a) Xue Q, Xie J, Li H, Cheng Y, Zhu C. *Chem Commun*, 2013, 49: 3700–3702; (b) Xia Q, Chen W, Qiu H. *J Org Chem*, 2011, 76: 7577–7582
9 For recent reviews on organic electrosynthesis: (a) Meyer TH, Finger LH, Gandeepan P, Ackermann L. *Trends Chem*, 2019, 1: 63–76; (b) Waldvogel SR, Lips S, Selt M, Riehl B, Kampf CJ. *Chem Rev*, 2018, 118: 6706–6765; (c) Tang S, Liu Y, Lei A. *Chem*, 2018, 4: 27–45; (d) Hou ZW, Mao ZY, Xu HC. *Synlett*, 2017, 28: 1867–1872; (e) Cardoso DSP, Šljukić B, Santos DMF, Sequeira CAC. *Org Process Res Dev*, 2017, 21: 1213–1226; (f) Horn EJ, Rosen BR, Baran PS. *ACS Cent Sci*, 2016, 2: 302–308; (g) Francke R, Little RD. *Chem Soc Rev*, 2014, 43: 2492–2521; (h) Francke R. *Beilstein J Org Chem*, 2014, 10: 2858–2873; (i) Yoshida J, Kataoka K, Horcajada R, Nagaki A. *Chem Rev*, 2008, 108: 2265–2299; (j) Jutand A. *Chem Rev*, 2008, 108: 2300–2347; (k) Minteer SD, Baran P. *Acc Chem Res*, 2020, 53: 545–546; (l) Kingston C, Palkowitz MD, Takahira Y, Vantourout JC, Peters BK, Kawamata Y, Baran PS. *Acc Chem Res*, 2020, 53: 72–83; (m) Röckl JL, Pollok D, Franke R, Waldvogel SR. *Acc Chem Res*, 2020, 53: 45–61; (n) Siu JC, Fu N, Lin S. *Acc Chem Res*, 2020, 53: 547–560; (o) Jiao KJ, Xing YK, Yang QL, Qiu H, Mei TS. *Acc Chem Res*, 2020, 53: 300–310; (p) Leech MC, Lam K. *Acc Chem Res*, 2020, 53: 121–134; (q) Yamamoto K, Kuriyama M, Onomura O. *Acc Chem Res*, 2020, 53: 105–120; (r) Ackermann L. *Acc Chem Res*, 2020, 53: 84–104; (s) Xiong P, Xu HC. *Acc Chem Res*, 2019, 52: 3339–3350; (t) Meyer TH, Choi I, Tian C, Ackermann L. *Chem*, 2020, 6: 2484–2496; (u) Zhang S, Samanta RC, Del Vecchio A, Ackermann L. *Chem Eur J*, 2020, 26: 10936–10947
10 (a) Wang H, Gao X, Lv Z, Abdelilah T, Lei A. *Chem Rev*, 2019, 119: 6769–6787; (b) Yuan Y, Lei A. *Acc Chem Res*, 2019, 52: 3309–3324
11 (a) Feng P, Ma G, Chen X, Wu X, Lin L, Liu P, Chen T. *Angew Chem Int Ed*, 2019, 58: 8400–8404; (b) Qiu Y, Struwe J, Meyer TH, Oliveira JCA, Ackermann L. *Chem Eur J*, 2018, 24: 12784–12789; (c) Petrosyan VA, Burasov AV, Vakhotina TS. *Russ Chem Bull*, 2005, 54: 1197–1202; (d) Hu K, Niyazymbetov ME, Evans DH. *Tetrahedron Lett*, 1995, 36: 7027–7030; (e) de Robillard G, Makni O, Cattey H, Andrieu J, Devillers CH. *Green Chem*, 2015, 17: 4669–4679
12 (a) Wan Z, Wang D, Yang Z, Zhang H, Wang S, Lei A. *Green Chem*, 2020, 22: 3742–3747; (b) Wu J, Zhou Y, Zhou Y, Chiang CW, Lei A. *ACS Catal*, 2017, 7: 8320–8323; (c) Shao X, Tian L, Wang Y. *Eur J Org Chem*, 2019, 2019(25): 4089–4094; (d) Yang YZ, Song RJ, Li JH. *Org Lett*, 2019, 21: 3228–3231
13 (a) Zeng C, Zhang N, Lam CM, Little RD. *Org Lett*, 2012, 14: 1314–1317; (b) Xiong P, Zhao HB, Fan XT, Jie LH, Long H, Xu P, Liu ZJ, Wu ZJ, Cheng J, Xu HC. *Nat Commun*, 2020, 11: 2706–2714
14 Morofuji T, Shimizu A, Yoshida J. *J Am Chem Soc*, 2014, 136: 4496–4499
15 (a) Lee BJ, DeGlopper KS, Yoon TP. *Angew Chem Int Ed*, 2020, 59: 197–202; (b) Wang H, Liang K, Xiong W, Samanta S, Li W, Lei A. *Sci Adv*, 2020, 6: eaaz0590
16 Baciocchi E, Bietti M, Lanzalunga O. *Acc Chem Res*, 2000, 33: 243–251
17 (a) Xu Z, Li Y, Mo G, Zheng Y, Zeng S, Sun PH, Ruan Z. *Org Lett*, 2020, 22: 4016–4020; (b) Xu Z, Huang Z, Li Y, Kuniyil R, Zhang C, Ackermann L, Ruan Z. *Green Chem*, 2020, 22: 1099–1104; (c) Ruan Z, Huang Z, Xu Z, Mo G, Tian X, Yu XY, Ackermann L. *Org Lett*, 2019, 21: 1237–1240; (d) Li Y, Huang Z, Mo G, Jiang W, Zheng C, Feng P, Ruan Z. *Chin J Chem*, 2020, https://doi.org/10.1002/cjoc.202000586
18 When we are preparing the manuscript, a similar elegant work was reported by Xu, see: (a) Hou Z, Liu D, Xiong P, Lai X, Song J, Xu H. *Angew Chem Int Ed*, 2021, 60: 2943–2947; (b) The methodology was mainly focused on amination of the secondary benzylic positions and less electronic benzylic substrates. Herein, our work mainly addressed the amination of electron-rich substrates with primary, secondary and tertiary benzylic positions
19 (a) Garrett C, Prasad K. *Adv Synthesis Catal*, 2004, 346: 889–900; (b) Caron S, Dugger RW, Ruggeri SG, Ragan JA, Ripin DHB. *Chem Rev*, 2006, 106: 2943–2989
20 The anodic oxidation of **1a** was mainly affected by the specific electrode area and current density, see: Pletcher D. *Industrial Electrochemistry*. London, New York: Chapmann and Hall. 2ed. 1990. 79–90
21 Herein, the electrolyte of Et_4NClO_4 was employed for the CV test, because the CV of **2a** was interfered by the oxidation of nBu$_4$NHSO$_4$