Photocatalysis

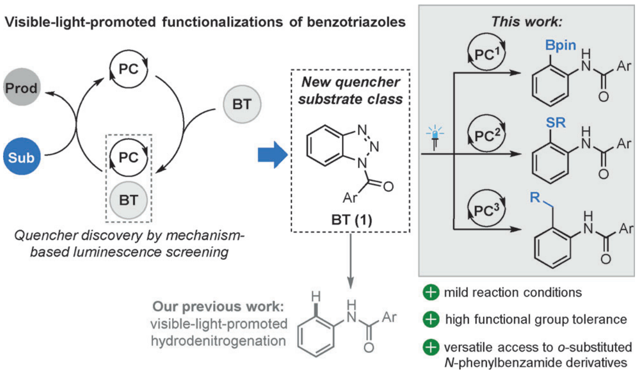
International Edition: DOI: 10.1002/anie.201609393
German Edition: DOI: 10.1002/ange.201609393

Diverse Visible-Light-Promoted Functionalizations of Benzotriazoles Inspired by Mechanism-Based Luminescence Screening

*Michael Teders, Adrián Gómez-Suárez+, Lena Pitzer+, Matthew N. Hopkinson, and Frank Glorius**

Abstract: *Three new visible-light-promoted functionalizations of benzotriazole substrates were discovered using a mechanism-based screening method. ortho-Thiolated, borylated, and alkylated N-arylbenzamide products were obtained under mild reaction conditions in a new denitrogenative synthetic approach to functionalized aniline derivatives. The functional group tolerance of the borylation reaction was further analyzed in the first application of an additive-based robustness screen in a photocatalytic transformation. All the functionalizations proceed via photocatalytically initiated chain mechanisms as indicated by determination of the reaction quantum yields and Stern–Volmer analyses.*

Recently, the use of photocatalysts capable of effectively transferring energy from visible light to non-absorbing compounds has gained increasing attention. This approach allows for the mild and selective generation of radicals in a controlled fashion and has led to new transformations involving unique bond constructions.[1] A fundamental step, common to all photocatalytic processes, involves the direct interaction of the excited catalyst with a quencher substrate and many research programs are duly focused on identifying and applying new classes of quenchers. We recently reported a conceptually novel mechanism-based screening method that accelerates this discovery process using luminescence spectroscopy.[2] Whereas most screening approaches are “reaction-based” and look for the formation of an overall reaction product,[3] a mechanism-based screening focuses directly on a single key mechanistic step central to a general reaction class.[4] While not providing individual working reactions, this approach leads to the identification of new substrates, potentially suitable for many transformations within that reaction class, and can furthermore provide insights into the key steps that are useful for reaction optimization and mechanistic elucidation. During our mechanism-based screen of one hundred potential substrates for photocatalysis, we discovered benzotriazoles as a new quencher class. Aided by data obtained, we designed and realized a novel photocatalytic hydro-denitrogenation reaction of various 1-(benzoyl)benzotriazoles (**1**) leading to *N*-arylbenzamides (see Scheme 1).[2] While benzotriazoles have demonstrated activity under irradiation with ultraviolet light such as in the photolytic Graebe–Ullmann carbazole synthesis,[5] functionalization of these compounds by visible-light photocatalysis has, to the best of our knowledge, not been reported before. Herein, building on the discovery of this new quencher class, we greatly expand the scope of visible-light photocatalysis with benzotriazoles by developing three new *o*-functionalization reactions. Denitrogenative routes to *o*-borylated, -thiolated, and -alkylated *N*-arylbenzamide derivatives directly from bench-stable substrates have been developed by a novel disconnection strategy for the synthesis of these common organic building blocks (Scheme 1).



Scheme 1. Quencher identification based on luminescence quenching and diverse functionalization strategies. PC = photocatalyst, BT = benzotriazole.

Firstly, we turned to the results of the mechanism-based screening study to obtain information on the operating quenching mode and to identify the optimum photocatalyst and substrate combination. By monitoring the luminescence of eight widely employed polypyridyl metal photocatalysts in the presence of 1-(benzoyl)benzotriazole (**1a**) using a standard luminescence spectrometer, we observed efficient quenching with *fac*-[Ir(ppy)$_3$] (ppy = 2-phenylpyridine) and the NHC-containing iridium complex [Ir(ppy)$_2$(NHC-F$_2$)] (**A**) (NHC-F$_2$ = 1-(2,4-difluorophenyl)-3-methyl-2,3-dihydro-1*H*-imidazolydene) as well as moderate quenching with *fac*-[Ir(dF(ppy)$_3$)] (dF(ppy) = 2-(2,4-difluorophenyl)pyridine).[6] These results are highly indicative of an oxidative quenching pathway since these catalysts possess high excited-state

---

[*] M. Teders, Dr. A. Gómez-Suárez,[+] L. Pitzer,[+] Prof. Dr. F. Glorius
Organisch-Chemisches Institut
Westfälische Wilhelms-Universität Münster
Corrensstrasse 40, 48149 Münster (Germany)
E-mail: glorius@uni-muenster.de

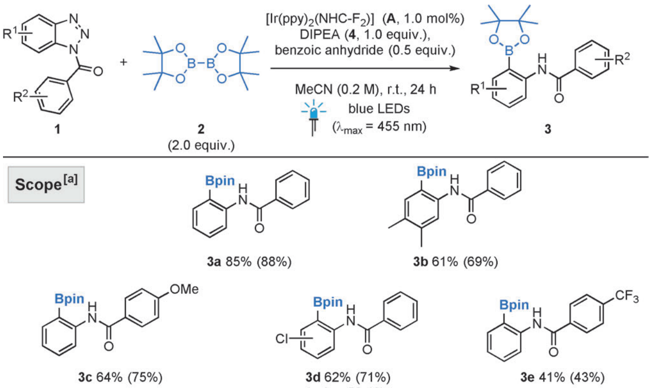
Prof. Dr. M. N. Hopkinson
Institut für Chemie und Biochemie
Freie Universität Berlin
Takustrasse 3, 14195 Berlin (Germany)

[+] These authors contributed equally to this work.

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.201609393.

reduction potentials. A mechanistic scenario involving photo-induced single-electron reduction is consistent with literature reports on benzotriazoles bearing electron-withdrawing substituents on the nitrogen, which are thought to stabilize the ring-opened zwitterionic diazonium form of these compounds in polar solvents.[7] Regarding benzotriazoles as masked diazonium compounds led us to consider whether analogous light-promoted functionalization reactions to those achieved with commonly employed diazonium salt quenchers could be developed.[8,9]

Inspired by a report on a synthetic route to arylboronates via visible-light-induced borylation of aryldiazonium salts,[10] we first designed a denitrogenative borylation of benzotriazoles leading to *o*-borylated *N*-arylbenzamides **3** (see Scheme 2). The obtained aromatic arylboronic esters are important building blocks in organic synthesis that are widely applied in cross-coupling chemistry.[11] In a preliminary experiment, a solution of **1a** (0.10 M) in acetonitrile was irradiated with visible light from blue LEDs in the presence of bis(pinacolato)diboron (B_2pin_2 **2**; 3.0 equiv) and photocatalyst **A** (2.5 mol %), which was identified as an optimal photocatalyst in the screening. Since only trace amounts of the desired borylated product **3a** were observed, we considered possible factors hindering a successful reaction. One potential pitfall concerns the turnover of the photocatalytic cycle, that is, the regeneration of the Ir^{III} catalyst from the Ir^{IV} species, obtained upon oxidative quenching. We hypothesized that the addition of *N*,*N*-diisopropylethylamine (DIPEA, **4**) as a sacrificial electron donor should alleviate this problem and, indeed, when **4** was added under otherwise the same conditions, the desired product was obtained in 47 % GC yield. After optimization, the yield of isolated **3a** could be increased to 85 %.[6]



3a 85% (88%)

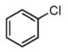
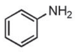
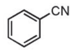
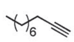
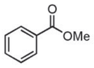
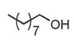
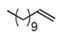
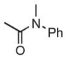
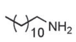
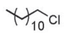
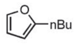
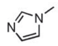
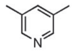
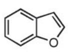
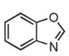
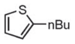
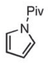
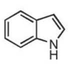
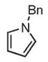
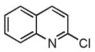
3b 61% (69%)

3c 64% (75%)

3d 62% (71%) (*m*/*p* = 58:42)

3e 41% (43%)

Robustness Screen

Entry	Additive	Yield of 3a %[b]	Additive remaining %[b]
1	none	✓ 92	
2		✓ 96	✓ 89
3		x <5	x 21
4		✓ 67	✓ >95
5		✓ 94	✓ 93
6		✓ 69	✓ 80
7		✓ 89	x 7
8		✓ 84	✓ >95
9		✓ 91	✓ 75
10		✓ 78	x 27
11		✓ 88	x 12
12		✓ 92	✓ 93
13		- 39	✓ 70
14		✓ 92	✓ 77
15		✓ 83	- 55
16		✓ >95	✓ >95
17		✓ 86	✓ 84
18		✓ 67	✓ 79
19		- 44	✓ 88
20		✓ >95	✓ >95
21		- 59	✓ >95

Scheme 2. Substrate scope and robustness screen for the borylation. [a] **1** (0.30 mmol), **2** (2.0 mmol), **4** (0.30 mmol), benzoic anhydride (0.15 mmol), **A** (0.5 mol %), MeCN (0.20 M). NMR yields in paranthesis. [b] GC yield. Piv = pivaloyl.

Having found suitable conditions, we next investigated the scope of this C−B bond-forming reaction (Scheme 2). The presence of electron-donating or -withdrawing substituents on the benzotriazole core was tolerated and products **3b** and **3d** were isolated in 61 % and 62 % yield, respectively. *para*-MeO-Substitution on the benzoyl fragment led to the borylated product **3c** in 64 % yield, whereas the addition of an electron-withdrawing *para*-CF_3 substituent resulted in a lower yield (41 %).

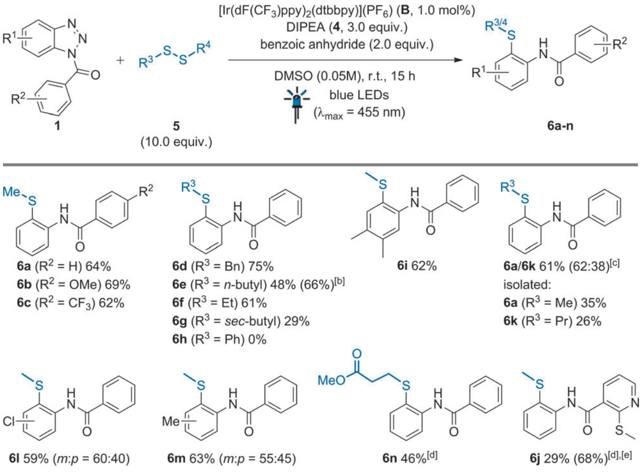
For a deeper understanding of the scope and limitations of this denitrogenative borylation, we conducted an additive-based robustness screen,[12] which is the first application of this method to a photocatalytic reaction. To our delight, most of the additives representing various functional groups neither inhibited product formation nor decomposed under the reaction conditions. The addition of aniline (Scheme 2, entry 3), however, led to the complete shutdown of product formation and consumption of the additive. 1-Nonanol (entry 7), 1-aminododecane (entry 10), 1-chlorododecane (entry 11), and benzofuran (entry 15) were consumed under the reaction conditions but did not affect the formation of the product **3a**. *N*-Methylimidazole (entry 13), indole (entry 19), and 2-chloroquinoline (entry 21) slightly inhibited the photocatalytic transformation of **3a**. These results indicate a high functional-group tolerance of this transformation and suggest that this approach may be useful for the synthesis of *ortho*-borylated aniline derivatives.

Inspired by a report by Jacobi von Wangelin and Majek on a visible-light-mediated synthesis of aryl sulfides from aryl diazonium salts,[13] we next focused on the development of a thiolation of benzotriazoles. The obtained *ortho*-thiolated *N*-arylbenzamides **6a–n** are useful intermediates for the synthesis of bicyclic 4*H*-[1,2,4]thiadiazine heterocycles,[14] which feature in several important drug molecules.[15] Initially, **1a** was reacted with 10.0 equiv of dimethyl disulfide in DMSO (0.05 M) in the presence of photocatalyst **A** (2.5 mol %). After 15 h of visible-light irradiation, we observed the desired product **6a** in 29 % GC yield. Optimization studies on solvents, stoichiometries, and reaction conditions, however, did not reveal an appropriate protocol with one of the three highly reducing photocatalysts identified through the mechanism-based screening.[6]

At this stage, we considered whether an alternative reductive quenching manifold may lead to a more efficient process. In this scenario, substrate **1** is not reduced by the excited photocatalyst but, rather, in a subsequent step in the cycle by a Ru^{I} or Ir^{II} species generated upon electron reduction by a suitable reductive quencher. While our mechanism-based screening method does not provide direct information on this step, the insights obtained previously still prove useful for selecting an appropriate catalyst and quencher combination. For example, analysis of the excited-state oxidation potentials of the three successful Ir complexes for oxidative quenching suggest that a photocatalyst with a ground-state reduction potential ($E(\mathrm{M}^{n-1}{-}\mathrm{M}^{n})$) of around −1.35 V vs. SCE in MeCN would be required. Additionally, a fast screen of these complexes with various reductive quenchers reveals which electron donors would be suitable for each catalyst. Complex $[\mathrm{Ir(dF(CF_3)ppy)_2(dtbbpy)}]\mathrm{PF_6}$ (**B**; $\mathrm{(dF(CF_3)ppy}$ = 2-(2,4-difluorophenyl)-3-trifluoromethylpyridine, dtbbpy = 4,4′-di-*tert*-butyl-2,2′-bipyridine), which was not quenched by **1a** during screening, seemed to fit these criteria, having a ground-state reduction potential ($E(\mathrm{Ir^{II}{-}Ir^{III}})$) of −1.37 V vs. SCE in MeCN and demonstrating efficient quenching with **4**. Indeed, switching to this photocatalyst in the presence of **4** resulted in formation of **6a** in 67 % yield.[6]

With the optimized reaction conditions in hand, we explored the scope and the limitations of this thiolation reaction (Table 1). Changing the electronic properties of the aroyl fragment by adding *para*-MeO or *para*-$\mathrm{CF_3}$ substituents delivered the desired products **6b** and **6c** in good yields (62 % and 69 %, respectively). Substrates with Cl or Me substituents on the benzotriazole gave the desired isolated products in 59–63 % yield. In terms of the disulfide, alkyl and benzyl derivatives gave the corresponding products in moderate to good yields (**6d**–**6f**; 48–75 % yield). Aryl disulfides, however, were not suitable coupling partners. The sterically demanding *sec*-butyl disulfide led to a lower yield of 29 % of **6g**, while the ester-containing disulfide was marginally better tolerated (**6n**, 46 %). When a benzotriazole featuring a 1-(3-pyridoyl) substituent was used, the bis-thiolated compound **6j** was identified as the major product (29 %). When an intramolecular competition experiment was performed by using the unsymmetrical methyl propyl disulfide, a 62:38 mixture of products was obtained in an overall yield of 61 % with the methyl-substituted product **6a** as the major compound.

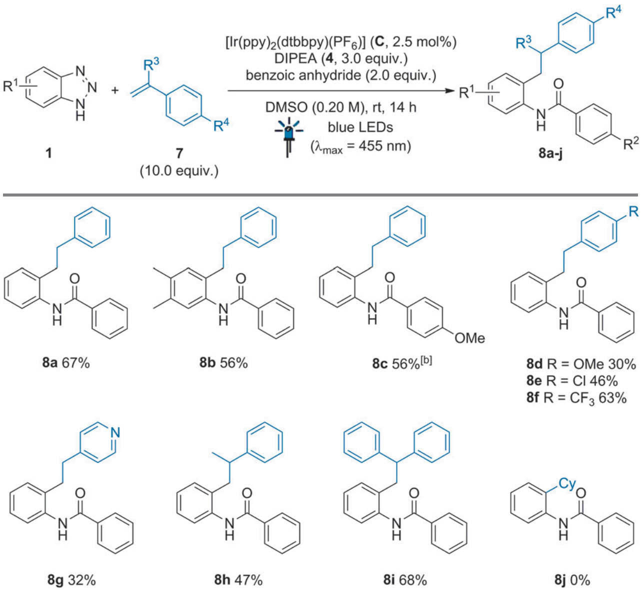
Table 1: Substrate scope of the denitrogenative thiolation.[a]



[a] **1a**–**n** (0.30 mmol), **5** (3.0 mmol), **4** (0.90 mmol), benzoic anhydride (0.60 mmol), **B** (1.0 mol %), DMSO (0.05 м). [b] NMR yield in parenthesis. [c] Unsymmetrical disulfide was used. [d] NMR yield. [e] With benzotriazole featuring a 1-(3-pyridoyl) substituent.

After having applied benzotriazoles **1** in visible-light-mediated C−S and C−B bond-forming reactions, we next focused on the development of a novel C−C bond-forming reaction. As pioneered by the König group, aryl radicals generated upon photoredox decomposition of aryldiazonium salts can be engaged in various Meerwein-type addition processes with alkenes.[8b] Inspired by this work, we designed a reductive coupling of benzotriazoles with styrene derivatives that we hoped would provide facile access to diverse *ortho*-alkylated benzamides. As before, we started our optimization using a photocatalyst identified during screening: photocatalyst **A** (2.5 mol %) in the presence of **4** (3.0 equiv) as an electron and hydrogen source and DMSO (0.10 м) as solvent. After 15 h irradiation, the alkylated product **8a** was observed in 9 % GC yield. In analogy to the thiolation reaction, switching to the reductive quenching manifold using sacrificial reductive quencher **4** and photocatalyst **B** or $[\mathrm{Ir(ppy)_2(dtbbpy)}]\mathrm{PF_6}$ (**C**) led to an increase in efficiency. After an optimization study, the yield of **8a** could be increased to 67 % using the latter catalyst and generating the 1-(benzoyl)-substituted substrates in situ from 1*H*-benzotriazoles and benzoic anhydride.[6] Exploring the scope (Table 2) we found that substrates having methyl substituents at the *meta*- and *para*-positions of the benzotriazole gave the

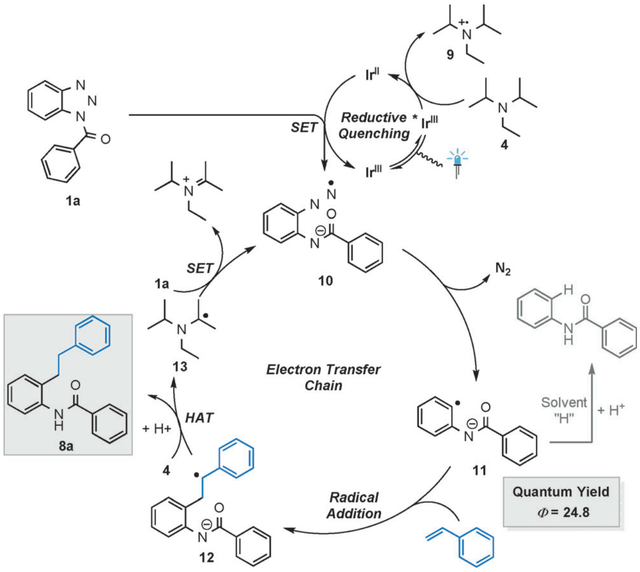
Table 2: Substrate scope of the denitrogenative alkylation.[a]



[a] **1a**–**j** (0.30 mmol), **7** (3.0 mmol), **4** (0.90 mmol), benzoic anhydride (0.60 mmol), **C** (2.5 mol %), DMSO (0.20 м). [b] Using 4-methoxybenzoic anhydride. Cy = cyclohexyl.

corresponding product **8b** in 56 % yield, while the addition of a *para*-MeO substituent on the benzoyl fragment resulted in the formation of product **8c** in 56 % yield. Various styrenes with different electronic properties could be employed affording alkylated products **8d**–**8i** in moderate to good yields (30–68 %). The obtained products have, to the best of our knowledge, not been described previously. However, related structural motifs can be found in several novel drug candidates for the regulation of estrogen receptors[16] and for the inhibition of factor Xa.[17] In accordance with other Meerwein-type addition processes of aryl radicals, aliphatic alkenes, which are comparatively poor radical acceptors, were not suitable coupling partners.

A plausible mechanism for the photocatalytic alkylation of benzotriazoles, which is consistent with the screening results and a full Stern–Volmer analysis, is shown in Scheme 3.[6] Upon irradiation, the excited photocatalyst undergoes single-electron transfer with the reductive quencher **4,** resulting in the generation of an amine radical cation **9** and a highly reducing Ir^{II} species. Electron transfer from this complex to the benzotriazole **1a** regenerates the photocatalyst and results in the formation of the highly reactive species **10**, which immediately extrudes nitrogen to give the aryl radical **11**. The intermediate **11** can then add to the styrene coupling partner to give the stabilized radical **12**. At this stage, hydrogen-atom abstraction is thought to occur either from another molecule of **4** or from the radical cation **9** generating the alkylated benzamide product **8a**. When DIPEA (**4**) is the hydrogen atom source, the resulting amino radical species **13** seems to act as a potent single-electron donor, reducing another molecule of the benzotriazole starting material as part of a radical chain mechanism.[18] Indeed, quantum yield measurements of this alkylation process ($\Phi = 24.8$) and also of the borylation ($\Phi = 64.7$) and thiolation ($\Phi = 48.5$) reactions indicate that radical chains are the major product-forming pathway in these transformations.[19]



Scheme 3. Plausible mechanism for the alkylation of **1**. SET = single-electron transfer, HAT = hydrogen-atom transfer.

In conclusion, we have applied benzotriazole substrates identified by a mechanism-based screening approach, in three new visible-light-mediated functionalization reactions. C–S, C–B, and C–C bond-forming denitrogenative transformations were achieved under mild conditions giving straightforward access to *ortho*-functionalized *N*-arylbenzamides via a novel synthetic approach. In addition to providing the inspiration for these processes through the discovery of the benzotriazoles as new oxidative quenchers, the mechanism-based screening also revealed insights into the quenching step which were helpful in the optimization of each reaction, especially when the alternative reductive quenching manifold proved more efficient. Mechanism-based luminescence screening is a useful tool for accelerating the development of new photocatalytic reactions and further applications of this method are under exploration in our laboratory.

Acknowledgements

We thank Prof. B. J. Ravoo for use of the UV/Vis spectrometer and S. Mukherjee and L. Schlatt (all WWU) for experimental support. This work was supported by the Deutsche Forschungsgemeinschaft (Leibniz Award) and the Alexander von Humboldt Foundation (M.N.H).

Keywords: benzotriazoles · luminescence · photocatalysis · radicals · screening

---

[1] For selected reviews on visible-light photoredox catalysis, see: a) K. Zeitler, *Angew. Chem. Int. Ed.* **2009**, *48*, 9785; *Angew. Chem.* **2009**, *121*, 9969; b) T. P. Yoon, M. A. Ischay, J. Du, *Nat. Chem.* **2010**, *2*, 527; c) J. M. R. Narayanam, C. R. J. Stephenson, *Chem. Soc. Rev.* **2011**, *40*, 102; d) L. Shi, W. Xia, *Chem. Soc. Rev.* **2012**, *41*, 7687; e) Y. Xi, H. Yi, A. Lei, *Org. Biomol. Chem.* **2013**, *11*, 2387; f) C. K. Prier, D. A. Rankic, D. W. C. MacMillan, *Chem. Rev.* **2013**, *113*, 5322; g) M. N. Hopkinson, B. Sahoo, J.-L. Li, F. Glorius, *Chem. Eur. J.* **2014**, *20*, 3874; h) E. Meggers, *Chem. Commun.* **2015**, *51*, 3290.

[2] M. N. Hopkinson, A. Gómez-Suárez, M. Teders, B. Sahoo, F. Glorius, *Angew. Chem. Int. Ed.* **2016**, *55*, 4361; *Angew. Chem.* **2016**, *128*, 4434.

[3] For examples of reaction-based screening approaches, see: a) A. McNally, C. K. Prier, D. W. C. MacMillan, *Science* **2011**, *334*, 1114; b) D. W. Robbins, J. F. Hartwig, *Science* **2011**, *333*, 1423; c) A. B. Santanilla et al., *Science* **2015**, *347*, 49; d) E. Wolf, E. Richmond, J. Moran, *Chem. Sci.* **2015**, *6*, 2501.

[4] For selected examples of mechanism-based screening used for reaction optimization or mechanistic elucidation, see: a) C. Markert, A. Pfaltz, *Angew. Chem. Int. Ed.* **2004**, *43*, 2498; *Angew. Chem.* **2004**, *116*, 2552; b) C. Markert, P. Rösel, A. Pfaltz, *J. Am. Chem. Soc.* **2008**, *130*, 3234; c) A. Teichert, A. Pfaltz, *Angew. Chem. Int. Ed.* **2008**, *47*, 3360; *Angew. Chem.* **2008**, *120*, 3408; d) C. Hinderling, P. Chen, *Angew. Chem. Int. Ed.* **1999**, *38*, 2253; *Angew. Chem.* **1999**, *111*, 2393; e) B. Dominguez, N. S. Hodnett, G. C. Lloyd-Jones, *Angew. Chem. Int. Ed.* **2001**, *40*, 4289; *Angew. Chem.* **2001**, *113*, 4419; h) J. Wassenaar, E. Jansen,

W.-J. van Zeist, F. M. Bickelhaupt, M. A. Siegler, A. L. Spek, J. N. H. Reek, *Nat. Chem.* **2010**, *2*, 417.

[5] a) C. Graebe, F. Ullmann, *Liebigs Ann. Chem.* **1896**, *291*, 16; For a review on *N*-substituted benzotriazoles, see: b) A. R. Katritzky, X. Lan, J. Z. Yang, O. V. Denisko, *Chem. Rev.* **1998**, *98*, 409.

[6] See Supporting Information for further details.

[7] a) A. R. Katritzky, F. B. Ji, W. Q. Fan, J. K. Gallos, J. V. Greenhill, R. W. King, P. J. Steel, *J. Org. Chem.* **1992**, *57*, 190; b) I. Nakamura, T. Nemoto, N. Shiraiwa, M. Terada, *Org. Lett.* **2009**, *11*, 1055.

[8] a) D. P. Hari, T. Hering, B. König, *Angew. Chem. Int. Ed.* **2014**, *53*, 725; *Angew. Chem.* **2014**, *126*, 743; b) For a review on photocatalyzed Meerwein arylations, see: D. P. Hari, B. König, *Angew. Chem. Int. Ed.* **2013**, *52*, 4734; *Angew. Chem.* **2013**, *125*, 4832; c) H. Wang, S. Yu, *Org. Lett.* **2015**, *17*, 4272; d) T. Xiao, X. Dong, Y. Tang, L. Zhou, *Adv. Synth. Catal.* **2012**, *354*, 3195.

[9] For examples on the use of aryl diazonium salts in dual catalytic processes, see: a) D. Kalyani, K. B. McMurtrey, S. R. Neufeldt, M. S. Sanford, *J. Am. Chem. Soc.* **2011**, *133*, 18566; b) B. Sahoo, M. N. Hopkinson, F. Glorius, *J. Am. Chem. Soc.* **2013**, *135*, 5505; c) X. Shu, M. Zhang, Y. He, H. Frei, F. D. Toste, *J. Am. Chem. Soc.* **2014**, *136*, 5844.

[10] J. Yu, L. Zhang, G. Yan, *Adv. Synth. Catal.* **2012**, *354*, 2625.

[11] a) *Boronic Acids*: *Preparation and Applications in Organic Synthesis and Medicine* (Ed.: D. G. Hall), Wiley-VCH, Weinheim, **2005**; b) N. Miyaura, A. Suzuki, *Chem. Rev.* **1995**, *95*, 2457; c) Y.-M. Wang, J. Wu, C. Hoong, V. Rauniyar, F. D. Toste, *J. Am. Chem. Soc.* **2012**, *134*, 12928.

[12] a) K. D. Collins, F. Glorius, *Nat. Chem.* **2013**, *5*, 597; b) K. D. Collins, A. Rühling, F. Glorius, *Nat. Protoc.* **2014**, *9*, 1348; K. D. Collins, F. Glorius, *Acc. Chem. Res.* **2015**, *48*, 619.

[13] a) M. Majek, A. J. von Wangelin, *Chem. Commun.* **2013**, *49*, 5507.

[14] J. Zienkiewicz, P. Kaszynski, V. G. Young, *J. Org. Chem.* **2004**, *69*, 2551.

[15] a) B. M. Winer, *Circulation* **1961**, *23*, 211; b) F. W. Wolff, W. W. Parmley, *Diabetes* **1964**, *13*, 115.

[16] A. Kamada, A. Sasaki, N. Kitazawa, T. Okabe, K. Nara, S. Hamaoka, S. Araki, H. Hagiwara, *Chem. Pharm. Bull.* **2004**, *52*, 79.

[17] H. Koshio et al., *Bioorg. Med. Chem.* **2005**, *13*, 1305.

[18] H. Ismaili, S. P. Pitre, J. C. Scaiano, *Catal. Sci. Technol.* **2013**, *3*, 935.

[19] Mechanistic hypotheses for the photocatalytic thiolation and borylation reactions can be found in the Supporting Information.

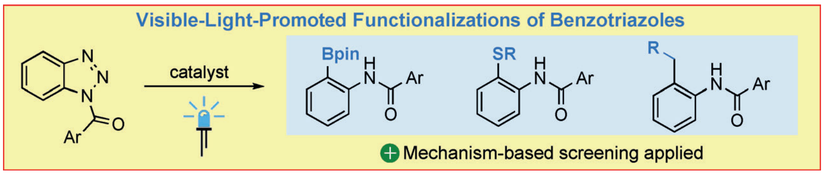
Manuscript received: September 24, 2016
Final Article published: ■■ ■■, ■■■■

Communications

Photocatalysis

M. Teders, A. Gómez-Suárez, L. Pitzer,
M. N. Hopkinson,
F. Glorius* ____________ ■■■■–■■■■

Diverse Visible-Light-Promoted Functionalizations of Benzotriazoles Inspired by Mechanism-Based Luminescence Screening



Trinity! Three visible-light-promoted functionalization reactions of benzotriazole substrates were discovered using a mechanism-based screening method and provided *ortho*-thiolated, -borylated, and -alkylated *N*-arylbenzamide products. The functional group tolerance of the borylation reaction was further analyzed by the first application of an additive-based robustness screen in a photocatalytic transformation.