ChemPubSoc Europe
DOI: 10.1002/chem.201304120
CHEMISTRY
A European Journal
Full Paper

Arylation

Direct Arylation of N-Heteroarenes with Aryldiazonium Salts by Photoredox Catalysis in Water

Dong Xue,*[a] Zhi-Hui Jia,[a] Cong-Jun Zhao,[a] Yan-Yan Zhang,[a] Chao Wang,[a] and Jianliang Xiao[a, b]

Abstract: A highly effective visible light-promoted “radical-type” coupling of N-heteroarenes with aryldiazonium salts in water has been developed. The reaction proceeds at room temperature with $[Ru(bpy)_3]Cl_2{\cdot}6\,H_2O$ as a photosensitizer and a commercial household light bulb as a light source. Pyridine and a variety of substituted pyridines are effective substrates under these reaction conditions, and only monosubstituted products are formed with different regioselectivities. Using aqueous formic acid as solvent, an array of xanthenes, thiazole, pyrazine, and pyridazine are compatible with this new arylation approach. The broad substrate scope, mild reaction conditions, and use of water as reaction solvent make this procedure a practical and environmentally friendly method for the synthesis of compounds containing aryl-heteroaryl motifs.

Introduction

Aryl-heteroaryl motifs are ubiquitous in natural products, pharmaceuticals, agrochemicals, and organic materials.[1] Transition metal-catalyzed cross-coupling reactions between an organometallic aryl reagent and an aryl halide or pseudohalide under thermal conditions are now well-established for aryl-heteroaryl formation.[2]

Direct functionalization of heteroarenes through C–H bond activation provides a highly attractive strategy.[3] However, electron-deficient N-heteroarenes, such as pyridines, pyrazines, pyridazines, and pyrimidines, are often difficult to derivatize directly.[4] Although several metal catalysts have proven to be highly effective in such direct coupling,[5–8] the synthesis of aryl-heteroaryl compounds remains very challenging owing to the high temperatures and harsh conditions required for these processes. As a result, the development of more efficient and milder direct arylations of complex electron-deficient heteroaromatic bases is still a major challenge for chemists.

Direct functionalization of electron-deficient heteroarenes through radical addition[9] is one of the most straightforward methods for constructing aryl-heteroaryl motifs. Recently, Baran[9b] reported a “radical-type” arylation of *N*-heterocycles using arylboronic acids as an aryl radical source. However, the Gomberg–Bachmann reaction[10] is the classic “radical-type” coupling between arene compounds and diazonium salts in the presence of a base, leading to biaryls through an intermediate aryl radical. The reaction offers wide scope in terms of both diazonium salts and arenes, but yields are generally low due to many side-reactions. Attempts have been made to make the reaction applicable in organic synthesis by using catalytic or stoichiometric amounts of transition metal salts[11] or by employing phase-transfer catalysis.[12]

Visible light-promoted photoredox catalysis provides a green, sustainable, and catalytic process for generating aryl radicals.[13–17] Recently, Sanford,[18a] König,[18b] Li,[18c] and our group[19] reported the “radical-type” construction of aryl-aryl bonds by visible light-driven catalysis. Since the reported methodologies are most efficient with electron-rich arenes, the direct addition of an aryl radical to an electron-deficient heteroarene under visible light-promoted photoredox catalysis is rare. In continuation of our work on aryl-aryl coupling driven by visible light photoredox catalysis,[15] we report herein a “radical-type” arylation of electron-deficient heteroarenes, such as pyridines, xanthenes, thiazole, pyrazine, and pyridazine, with aryldiazonium salts in water. This provides a general and valuable method for the direct functionalization of electron-deficient arenes.

Results and Discussion

Initial investigations focused on the direct arylation of 4-(trifluoromethyl)pyridine hydrochloride **1 a** with the aryldiazonium salt **2 a**. $[Ru(bpy)_3]Cl_2{\cdot}6\,H_2O$ was employed as the photocatalyst, and a 3 W blue LED was utilized as the source of visible light. The cross-coupling product 2-(4-methoxyphenyl)-4-(trifluoromethyl)pyridine hydrochloride was obtained in low yield in the

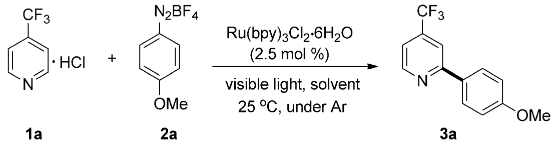
---

[a] *Prof. Dr. D. Xue, Z.-H. Jia, C.-J. Zhao, Y.-Y. Zhang, Prof. Dr. C. Wang,*
Prof. Dr. J. Xiao
Key Laboratory of Applied Surface and Colloid Chemistry
Ministry of Education, School of Chemistry and Chemical Engineering
Shaanxi Normal University
Xi’an 710062 (China)
E-mail: Xuedong_welcome@snnu.edu.cn

[b] *Prof. Dr. J. Xiao*
Liverpool Centre for Materials and Catalysis, University of Liverpool
Liverpool, L69 7ZD (UK)

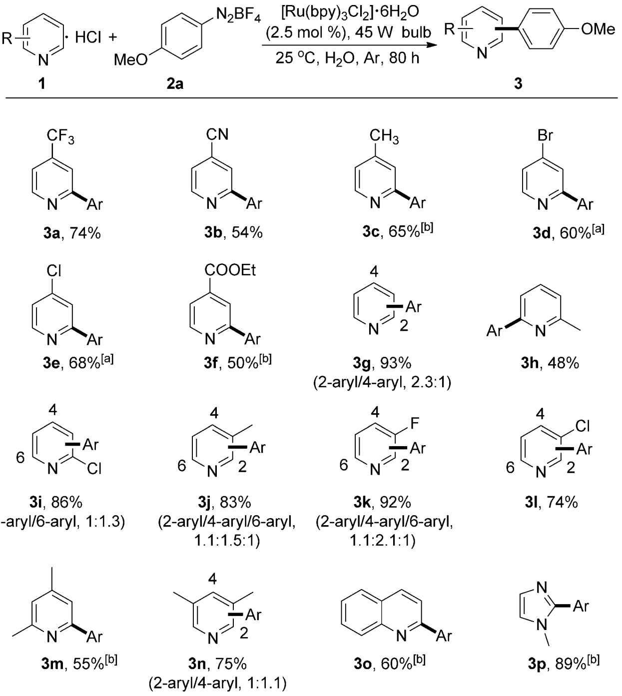
Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/chem.201304120.

Table 1. Optimization of the reaction conditions.[a]



Entry	Conditions	Solvent	Time [h]	Yield [%][b]
1	catalyst, light[c]	MeOH	24	trace
2	catalyst, light[c]	HCOOH	24	18
3	catalyst, light[c]	MeCN	24	13
4	catalyst, light[c]	H_2O	24	35
5	catalyst, light[c,d]	H_2O	24	30
6	catalyst, light[c,e]	H_2O	24	21
7	catalyst, light[f]	H_2O	24	40
8	catalyst, light[f, g]	H_2O	24	20
9	catalyst, light[c]	H_2O	80	65
10	catalyst, light[f]	H_2O	80	74
11	no catalyst, no light	H_2O	60	no reaction
12	catalyst, no light	H_2O	60	no reaction
13	no catalyst, light	H_2O	60	trace

[a] All reactions were carried out on a scale of 0.3 mmol of **2a** and 1.5 mmol of **1a** in 1 mL of solvent. [b] Yields of isolated product. [c] A 3 W blue LED was used. [d] 4 mol% Ru^{II} catalyst was used. [e] 1 mol% Ru^{II} catalyst was used. [f] A 45 W fluorescent bulb was used. [g] 4-(Trifluoromethyl)pyridine was used.



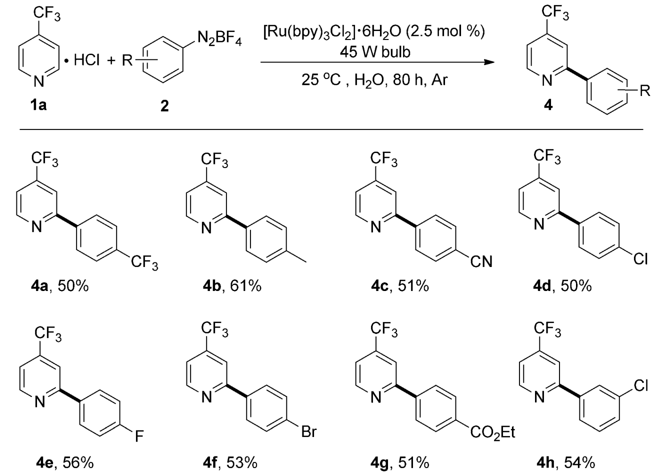
Scheme 1. Radical arylation of five- and six-membered heteroarenes by photoredox catalysis in water. Reactions were carried out on a scale of 0.3 mmol of **2a** and 1.5 mmol of **1** in H_2O (1 mL). Yields were determined upon isolation. [a] Heterocycle (3 mmol). [b] Heterocycle (9 mmol).

organic solvents screened at room temperature (Table 1, entries 1–3). To our delight, when H_2O was used as the solvent, the yield was increased to 35% under identical conditions (Table 1, entry 4). On extending the reaction time, 65% isolated yield was obtained. Further improvement was seen by changing the visible light source to a 45 W fluorescent bulb, whereupon **3a** was isolated in 74% yield (Table 1, entry 10). Water appears to be an ideal solvent for reactions of this nature, as both the substrates and catalyst are soluble and stable in aqueous solution. The solubility of a substrate in water is crucial to the reaction yield. When 4-(trifluoromethyl)pyridine was used under identical reaction conditions, a low product yield was obtained (Table 1, entry 8 vs 10). It is notable that the Ru^{II} photocatalyst and visible light were both critical for this reaction. In the absence of either of these components, no reaction product was observed (Table 1, entries 11–13).

Having established the optimal conditions,[20] we proceeded to investigate the substrate scope. As illustrated in Scheme 1, we found that this new arylation protocol allows the direct coupling of arene units with a broad range of N-heteroarene hydrochlorides using aryldiazonium salts in water. Pyridine and a variety of substituted pyridines are effective substrates under these reaction conditions, and only monosubstituted products were formed, albeit with different regioselectivities. 4-Substituted pyridines with electron-donating or electron-withdrawing groups such as Me, CF_3, Br, and COOEt gave only 2-arylated products in good yields. With pyridine, however, both 2- and 4-arylated products were isolated in 93% total yield. With 2-substituted pyridines, 4- or 6-arylated products were obtained in high yield. With 3-substituted pyridines, mixtures of 2-, 4-, and 6-arylated products were obtained in high yield. 3,5-Dimethylpyridine gave 2- and 4-arylated products in 75% total isolated yield. Quinoline also gave the 2-arylated product in good yield, as did 2,4-dimethylpyridine. Clearly, arylation occurs only at the *meta* and *para* positions of the pyridine ring. Five-membered *N*-methyl-imidazole also proved to be a good substrate for this methodology; the 2-arylated product was isolated in 89% yield. In contrast to metal-catalyzed[5–8] arylations, which require high temperature, our reaction conditions are milder and, moreover, water is used as the solvent, highlighting the potential of the methodology in organic synthesis.

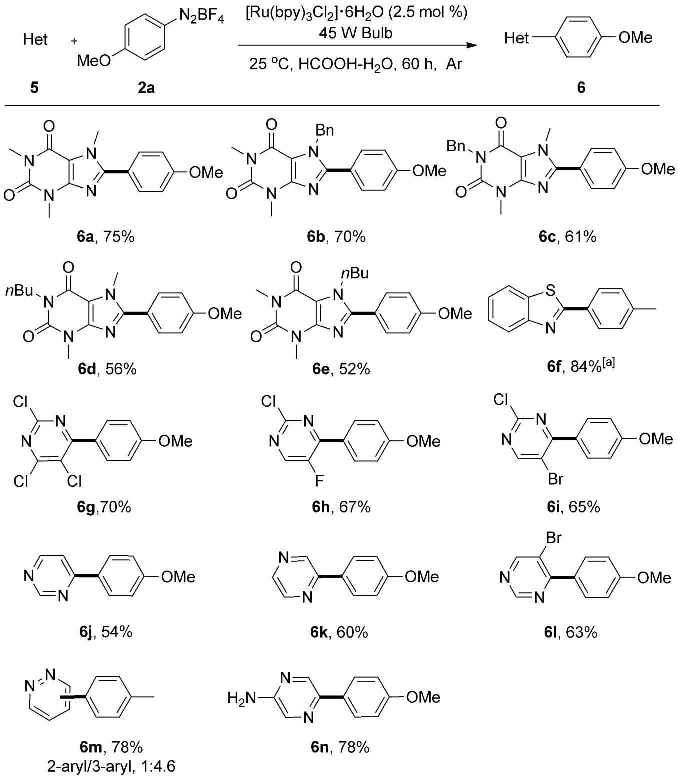
Next, we evaluated the substrate scope in terms of aryldiazonium salts. A wide range of aryldiazonium salts **2** with useful functional groups, such as CN, COOEt, Br, Cl, F, and CF_3, underwent coupling with 4-(trifluoromethyl)pyridine hydrochloride **1a** at ambient temperature in water. As can be seen from Scheme 2, for most of the substrates, the desired products were isolated in good yields. C–X (X = F, Cl, and Br) substituents on the aryldiazonium salts were tolerated under the reaction conditions, making them available for further functionalization.

Xanthines, such as caffeine, theophylline, and theobromine, are important bioactive alkaloids that contain imidazole skeletons. For instance, 8-(hetero)aryl-substituted xanthines are highly potent and selective antagonists at human A_2B adenosine receptors.[21] To find interesting applications of our methodology, we attempted the coupling of caffeine **5a** with aryldiazonium salts **2a** under the conditions of photoredox catalysis. It was interesting to find that the solvent played a vital role in the reaction.[20] Arylated product was obtained, but only in

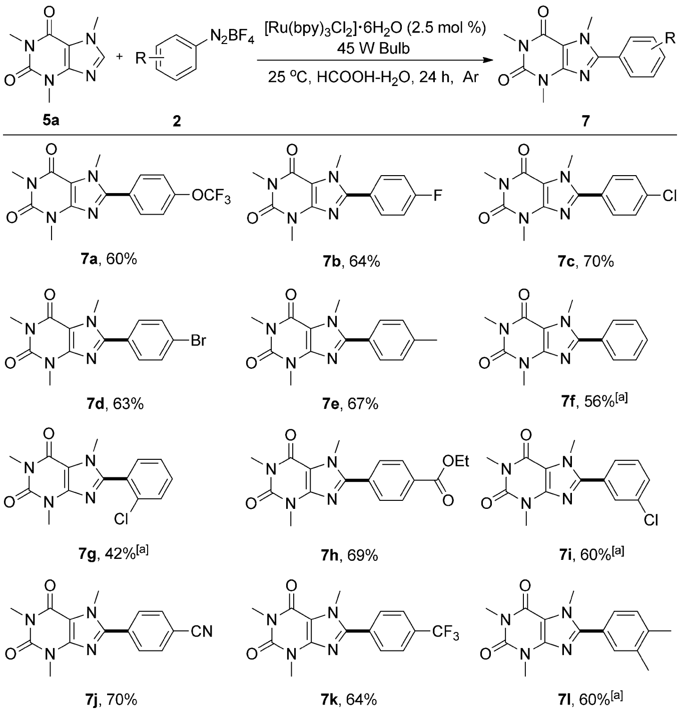


Scheme 2. The coupling of 4-(trifluoromethyl)pyridine hydrochloride **1a** with aryldiazonium salts. All reactions were carried out on a scale of 0.3 mmol of **2** and 1.5 mmol of **1a** in H_2O (1 mL). Yields were determined upon isolation.

low yield under the conditions used for pyridine hydrochloride with water as the solvent. Remarkably, on changing the solvent to 88% aqueous formic acid, the yield increased to 75%. This may be partly attributed to the good solubility of caffeine in this acidic medium. As shown in Scheme 3, an array of xanthenes, thiazole, pyrazine, and pyridazine proved to be compatible with this new arylation approach, affording the arylated derivatives in good to excellent yields. Additional benefits of this process are the tolerance of halides, multiple substitution, steric bulk, and diversity in the electronic properties of the N-heteroarenes. It was also satisfying to find that arylations of caffeine with a wide range of aryldiazonium tetrafluoroborates proceeded well in aqueous formic acid. The results are shown in Scheme 4. Irrespective of whether the aryldiazonium salts were electron-poor or electron-rich, they all afforded good yields. However, increasing steric bulk of the diazonium salts had a negative effect on the yields.



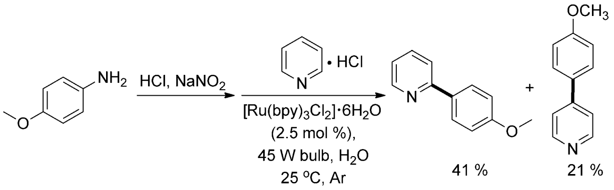
Scheme 3. Radical arylation of heteroarenes by photoredox catalysis in aqueous formic acid. All reactions were carried out on a scale of 0.2 mmol of **2a** and 2 mmol of **5** in 1 mL of solvent. Yields were determined upon isolation. [a] *p*-Methylphenyl diazonium salt was used.



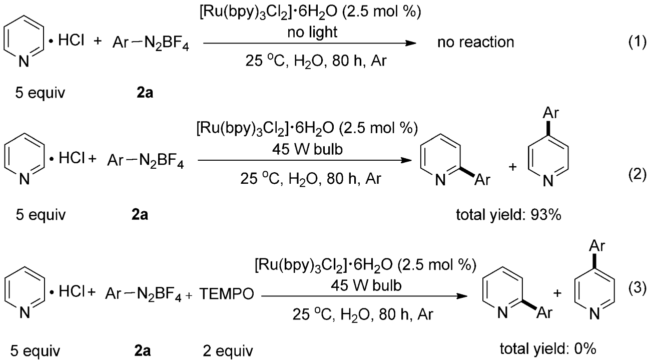
Scheme 4. The coupling of caffeine with aryldiazonium salts. All reactions were carried out on a scale of 0.2 mmol of **2** and 2.0 mmol of **5a** in 1 mL of solvent. Yields were determined upon isolation. [a] 60 h.

It is noted that most aryldiazonium salts are rather unstable. To simplify the synthetic procedure and in particular to avoid the problem of substrate instability, the photoredox arylation can be carried out in a one-pot fashion, starting with an amine. Thus, upon completion of the diazotization, a pyridine hydrochloride and the photosensitizer were added directly to the reaction mixture to afford the coupling product. An example is shown in Scheme 5. Such a one-pot process avoids the inconvenient purification step for an aryldiazonium salt, further enhancing the applicability of this new arylation method.

The described C–H arylation is likely to proceed through a radical mechanism, and this is supported by our preliminary mechanistic investigations (Scheme 6) and literature reports.[18,19] Thus, when the aryldiazonium salt **2a** was irradiated with a 45 W bulb in the presence of pyridine hydrochloride and photosensitizer in water, the arylated compound was formed and could be isolated in 93% yield [Scheme 6, Eq. (2)]. However, when the radical trap 2,2,6,6-tetramethylpiperidinox-



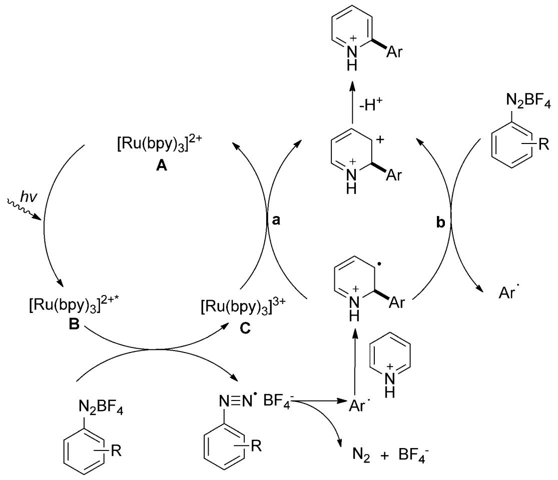
Scheme 5. Sequential radical arylation of heteroarenes by photoredox catalysis.



Scheme 6. Mechanistic investigations.

yl (TEMPO) was added to the same reaction mixture, the arylation process was significantly suppressed and the arylated product was not isolated [Scheme 6, Eq. (3)]. The suppression of the arylation reaction in the presence of TEMPO lends support to radical species being involved in the photocatalytic arylation.

On the basis of the above experiments and literature reports,[18a,b] a plausible mechanism is shown in Scheme 7. There are three key steps: (1) irradiation of the catalyst in the ground state **A**, generating the excited $[Ru(bpy)_3]^{II}$* **B**; (2) single electron transfer from **B** to the aryldiazonium salt, releasing a phenyl radical while oxidizing the catalyst to $[Ru(bpy)_3]^{III}$ **C**; and (3) addition of the phenyl radical to the pyridine hydrochloride to give a new radical intermediate. The latter is subsequently transformed into a carbocation intermediate by two possible pathways: oxidation by the strongly oxidizing $[Ru(bpy)_3]^{III}$ (photocatalytic arylation, pathway a) or by the aryldiazonium salt (pathway b). The latter would lead to a radical chain-transfer reaction and appears to be less likely, considering the reduction potentials of the two oxidants (1.3 against 0.05 V, vs SCE)[18b,22] and the observation that switching off the light stopped the arylation [Scheme 6, Eq. (1)]. Finally, deprotonation of the carbocation intermediate regenerates the aromatic systems, furnishing the desired coupling adduct.



Scheme 7. Proposed mechanistic cycle for the radical arylation of heteroarenes by photoredox catalysis.

Conclusion

A highly effective visible light-promoted “radical-type” coupling of N-heteroarenes with aryldiazonium salts in water has been developed. The reaction proceeds at room temperature with $[Ru(bpy)_3]Cl_2{\cdot}6H_2O$ as a photosensitizer and a commercial household light bulb as a light source. Pyridine and a variety of substituted pyridines are effective substrates under these reaction conditions and only monosubstituted products were formed with different regioselectivities. Using aqueous formic acid as solvent, an array of xanthenes, thiazole, pyrazine, and pyridazine are compatible with this new arylation approach. The broad substrate scope, mild reaction conditions, and use of water as reaction solvent make this procedure a practical and environmentally friendly method for the synthesis of compounds containing aryl-heteroaryl motifs.

Experimental Section

General procedure for radical arylation of five- and six-membered heteroarenes by photoredox catalysis in water

A flame-dried 10 mL tube was equipped with a rubber septum and a magnetic stir bar and charged with $[Ru(bpy)_3]Cl_2{\cdot}6H_2O$ (0.0075 mmol, 0.025 equiv), the requisite *N*-heterocycle hydrochloride **1** (1.5 mmol, 5.0 equiv), the aryldiazonium tetrafluoroborate **2a** (0.3 mmol, 1.0 equiv), and H_2O (1.0 mL). The mixture was degassed by the freeze-pump-thaw procedure under Ar and then irradiated with a 45 W compact fluorescent light bulb. The resulting mixture was stirred for 80 h and then diluted with 5% aqueous sodium hydrogencarbonate solution. After extraction with dichloromethane (3×30 mL), the combined organic phases were washed with saturated aqueous sodium chloride solution (30 mL) and dried over sodium sulfate. The solvent was removed under reduced pressure, and the residue was purified by flash chromatography (petroleum ether/ethyl acetate) to afford the product **3**. The identity and purity of the known product were confirmed by ^1H NMR, ^{13}C NMR, and MS.

General procedure for the arylation of heteroarenes by photoredox catalysis in aqueous formic acid

A flame-dried 10 mL tube was equipped with a rubber septum and a magnetic stir bar and charged with $[Ru(bpy)_3]Cl_2{\cdot}6H_2O$ (0.005 mmol, 0.025 equiv), the requisite *N*-heterocycle **5a** (2 mmol, 10.0 equiv), the aryldiazonium tetrafluoroborate **2a** (0.2 mmol, 1.0 equiv), and 88% aqueous HCOOH (1.0 mL). The mixture was degassed by the freeze-pump-thaw procedure under Ar and then irradiated with a 45 W compact fluorescent light bulb. The resulting mixture was stirred for 80 h and then diluted with 5 % aqueous sodium hydrogencarbonate solution. After extraction with dichloromethane (3×30 mL), the combined organic phases were washed with saturated aqueous sodium chloride solution (30 mL) and dried over sodium sulfate. The solvent was removed under reduced pressure, and the residue was purified by flash chromatography (petroleum ether/ethyl acetate) to afford the products.

Acknowledgements

We are grateful for the financial support of the National Natural Science Foundation of China (21372148), the Program for Changjiang Scholars and Innovative Research Team in University (IRT 1070), and the Shaanxi Innovative Team of Key Science and Technology (2013KCT-17).

Keywords: aryldiazonium salts · cross-coupling · green chemistry · N-heteroarenes · photoredox catalysis · water

[1] a) A. R. Katritzky, C. A. Ramsden, E. F. V. Scriven, R. J. K. Taylor, *Comprehensive Heterocyclic Chemistry, Vol. 7*, Elsevier, Oxford, **2008**; b) G. D. Henry, *Tetrahedron* **2004**, *60*, 6043–6061; c) J. Hassan, M. Sevignon, C. Gozzi, E. Schulz, M. Lemaire, *Chem. Rev.* **2002**, *102*, 1359–1470.

[2] a) E. Tyrrell, P. Brookes, *Synthesis* **2004**, 469–483; b) K. L. Billingsley, S. L. Buchwald, *J. Am. Chem. Soc.* **2007**, *129*, 3358–3366; c) K. L. Billingsley, S. L. Buchwald, *Angew. Chem.* **2008**, *120*, 4773–4776; *Angew. Chem. Int. Ed.* **2008**, *47*, 4695–4698.

[3] a) D. Alberico, M. E. Scott, M. Lautens, *Chem. Rev.* **2007**, *107*, 174–238; b) L. Ackermann, R. Vicente, A. R. Kapdi, *Angew. Chem.* **2009**, *121*, 9976–10011; *Angew. Chem. Int. Ed.* **2009**, *48*, 9792–9826; c) D. A. Colby, R. G. Bergman, J. A. Ellman, *Chem. Rev.* **2010**, *110*, 624–655.

[4] F. O'Hara, D. G. Blackmond, P. S. Baran, *J. Am. Chem. Soc.* **2013**, *135*, 12122–12134 and references therein.

[5] a) J. C. Lewis, A. M. Berman, R. G. Bergman, J. A. Ellman, *J. Am. Chem. Soc.* **2008**, *130*, 2493–2500; b) P. Guo, J. M. Joo, S. Rakshit, D. Sames, *J. Am. Chem. Soc.* **2011**, *133*, 16338–16341; c) J. Kwak, M. Kim, S. Chang, *J. Am. Chem. Soc.* **2011**, *133*, 3780–3783.

[6] a) A. Larivée, J. J. Mousseau, A. B. Charette, *J. Am. Chem. Soc.* **2008**, *130*, 52–54; b) S. D. Yang, C.-L. Sun, Z. Fang, B.-J. Li, Y.-Z. Li, Z.-J. Shi, *Angew. Chem.* **2008**, *120*, 1495–1498; *Angew. Chem. Int. Ed.* **2008**, *47*, 1473–1476; c) L.-C. Campeau, D. R. Stuart, J.-P. Leclerc, M. Bertrand-Laperle, E. Villemure, H.-Y. Sun, S. Lasserre, N. Guimond, M. Lecavallier, K. Fagnou, *J. Am. Chem. Soc.* **2009**, *131*, 3291–3306; d) M. Tobisu, I. Hyodo, N. Chatani, *J. Am. Chem. Soc.* **2009**, *131*, 12070–12071; e) A. M. Wasa, B. Worrell, J.-Q. Yu, *Angew. Chem.* **2010**, *122*, 1297–1299; *Angew. Chem. Int. Ed.* **2010**, *49*, 1275–1277; f) M. Ye, G.-L. Gao, A. J. F. Edmunds, P. A. Worthington, J. A. Morris, J.-Q. Yu, *J. Am. Chem. Soc.* **2011**, *133*, 19090–19093.

[7] a) J. Norinder, A. Matsumoto, N. Yoshikai, E. Nakamura, *J. Am. Chem. Soc.* **2008**, *130*, 5858–5859; b) H.-Q. Do, R. M. K. Khan, O. Daugulis, *J. Am. Chem. Soc.* **2008**, *130*, 15185–15192; c) P. B. Arockiam, C. Fischmeister, C. Bruneau, P. H. Dixneuf, *Angew. Chem.* **2010**, *122*, 6779–6782; *Angew. Chem. Int. Ed.* **2010**, *49*, 6629–6632.

[8] a) D. Zhao, W. Wang, S. Lian, F. Yang, J. Lan, J. You, *Chem. Eur. J.* **2009**, *15*, 1337–1340; b) D. Zhao, W. Wang, F. Yang, J. Lan, L. Yang, G. Gao, J. You, *Angew. Chem.* **2009**, *121*, 3346–3350; *Angew. Chem. Int. Ed.* **2009**, *48*, 3296–3300; c) B. Liu, X. Qin, K. Li, X. Li, Q. Guo, J. Lan, J. You, *Chem. Eur. J.* **2010**, *16*, 11836–11839; d) P. Xi, F. Yang, S. Qin, D. Zhao, J. Lan, G. Gao, C. Hu, J. You, *J. Am. Chem. Soc.* **2010**, *132*, 1822–1824; e) Z. Wang, K. Li, D. Zhao, J. Lan, J. You, *Angew. Chem.* **2011**, *123*, 5477–5481; *Angew. Chem. Int. Ed.* **2011**, *50*, 5365–5369; f) C. C. Malakar, D. Schmidt, J. Conrad, U. Beifuss, *Org. Lett.* **2011**, *13*, 1378–1381.

[9] a) F. Vallée, J. J. Mousseau, A. B. Charette, *J. Am. Chem. Soc.* **2010**, *132*, 1514–1516; b) I. B. Seiple, S. Su, R. A. Rodriguez, R. Gianatassio, Y. Fujiwara, A. L. Sobel, P. S. Baran, *J. Am. Chem. Soc.* **2010**, *132*, 13194–13196; c) Y. Fujiwara, V. Domingo, I. B. Seiple, R. Gianatassio, M. D. Bel, P. S. Baran, *J. Am. Chem. Soc.* **2011**, *133*, 3292–3295; d) Y. Ji, T. Brueckl, R. D. Baxter, Y. Fujiwara, I. B. Seiple, S. Su, D. G. Blackmond, P. S. Baran, *Proc. Natl. Acad. Sci. USA* **2011**, *108*, 14411–14415; e) Y. Fujiwara, J. A. Dixon, F. O'Hara, E. D. Funder, D. D. Dixon, R. A. Rodriguez, R. D. Baxter, B. Herlé, N. Sach, M. R. Collins, Y. Ishihara, P. S. Baran, *Nature* **2012**, *492*, 95–99.

[10] a) R. Möhlau, R. Berger, *Chem. Ber.* **1893**, *26*, 1196–1200; b) M. Gomberg, W. E. Bachmann, *J. Am. Chem. Soc.* **1924**, *46*, 2339–2343; c) R. Pschorr, *Chem. Ber.* **1896**, *29*, 496–501.

[11] a) M. R. Heinrich, O. Blank, S. Wöfel, *Org. Lett.* **2006**, *8*, 3323–3325; b) M. R. Heinrich, O. Blank, D. Ullrich, M. Kirschstein, *J. Org. Chem.* **2007**, *72*, 9609–9616; c) A. Wetzel, V. Ehrhardt, M. R. Heinrich, *Angew. Chem.* **2008**, *120*, 9270–9273; *Angew. Chem. Int. Ed.* **2008**, *47*, 9130–9133; d) A. Wetzel, G. Pratsch, R. Kolb, M. R. Heinrich, *Chem. Eur. J.* **2010**, *16*, 2547–2556; e) G. Pratsch, C. A. Anger, K. Ritter, M. R. Heinrich, *Chem. Eur. J.* **2011**, *17*, 4104–4108.

[12] T. B. Patrick, R. P. Willaredt, D. J. DeGonia, *J. Org. Chem.* **1985**, *50*, 2232–2235.

[13] For reviews on photoredox catalysis, see: a) D. P. Hari, B. König, *Angew. Chem.* **2013**, *125*, 4832–4842; *Angew. Chem. Int. Ed.* **2013**, *52*, 4734–4743; b) C. K. Prier, D. A. Rankic, D. W. C. MacMillan, *Chem. Rev.* **2013**, *113*, 5322–5363; c) J. Xuan, W.-J. Xiao, *Angew. Chem.* **2012**, *124*, 6934–6944; *Angew. Chem. Int. Ed.* **2012**, *51*, 6828–6838; d) J. W. Tucker, C. R. J. Stephenson, *J. Org. Chem.* **2012**, *77*, 1617–1622; e) K. Zeitler, *Angew. Chem.* **2009**, *121*, 9969–9974; *Angew. Chem. Int. Ed.* **2009**, *48*, 9785–9789; f) T. P. Yoon, M. A. Ischay, J. Du, *Nat. Chem.* **2010**, *2*, 527–532; g) J. M. R. Narayanam, C. R. J. Stephenson, *Chem. Soc. Rev.* **2011**, *40*, 102–113; h) F. Teplý, *Collect. Czech. Chem. Commun.* **2011**, *76*, 859–917.

[14] For selected works from the MacMillan group, see: a) A. McNally, C. K. Prier, D. W. C. MacMillan, *Science* **2011**, *334*, 1114–1117; b) D. A. Nagib, D. W. C. MacMillan, *Nature* **2011**, *480*, 224–228; c) P. V. Pham, D. A. Nagib, D. W. C. MacMillan, *Angew. Chem.* **2011**, *123*, 6243–6246; *Angew. Chem. Int. Ed.* **2011**, *50*, 6119–6122; d) H.-W. Shih, M. N. V. Wal, R. L. Grange, D. W. C. MacMillan, *J. Am. Chem. Soc.* **2010**, *132*, 13600–13603; e) D. A. Nagib, M. E. Scott, D. W. C. MacMillan, *J. Am. Chem. Soc.* **2009**, *131*, 10875–10877; f) D. A. Nicewicz, D. W. C. MacMillan, *Science* **2008**, *322*, 77–80.

[15] For selected works from the Yoon group, see: a) Z. Lu, M. Shen, T. P. Yoon, *J. Am. Chem. Soc.* **2011**, *133*, 1162–1164; b) M. A. Ischay, Z. Lu, T. P. Yoon, *J. Am. Chem. Soc.* **2010**, *132*, 8572–8574; c) J. Du, T. P. Yoon, *J. Am. Chem. Soc.* **2009**, *131*, 14604–14606; d) M. A. Ischay, M. E. Anzovino, J. Du, T. P. Yoon, *J. Am. Chem. Soc.* **2008**, *130*, 12886–12887.

[16] For selected works from the Stephenson group, see: a) C.-J. Wallentin, J. D. Nguyen, P. Finkbeiner, C. R. J. Stephenson, *J. Am. Chem. Soc.* **2012**, *134*, 8875–8884; b) L. Furst, J. M. R. Narayanam, C. R. J. Stephenson, *Angew. Chem.* **2011**, *123*, 9829–9833; *Angew. Chem. Int. Ed.* **2011**, *50*, 9655–9659; c) J. D. Nguyen, J. W. Tucker, M. D. Konieczynska, C. R. J. Stephenson, *J. Am. Chem. Soc.* **2011**, *133*, 4160–4163; d) C.-H. Dai, J. M. R. Narayanam, C. R. J. Stephenson, *Nat. Chem.* **2011**, *3*, 140–145; e) J. M. R. Narayanam, J. W. Tucker, C. R. J. Stephenson, *J. Am. Chem. Soc.* **2009**, *131*, 8756–8757.

[17] For selected works from other research groups, see: a) T. Koike, M. Akita, *Chem. Lett.* **2009**, *38*, 166–167; b) S. Maity, M. Zhu, R. S. Shinabery, N. Zheng, *Angew. Chem.* **2012**, *124*, 226–230; *Angew. Chem. Int. Ed.* **2012**, *51*, 222–226; c) S. Maity, N. Zheng, *Angew. Chem.* **2012**, *124*, 9700–9704; *Angew. Chem. Int. Ed.* **2012**, *51*, 9562–9566; d) Y.-Q. Zou, J.-R. Chen, X.-P. Liu, L.-Q. Lu, R. L. Davis, K. A. Jøgensen, W.-J. Xiao, *Angew. Chem.* **2012**, *124*, 808–812; *Angew. Chem. Int. Ed.* **2012**, *51*, 784–788; e) T. Courant, G. Masson, *Chem. Eur. J.* **2012**, *18*, 423–427; f) Y.-Q. Zou, L.-Q. Lu, L. Fu, N.-J. Chang, J. Rong, J.-R. Chen, W.-J. Xiao, *Angew. Chem.* **2011**, *123*, 7309–7313; *Angew. Chem. Int. Ed.* **2011**, *50*, 7171–7175; g) M.-H. Larraufie, R. Pellet, L. Fensterbank, J.-P. Goddard, E. Lacote, M. Malacria, C. Ollivier, *Angew. Chem.* **2011**, *123*, 4555–4558; *Angew. Chem. Int. Ed.* **2011**, *50*, 4463–4466; h) M. Neumann, S. Fuldner, B. König, K. Zeitler, *Angew. Chem.* **2011**, *123*, 981–985; *Angew. Chem. Int. Ed.* **2011**, *50*, 951–954; i) M. Rueping, S. Zhu, R. M. Koenigs, *Chem. Commun.* **2011**, *47*, 8679–8681; j) Y. Su, L. Zhang, N. Jiao, *Org. Lett.* **2011**, *13*, 2168; k) T. Maji, A. Karmakar, O. Reiser, *J. Org. Chem.* **2011**, *76*, 736–739; l) R. S. Andrews, J. J. Becker, M. R. Gagne, *Angew. Chem.* **2010**, *122*, 7432–7434; *Angew. Chem. Int. Ed.* **2010**, *49*, 7274–7276.

[18] a) D. Kalyani, K. B. McMurtrey, S. R. Neufeldt, M. S. Sanford, *J. Am. Chem. Soc.* **2011**, *133*, 18566–18569; b) D. P. Hari, P. Schroll, B. König, *J. Am. Chem. Soc.* **2012**, *134*, 2958–2961; c) Y. Cheng, X. Gu, P. Li, *Org. Lett.* **2013**, *15*, 2664–2667.

[19] Y.-X. Liu, D. Xue, J.-D. Wang, C.-J. Zhao, Q.-Z. Zou, C. Wang, J. Xiao, *Synlett* **2013**, 507–513.

[20] For details, see the Supporting Information.

[21] a) J. W. Daly, W. Padgett, M. T. Shamim, P. Butts-Lamb, J. Waters, *J. Med. Chem.* **1985**, *28*, 487–492; b) Y.-C. Kim, X.-D. Ji, N. Melman, J. Linden, K. A. Jacobson, *J. Med. Chem.* **2000**, *43*, 1165–1172; c) R. V. Kalla, E. Elzein, T. Perry, X. Li, V. Palle, V. Varkhedkar, A. Gimbel, T. Maa, D. Zeng, J. Zablocki, *J. Med. Chem.* **2006**, *49*, 3682–3692; d) L. Yan, C. E. Mller, *J. Med. Chem.* **2004**, *47*, 1031–1043; e) A. M. Hayallah, J. S. Ramrez, U. Reith, U. Schobert, B. Preiss, B. Schumacher, J. W. Daly, C. E. Müller, *J. Med. Chem.* **2002**, *45*, 1500–1510; f) P. G. Baraldi, M. A. Tabrizi, D. Preti, A. Bovero, R. Romagnoli, F. Fruttarolo, N. A. Zaid, A. R. Moorman, K. Varani, S. Gessi, S. Merighi, P. A. Borea, *J. Med. Chem.* **2004**, *47*, 1434–1447.

[22] a) C. P. Andrieux, J. Pinson, *J. Am. Chem. Soc.* **2003**, *125*, 14801–14806; b) M. Mahesh, J. A. Murphy, F. LeStrat, H. P. Wessel, *Beilstein J. Org. Chem.* **2009**, *5*, no. 1.

Received: October 22, 2013
Revised: December 2, 2013