Electrochemistry Hot Paper

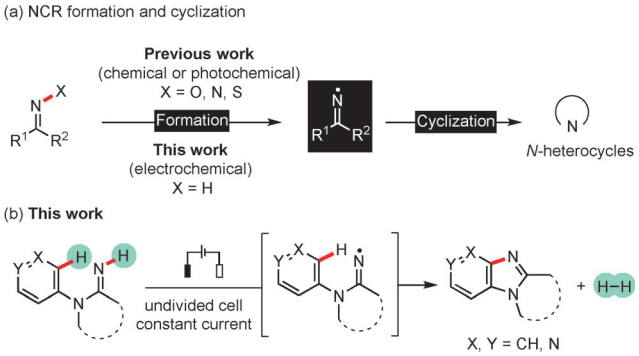
International Edition: DOI: 10.1002/anie.201610715
German Edition: DOI: 10.1002/ange.201610715

Amidinyl Radical Formation through Anodic N–H Bond Cleavage and Its Application in Aromatic C–H Bond Functionalization

*Huai-Bo Zhao, Zhong-Wei Hou, Zhan-Jiang Liu, Ze-Feng Zhou, Jinshuai Song, and Hai-Chao Xu**

Abstract: *We report herein an atom-economical and sustainable approach to access amidinyl radical intermediates through the anodic cleavage of N–H bonds. The resulting nitrogen-centered radicals undergo cyclizations with (hetero)arenes, followed by rearomatization, to afford functionalized tetracyclic benzimidazoles in a highly straightforward and efficient manner. This metal- and reagent-free C–H/N–H cross-coupling reaction exhibits a broad substrate scope and proceeds with high chemoselectivity.*

N-Heterocycles are ubiquitous motifs that play a critical role in both medicinal chemistry and biology.[1] As a result, the development of simple, efficient, and sustainable methods for their synthesis from easily available building blocks is an important research focus for organic chemists. In recent years, the cyclization of reactive nitrogen-centered radicals (NCRs), such as amidyl and iminyl radicals, onto unsaturated systems has been actively pursued for the construction of N-heterocycles.[2] The conventional approach for the preparation of NCRs involves the cleavage of an N–X (X = O, N, etc.) bond to give an iminyl radical intermediate (Scheme 1 a).[2,3] The generation of NCRs through cleavage of N–H bonds is an inherently more atom- and step-economical method and has attracted much attention recently.[4] Despite these advances, the reported methods involving N–H bond scission are limited in utility to the generation of amidyl or sulfonamidyl radicals. We have previously reported[5] electrochemical methods[6] for the generation of amidyl radicals from N–H amides. With our continued interest in the NCR-mediated synthesis of N-heterocycles,[5,7] we report herein an unprecedented electrochemical method for the generation of amidinyl radicals through anodic cleavage of N–H bonds (Scheme 1 b). The resultant NCR intermediates subsequently undergo cyclizations[8] with (hetero)arenes to give benzimidazoles and pyridoimidazoles. This metal- and reagent-free C–H/N–H cross-coupling reaction offers rapid and sustainable access to a series of structurally complex and diverse polycyclic benzimidazoles, as well as pyridoimidazoles.[9]



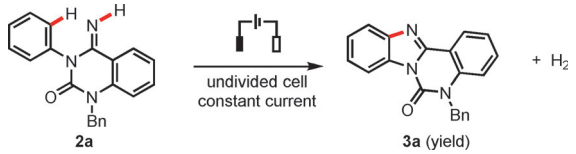
Scheme 1. Formation and cyclization of NCRs.

Benzimidazoles and pyridoimidazoles are ubiquitous structural motifs in pharmaceuticals and materials.[10] They are generally synthesized either from *ortho*-functionalized anilines,[10a] or more recently, through transition-metal-catalyzed or hypervalent-iodine-mediated C–H/N–H cross-coupling of N-arylamidines.[11] However, these C–H functionalization methods are often limited in scope and ill-suited to the preparation of the synthetically more difficult pyridoimidazoles. In addition, it is highly desirable, yet challenging, to develop metal-[12] and reagent-free[13] dehydrogenative cross-coupling processes with reduced environmental impact and safety concerns.

We first optimized the electrolysis conditions for the cyclization of **2a**, which was prepared in one step from 2-(benzylamino)benzonitrile (**1**). Extensive experimentation indicated that conducting the electrolysis in a three-necked round-bottomed flask containing an electrolyte solution of Et_4NPF_6 in refluxing MeOH, combined with the use of a reticulated vitreous carbon (RVC) anode and a platinum cathode with a constant current of 10 mA ($j_{anode} \cong 0.13\ mA\,cm^{-2}$), resulted in the highest yield (94%) for the benzimidazole product **3a** (Table 1, entry 1). While a lower current of 5 mA showed no negative effect on the reaction efficiency (entry 2), a reduction in yield was observed when the reaction was performed at 20 mA (entry 3), thus suggesting that a relatively low current density is potentially important. Other electrolytes such as nBu_4NBF_4 or Et_4NOTs could also be used without affecting the yield or current efficiency (entry 4). However, reacting **2a** in MeCN (entry 5) or lowering the reaction temperature to RT (entry 6) were found to be detrimental to the cyclization process. The choice of electrode material proved critical; no

[*] H.-B. Zhao, Z.-W. Hou, Z.-J. Liu, Z.-F. Zhou, Prof. Dr. H.-C. Xu
*i*ChEM, State Key Laboratory of Physical Chemistry of Solid Surfaces
Key Laboratory of Chemical Biology of Fujian Province and
College of Chemistry and Chemical Engineering
Xiamen University, Xiamen 361005 (P.R. China)
E-mail: haichao.xu@xmu.edu.cn
Homepage: http://chem.xmu.edu.cn/groupweb/hcxu/
Dr. J. Song
Fujian Institute of Research on Structure of Matter
Chinese Academy of Sciences, Fuzhou 350002 (P.R. China)
Supporting information and the ORCID identification number(s) for the author(s) of this article can be found under http://dx.doi.org/10.1002/anie.201610715.

Table 1: Optimization of reaction conditions.[a]



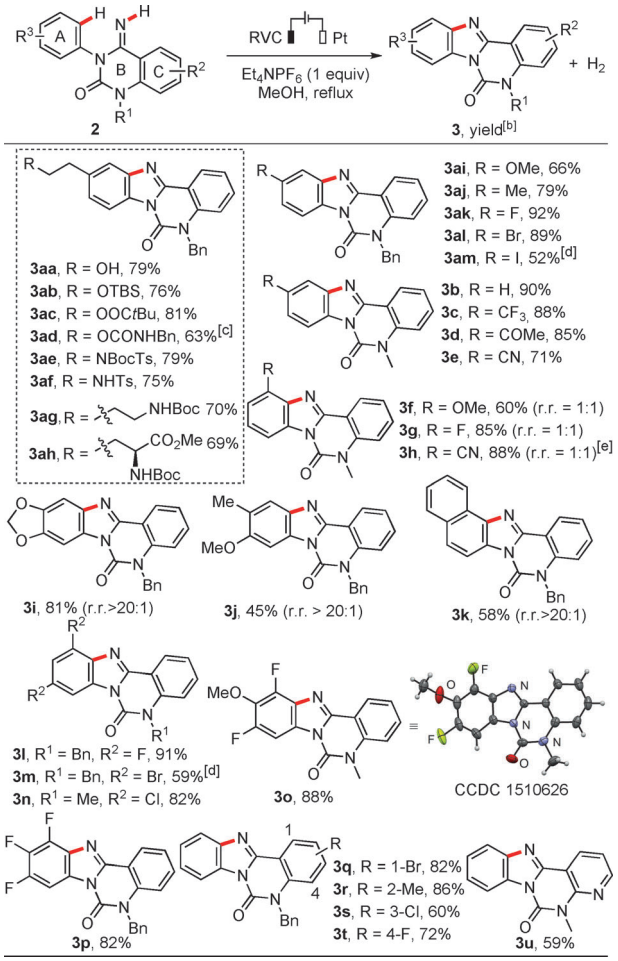
Entry	Electrolysis conditions[b]	Yield [%][c]
1	MeOH, Et_4NPF_6 (1 equiv), reflux, 10 mA	94
2	5 mA	93[d]
3	20 mA	82[e]
4	nBu_4NBF_4 or Et_4NOTs as electrolyte	91
5	MeCN as solvent	7 (53)[f]
6	Reaction at RT	26 (41)
7	Pt plate as anode	NR
8	Graphite rod as anode	50 (33)[f]
9	Graphite rod as cathode	30 (25)[f]
10	Reaction run under air	90

[a] Reaction conditions: RVC anode (100 PPI, 1.2 cm × 1 cm × 1 cm), Pt plate cathode (1 cm × 1 cm), **2a** (0.3 mmol), electrolyte (0.3 mmol), solvent (9 mL), reflux, argon, 3 h (3.7 F). [b] Conditions as for entry 1 except for the change noted. [c] Yield of isolated product. [d] Reaction time = 6 h. [e] Reaction time = 1.5 h. [f] Yield determined by ^{1}H-NMR analysis using 1,3,5-trimethoxybenzene as the internal standard. NR = no reaction.

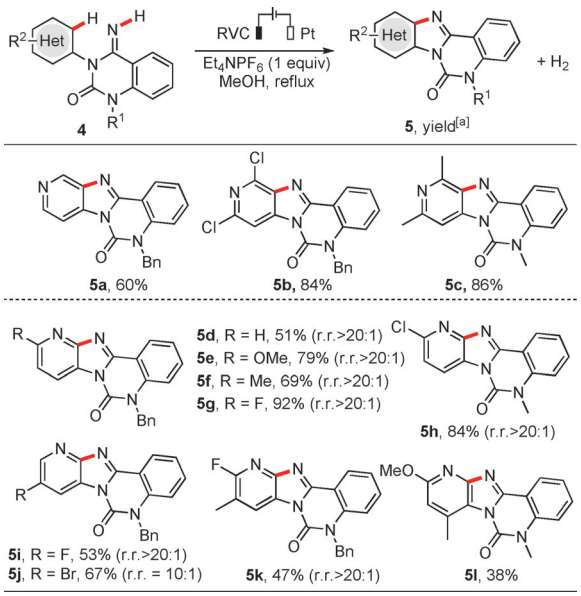
product formation was detected when we used a Pt anode (entry 7), and a dramatically lower amount of **3a** was afforded when either the anode or the cathode was graphite based (entry 8, 9). Meanwhile, the reaction showed little sensitivity to oxygen and could be run under atmospheric conditions (entry 10).

We subsequently investigated the effects of various functional groups on the efficiency of the electrochemical cyclization reaction (Scheme 2). A host of polar functionalities, including alcohol (**3aa**), ester (**3ac**), carbamate (**3ad**), sulfonamide (**3ae**, **3af**), and *tert*-butylcarbonyl (Boc)-protected amine (**3ag**) or aminoester (**3ah**) groups were found to be well tolerated. The reaction also demonstrated excellent compatibility with a series of amidine reactants containing substituents with different electronic and steric properties at the *para* or *meta* position of the reacting A ring (**3ai**–**am** and **3c**–**e**). Densely decorated benzimidazoles can be easily synthesized from substrates with a multisubstituted A ring (**3i**–**p**). It is worth noting that all *meta*-substituted amidines that we tested furnished a 1:1 mixture of regioisomers (**3f**–**h**), whereas the cyclization of *para*,*meta*-disubstituted substrates such as **2i** and **2j** led to benzimidazoles **3i** and **3j** as single regioisomers.[14] The reaction of a 2-aminonaphthalene-derived substrate also exhibited strict regioselectivity (**3k**). Further investigation revealed that the C ring of the bicyclic amidine could be functionalized with a halogen (**3q**, **3s**, **3t**), a methyl group (**3r**), or even a nitrogen atom (**3u**).

Functionalized pyridoimidazoles remained difficult to synthesize, even with the development of C–H functionalization methods.[10] However, as shown in Scheme 3, pyridoimidazoles could easily be prepared through the electrolysis of 4- and 3-aminopyridine-derived substrates. In particular, the products when using the latter (**5d**–**k**) were formed with excellent regioselectivity (see the Supporting Information for



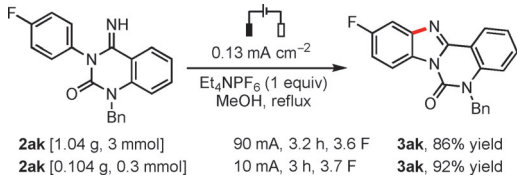
Scheme 2. Scope of benzimidazole formation. [a] Reaction conditions: constant current = 10 mA ($j_{anode} \cong 0.13$ mA cm^{-2}), **2** (0.3 mmol), Et_4NPF_6 (0.3 mmol), MeOH (9 mL), 3–4 h (3.7–5 F). [b] Yield of isolated product. [c] 10 F. [d] 20 F. [e] Partially separable. TBS = *tert*-butyldimethylsilyl, Ts = 4-toluenesulfonyl, Boc = *tert*-butoxycarbonyl.



Scheme 3. Scope of pyridoimidazole synthesis. Reaction conditions were the same as those of Scheme 2. [a] Yield of isolated product.

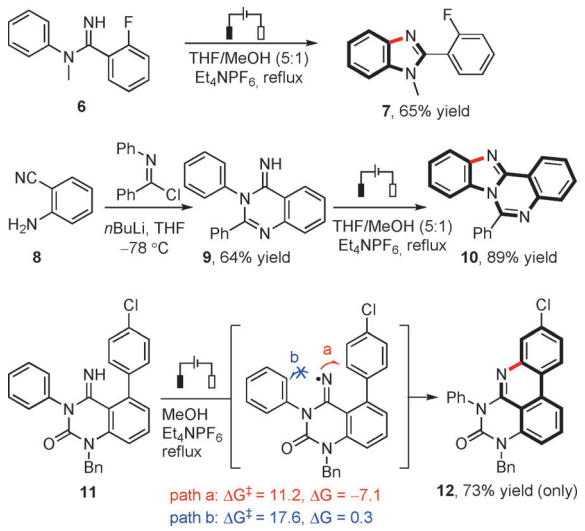
a possible explanation). In contrast, a previously reported cyclization of iminyl radicals afforded low selectivity.[15]

The synthetic potential of our C–H/N–H cross-coupling method was further demonstrated by conducting the electrolysis reaction on a gram scale (Scheme 4). For instance, we electrolyzed 1.04 g (3 mmol) of **2ak** using a constant current of 90 mA and obtained the desired benzimidazole **3ak** in 86% yield, which was on a par with what was obtained in a 0.3 mmol reaction (92% yield).



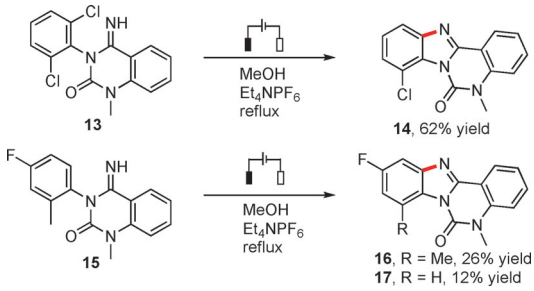
Scheme 4. Gram-scale synthesis.

The electrochemical cross-coupling reaction could also be used for the construction of other heterocycles of medicinal importance, such as the simple 1,2-disubstituted benzimidazole (**7**),[10a] benzo[4,5]imidazo[1,2-*c*]quinazoline (**10**),[16] and phenanthridine (**12**;[17] Scheme 5) from easily available amidines **6**, **9**, and **11**, respectively. For the electrolysis of **6** and **9**, a mixed solvent of THF/MeOH (5:1) was found to improve the yield. It is worth emphasizing that the favored formation of a six-membered ring was the driving force for the regioselective generation of phenanthridine (**12**). Density functional theory (DFT) calculations confirmed that the 6-*endo*-trig cyclization (path a) of the NCR intermediate to form a six-membered ring was both kinetically and thermodynamically preferred over the alternative five-membered-ring formation (path b).



Scheme 5. Extension of the current method. Energies are in kcal mol^{-1}.

To confirm that an amidinyl radical intermediate was indeed involved in the C–H/N–H cross-coupling reaction, we probed the cyclization of two *ortho*-substituted amidines (**13** and **15**; Scheme 6). Iminyl radicals are known to undergo homolytic aromatic substitution of carbon–carbon as well as carbon–heteroatom bonds.[15,18] Under standard conditions, we isolated benzimidazoles **14** and **17**, which were formed as a result of C–Cl and C–C bond cleavage, respectively (see the Supporting Information for additional mechanistic studies). Taken together, these studies provide strong evidence for the mechanistic involvement of a NCR intermediate in the C–H/N–H cross-coupling process.



Scheme 6. Mechanistic studies.

In summary, we have demonstrated for the first time that amidinyl radicals can be generated conveniently through anodic cleavage of N–H bonds. The electrochemically formed NCRs undergo efficient cyclizations onto (hetero)arenes to afford a diverse range of polycyclic benzimidazoles and pyridoimidazoles. Further studies to apply these anode-generated NCRs in the synthesis of other N-heterocycles are underway in our laboratory.

Acknowledgements

Financial support of this research from MOST (2016YFA0204100), NSFC (No. 21402164, 21672178, 21603227), the "Thousand Youth Talents Plan" (K08004), XMU (X170300109), Fujian province (Z0230106), and Xiamen (Z0330104).

Conflict of interest

The authors declare no conflict of interest.

Keywords: benzimidazoles · cyclization · electrochemistry · heterocycles · radicals

[1] A. T. Balaban, D. C. Oniciu, A. R. Katritzky, *Chem. Rev.* **2004**, *104*, 2777–2812.
[2] a) S. Z. Zard, *Chem. Soc. Rev.* **2008**, *37*, 1603–1618; b) A. Baralle, A. Baroudi, M. Daniel, L. Fensterbank, J.-P. Goddard, E. Lacote, M.-H. Larraufie, G. Maestri, M. Malacria, C. Ollivier in *Encyclopedia of Radicals in Chemistry, Biology and Materials* (Eds.: C. Chatgilialoglu, A. Studer), Wiley, Chichester, **2012**, pp. 767–816; c) J. R. Chen, X. Q. Hu, L. Q. Lu, W. J. Xiao,

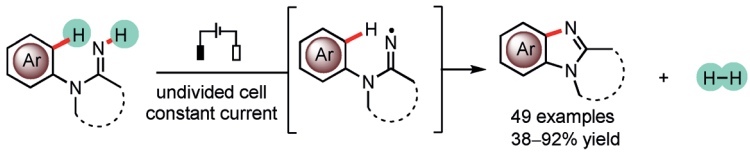
Chem. Soc. Rev. **2016**, *45*, 2044 – 2056; d) T. Xiong, Q. Zhang, *Chem. Soc. Rev.* **2016**, *45*, 3069 – 3087.
[3] Reviews on iminyl radicals: a) J. C. Walton, *Molecules* **2016**, *21*, 660 – 684; b) J. C. Walton, *Acc. Chem. Res.* **2014**, *47*, 1406 – 1416.
[4] Selected recent examples: a) K. C. Nicolaou, P. S. Baran, Y.-L. Zhong, S. Barluenga, K. W. Hunt, R. Kranich, J. A. Vega, *J. Am. Chem. Soc.* **2002**, *124*, 2233 – 2244; b) B. Janza, A. Studer, *J. Org. Chem.* **2005**, *70*, 6991 – 6994; c) Z. Li, L. Song, C. Li, *J. Am. Chem. Soc.* **2013**, *135*, 4640 – 4643; d) H.-C. Xu, K. D. Moeller, *J. Am. Chem. Soc.* **2010**, *132*, 2839 – 2844; e) X. Q. Hu, J. R. Chen, Q. Wei, F. L. Liu, Q. H. Deng, A. M. Beauchemin, W. J. Xiao, *Angew. Chem. Int. Ed.* **2014**, *53*, 12163 – 12167; *Angew. Chem.* **2014**, *126*, 12359 – 12363; f) G. J. Choi, R. R. Knowles, *J. Am. Chem. Soc.* **2015**, *137*, 9226 – 9229; g) T. Gieshoff, D. Schollmeyer, S. R. Waldvogel, *Angew. Chem. Int. Ed.* **2016**, *55*, 9437 – 9440; *Angew. Chem.* **2016**, *128*, 9587 – 9590; h) G. J. Choi, Q. Zhu, D. C. Miller, C. J. Gu, R. R. Knowles, *Nature* **2016**, DOI: 10.1038/nature19811; i) J. C. Chu, T. Rovis, *Nature* **2016**, DOI: 10.1038/nature19810.
[5] a) L. Zhu, P. Xiong, Z. Y. Mao, Y. H. Wang, X. Yan, X. Lu, H.-C. Xu, *Angew. Chem. Int. Ed.* **2016**, *55*, 2226 – 2229; *Angew. Chem.* **2016**, *128*, 2266 – 2269; b) Z. W. Hou, Z. Y. Mao, H. B. Zhao, Y. Y. Melcamu, X. Lu, J. Song, H.-C. Xu, *Angew. Chem. Int. Ed.* **2016**, *55*, 9168 – 9172; *Angew. Chem.* **2016**, *128*, 9314 – 9318.
[6] Selected recent reviews on electroorganic synthesis: a) R. Francke, R. D. Little, *Chem. Soc. Rev.* **2014**, *43*, 2492 – 2521; b) B. A. Frontana-Uribe, R. D. Little, J. G. Ibanez, A. Palma, R. Vasquez-Medrano, *Green Chem.* **2010**, *12*, 2099 – 2119; c) J. Yoshida, K. Kataoka, R. Horcajada, A. Nagaki, *Chem. Rev.* **2008**, *108*, 2265 – 2299; d) J. B. Sperry, D. L. Wright, *Chem. Soc. Rev.* **2006**, *35*, 605 – 621; e) R. Francke, *Beilstein J. Org. Chem.* **2014**, *10*, 2858 – 2873; f) S. R. Waldvogel, B. Janza, *Angew. Chem. Int. Ed.* **2014**, *53*, 7122 – 7123; *Angew. Chem.* **2014**, *126*, 7248 – 7249; g) S. R. Waldvogel, S. Möhle, *Angew. Chem. Int. Ed.* **2015**, *54*, 6398 – 6399; *Angew. Chem.* **2015**, *127*, 6496 – 6497; h) E. J. Horn, B. R. Rosen, P. S. Baran, *ACS Cent. Sci.* **2016**, *2*, 302 – 308.
[7] a) F. Xu, L. Zhu, S. B. Zhu, X. M. Yan, H.-C. Xu, *Chem. Eur. J.* **2014**, *20*, 12740 – 12744; b) P. Xiong, F. Xu, X. Y. Qian, Y. Yohannes, J. Song, X. Lu, H.-C. Xu, *Chem. Eur. J.* **2016**, *22*, 4379 – 4383.
[8] Reports on iminyl radical cyclization onto arenes have mainly dealt with 6-*endo* type ring closures leading to six-membered ring aza-arenes; see Ref. [3] and selected recent examples: a) H. Jiang, X. D. An, K. Tong, T. Y. Zheng, Y. Zhang, S. Y. Yu, *Angew. Chem. Int. Ed.* **2015**, *54*, 4055 – 4059; *Angew. Chem.* **2015**, *127*, 4127 – 4131; b) E. G. Mackay, A. Studer, *Chem. Eur. J.* **2016**, *22*, 13455 – 13458.
[9] Recent examples of electrochemical C–H functionalization: a) R. Hayashi, A. Shimizu, J. I. Yoshida, *J. Am. Chem. Soc.* **2016**, *138*, 8400 – 8403; b) T. Morofuji, A. Shimizu, J. Yoshida, *J. Am. Chem. Soc.* **2015**, *137*, 9816 – 9819; c) W. J. Gao, W. C. Li, C. C. Zeng, H. Y. Tian, L. M. Hu, R. D. Little, *J. Org. Chem.* **2014**, *79*, 9613 – 9618; d) S. J. Yoo, L. J. Li, C. C. Zeng, R. D. Little, *Angew. Chem. Int. Ed.* **2015**, *54*, 3744 – 3747; *Angew. Chem.* **2015**, *127*, 3815 – 3818; e) A. Wiebe, D. Schollmeyer, K. M. Dyballa, R. Franke, S. R. Waldvogel, *Angew. Chem. Int. Ed.* **2016**, *55*, 11801 – 11805; *Angew. Chem.* **2016**, *128*, 11979 – 11983; f) S. Lips, A. Wiebe, B. Elsler, D. Schollmeyer, K. M. Dyballa, R. Franke, S. R. Waldvogel, *Angew. Chem. Int. Ed.* **2016**, *55*, 10872 – 10876; *Angew. Chem.* **2016**, *128*, 11031 – 11035; g) H. Ding, P. L. DeRoy, C. Perreault, A. Larivee, A. Siddiqui, C. G. Caldwell, S. Harran, P. G. Harran, *Angew. Chem. Int. Ed.* **2015**, *54*, 4818 – 4822; *Angew. Chem.* **2015**, *127*, 4900 – 4904; h) E. J. Horn, B. R. Rosen, Y. Chen, J. Tang, K. Chen, M. D. Eastgate, P. S. Baran, *Nature* **2016**, *533*, 77 – 81.
[10] a) L. C. R. Carvalho, E. Fernandes, M. M. B. Marques, *Chem. Eur. J.* **2011**, *17*, 12544 – 12555; b) E. Vitaku, D. T. Smith, J. T. Njardarson, *J. Med. Chem.* **2014**, *57*, 10257 – 10274; c) V. Bavetsias et al., *J. Med. Chem.* **2013**, *56*, 9122 – 9135.
[11] a) G. Brasche, S. L. Buchwald, *Angew. Chem. Int. Ed.* **2008**, *47*, 1932 – 1934; *Angew. Chem.* **2008**, *120*, 1958 – 1960; b) Q. Xiao, W. H. Wang, G. Liu, F. K. Meng, J. H. Chen, Z. Yang, Z. J. Shi, *Chem. Eur. J.* **2009**, *15*, 7292 – 7296; c) S. K. Alla, R. K. Kumar, P. Sadhu, T. Punniyamurthy, *Org. Lett.* **2013**, *15*, 1334 – 1337.
[12] C. E. Garrett, K. Prasad, *Adv. Synth. Catal.* **2004**, *346*, 889 – 900.
[13] For the problems associated with the use of oxidants in pharmaceutical synthesis, see: S. Caron, R. W. Dugger, S. G. Ruggeri, J. A. Ragan, D. H. B. Ripin, *Chem. Rev.* **2006**, *106*, 2943 – 2989.
[14] J. M. Um, O. Gutierrez, F. Schoenebeck, K. N. Houk, D. W. C. MacMillan, *J. Am. Chem. Soc.* **2010**, *132*, 6001 – 6005.
[15] A. Beaume, C. Courillon, E. Derat, M. Malacria, *Chem. Eur. J.* **2008**, *14*, 1238 – 1252.
[16] E. A. Lyakhova, Y. A. Gusyeva, J. V. Nekhoroshkova, L. M. Shafran, S. A. Lyakhov, *Eur. J. Med. Chem.* **2009**, *44*, 3305 – 3312.
[17] B. Zhang, A. Studer, *Chem. Soc. Rev.* **2015**, *44*, 3505 – 3521.
[18] M. H. Larraufie, C. Courillon, C. Ollivier, E. Lacote, M. Malacria, L. Fensterbank, *J. Am. Chem. Soc.* **2010**, *132*, 4381 – 4387.

Manuscript received: November 2, 2016
Final Article published: ■■ ■■, ■■■■

Communications

Electrochemistry

H.-B. Zhao, Z.-W. Hou, Z.-J. Liu,
Z.-F. Zhou, J. Song,
H.-C. Xu* _____ ■■■■–■■■■



Amidinyl Radical Formation through Anodic N–H Bond Cleavage and Its Application in Aromatic C–H Bond Functionalization

Power trip: A conceptually new method for the generation of amidinyl radicals through the anodic cleavage of N–H bonds was developed and applied to the development of aromatic C–H functionalization reactions to give benzimidazoles and pyridoimidazoles. This metal- and reagent-free transformation exhibits a broad scope and proceeds with high chemoselectivity.