Screening Methods

International Edition: DOI: 10.1002/anie.201600995
German Edition: DOI: 10.1002/ange.201600995

Accelerated Discovery in Photocatalysis using a Mechanism-Based Screening Method

*Matthew N. Hopkinson, Adrián Gómez-Suárez, Michael Teders, Basudev Sahoo, and Frank Glorius**

Dedicated to Professor Andreas Pfaltz

Abstract: *Herein, we report a conceptually novel mechanism-based screening approach to accelerate discovery in photocatalysis. In contrast to most screening methods, which consider reactions as discrete entities, this approach instead focuses on a single constituent mechanistic step of a catalytic reaction. Using luminescence spectroscopy to investigate the key quenching step in photocatalytic reactions, an initial screen of 100 compounds led to the discovery of two promising substrate classes. Moreover, a second, more focused screen provided mechanistic insights useful in developing proof-of-concept reactions. Overall, this fast and straightforward approach both facilitated the discovery and aided the development of new light-promoted reactions and suggests that mechanism-based screening strategies could become useful tools in the hunt for new reactivity.*

To a large extent, inspiration for the design of new chemical transformations is rooted in deep understanding of reaction mechanisms and the fundamental reactivity trends and principles which underpin them. The scientific literature, however, is full of ground-breaking reports where the key advance was not planned but rather revealed as a result of experimental serendipity. Speeding up the discovery of such chance observations can be achieved through the use of screening technologies, which seek to unveil new reactivity by testing multiple substrates, reagents, and conditions in an efficient manner.[1,2] Regardless of the strategy employed, assessment of the outcome is most often conducted by analysis of the crude mixtures with the direct or indirect observation of a new product signifying a "hit". As such, these methodologies consider chemical reactions as discrete processes and can be loosely categorized as "reaction-based". As an alternative conceptual approach, we considered whether screening methodologies could be devised, which rather than looking for a new transformation as a whole, focus on a single key mechanistic step common to a general reaction class. Breaking up an overall reaction in this way can provide deeper insight into the fundamental reactivity and, as pioneered by Pfaltz[3] and others,[4] has proven beneficial for reaction optimization and mechanistic elucidation.[1]

An outline of this "mechanism-based" screening approach for the discovery of new reactivity is shown for a representative catalytic process in Figure 1 a. A mechanistic step involving an interaction between a substrate (Sub) and the catalyst (Cat) is crucial in this kind of reaction. If this process can be directly investigated, screening different compounds would reveal new potential substrates for this kind of catalysis without requiring them to also be competent at other steps in any specific transformation. In contrast to "reaction-based" approaches, a "hit" in this case corresponds to the identification of a new substrate class rather than to a successful overall reaction. Armed with this selection of pre-identified suitable substrates, a range of many specific reactions involving them could then be designed in a rational sense. This endeavor could also benefit from mechanistic

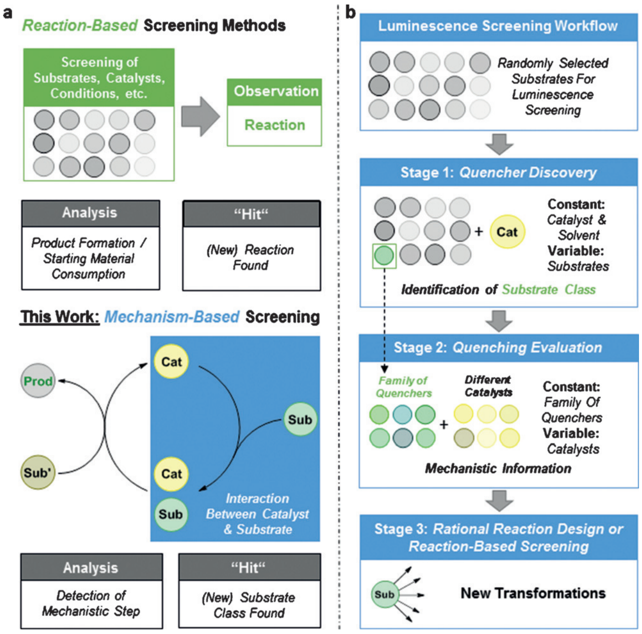


Figure 1. a) Conceptual distinctions between "reaction-focused" and "mechanism-focused" screening. b) Outline of our "mechanism-based" screening method applied to photocatalysis.

---

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

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.201600995.

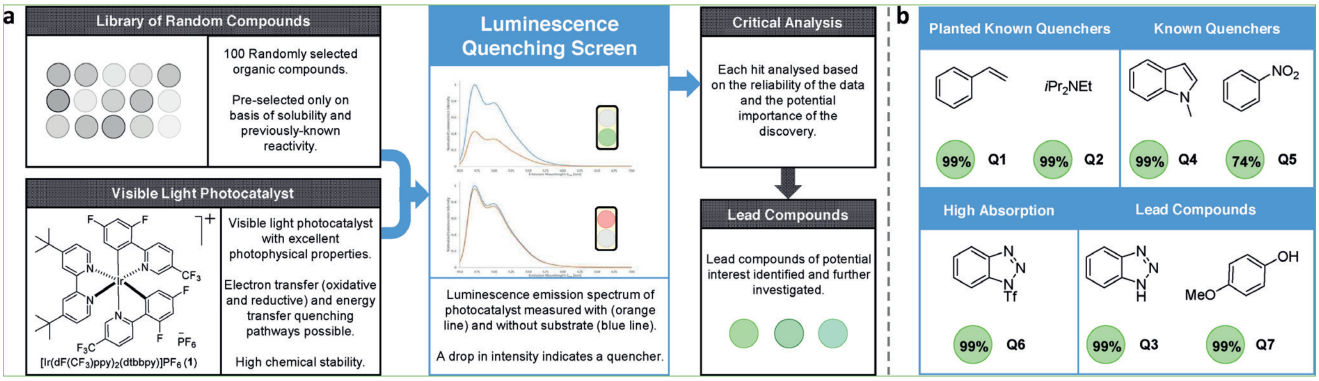
© 2016 Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim

insights obtained during the screening process upon evaluating the effects of different substrates, catalysts and reaction conditions. Alternatively, the discovered lead substrates could be subjected to a more focused "reaction-based" high-throughput screening method, thus combining the advantages of both approaches to unveil new reactivity.

To validate the concept of "mechanism-based" screening, our attention was drawn to the field of visible-light photocatalysis which has recently experienced a surge in interest.[5,6] A key mechanistic step common to all photocatalytic reactions involves the quenching of an excited catalyst by an organic substrate which leads to reactive radical species capable of undergoing a wide-range of downstream reactions.[5,7] This dynamic process, where energy from visible light is effectively passed on from the catalyst to a non-absorbing substrate, can be directly investigated using standard luminescence spectroscopy.[8,9] Simple comparison of the emission spectrum of the catalyst in the presence of various potential substrates with that of the photocatalyst in isolation allows for fast assessment of the quenching abilities of those compounds. As such, this approach provides direct experimental data and does not require pre-knowledge of the individual redox potentials or triplet-state energies of each compound.[10] Simply changing the solvent also allows for an easy assessment of the effect of the reaction medium on quenching efficiency.

Based on this principle, we devised a two-stage screening strategy to accelerate the discovery of new reactivity in photocatalysis (Figure 1b). The first stage of the method is a "quencher discovery" screen, which aims to identify new potential substrate classes by screening the quenching abilities of a range of organic compounds with a single representative photocatalyst. For this purpose, we selected the widely employed iridium(III) complex $[Ir(dF(CF_3)ppy)_2(dtbbpy)]PF_6$ (**1**, $dF(CF_3)ppy = 2$-(2,4-difluorophenyl)-3-trifluoromethylpyridine, dtbbpy = 4,4′-di-*tert*-butyl-2,2′-bipyridine), which has excellent photophysical properties and is chemically robust. Its excited state redox properties ($E_{1/2}(^*Ir^{III}–Ir^{II}) = +1.21$ V vs. SCE, $E_{1/2}(Ir^{IV}–^*Ir^{III}) = -0.89$ V vs. SCE. SCE = saturated calomel electrode) and triplet state energy ($E_T(\mathbf{1}) = 61\ \mathrm{kcal\,mol^{-1}}$) are also attractive for the development of new photoredox or photosensitized reactions, respectively.[11] A library of one hundred potential quenchers was compiled from stock compounds available in our laboratory essentially at random, pre-selecting only on the basis of solubility in acetonitrile. A cuvette containing photocatalyst **1** (10 μM) and 2500 equivalents of a substrate (25 mM) was then prepared under oxygen-free conditions in degassed acetonitrile. The intensity of the luminescence emission of **1** at 472 nm ($\lambda_{ex} = 420$ nm) under these conditions (I) was measured using a standard fluorescence spectrometer and compared with that of the photocatalyst measured in isolation (I_0). A "quenching percentage" (F) defined as the percentage decrease of the emission intensity at 472 nm ($100(1-I/I_0)$) of higher than 25 % was considered as worthy of further investigation so as to minimize the impact of experimental errors and inner-filter effects.[8]

An illustration of the procedure for this "quencher discovery" screen is shown in Figure 2a and individual luminescence spectra are provided in the Supporting Information. Among the library of one hundred potential quenchers, a total of seven resulted in quenching fractions (F) of greater than 25 %. Two of the identified compounds were already known to quench the excited state of **1**; styrene (**Q1**)[12] and the tertiary amine *N*,*N*-diisopropylethylamine (**Q2**),[13] which were deliberately planted to validate the screen. The other five discovered quenchers were 1*H*-benzotriazole (**Q3**), 1-methylindole (**Q4**), nitrobenzene (**Q5**), 1-(trifluoromethanesulfonyl) benzotriazole (**Q6**), and 4-methoxyphenol (**Q7**, Figure 2b). At this stage, a literature search was conducted to determine the novelty and potential importance of each discovered substrate. Further investigations were not carried out with 1-methylindole (**Q4**) and nitrobenzene (**Q5**) as these compounds have been widely shown to act as quenchers in visible-light-mediated reactions.[14,15] The validity of our interpretation of the observed luminescence intensity decreases as genuine dynamic quenching was also evaluated. This led to the removal from consideration of 1-(trifluoromethanesulfonyl)benzotriazole (**Q6**) as the UV/Vis spectrum of this compound revealed significant absorption of visible light by this compound ($A > 3$ at 420 nm). As such, the luminescence spectra obtained with **Q6** should be treated with caution owing to the non-linearity between emission intensity and luminophore concentration at



100 Randomly selected organic compounds.

Pre-selected only on basis of solubility and previously-known reactivity.

Visible light photocatalyst with excellent photophysical properties.

Electron transfer (oxidative and reductive) and energy transfer quenching pathways possible.

High chemical stability.

Luminescence emission spectrum of photocatalyst measured with (orange line) and without substrate (blue line).

A drop in intensity indicates a quencher.

Each hit analysed based on the reliability of the data and the potential importance of the discovery.

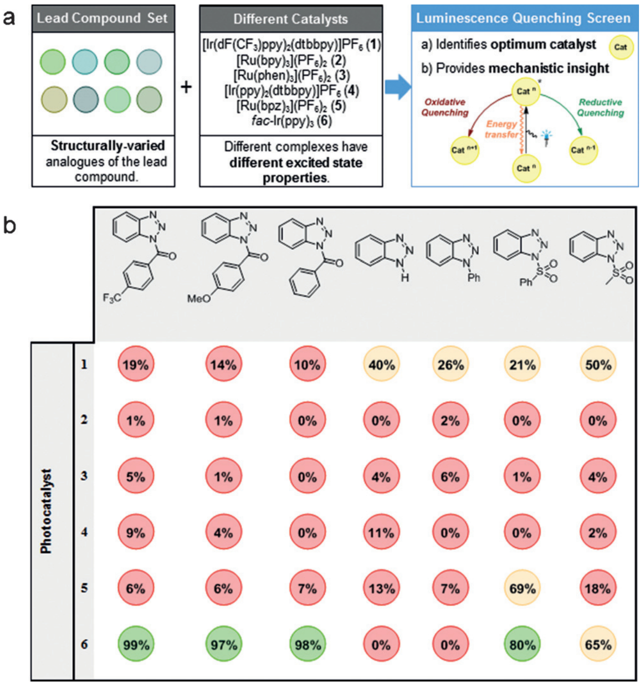
Lead compounds of potential interest identified and further investigated.

Figure 2. a) Conceptual outline of the "quencher-discovery" screening stage used to accelerate the discovery of quenchers of visible light photocatalysts. b) Structures of the seven compounds identified as quenchers (quenching fractions, *F*, are given in circles).

© 2016 Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim

high overall absorbance values.[8,16] The likelihood of the remaining two substrates, **Q3** and **Q7**, acting as dynamic quenchers of visible light photocatalysts was then assessed drawing on literature precedents and reported triplet-state energies and redox potentials. Although benzotriazoles have not previously been shown to act as quenchers of visible-light photocatalysts, these compounds have demonstrated extensive photoactivity upon ultraviolet light irradiation (e.g. the Graebe–Ullmann reaction)[17] while structurally similar azides and diazo compounds have found many applications in photocatalysis.[5h,18] On the other hand, direct reductive quenching by phenols has been documented with some visible light photocatalysts,[19] while the redox activity of tyrosine derivatives has been widely studied in vivo.[20] Previous applications of phenol derivatives as substrates in visible-light photocatalysis are, however, surprisingly scarce, with most examples not thought to involve direct quenching by the phenols themselves.[21]

With two lead compounds identified, we next turned our attention to the second "quenching evaluation" screening stage. Rather than concentrating on a single photocatalyst, this screen instead examines the ability of each compound to quench the excited states of a range of visible-light-active complexes and thus allows for easy identification of promising catalysts for reaction development. Moreover, through comparison of the quenching ability of the compound with the excited state redox potentials and triplet energies of each catalyst, insights that provide a good estimation of the operating quenching mechanisms can be obtained. An outline of the screen used to investigate the quenching by 1*H*-benzotriazole (**Q3**) is shown in Figure 3a. In addition to **Q3** itself, a selection of structurally varied analogues was assembled. This approach can provide additional information because trends in the quenching abilities of the substrates, as a function of their electronic properties, may give further insight into the operating quenching mode and allow for more enlightened matching of the appropriate catalyst to a particular substrate. The luminescence spectra of six different photocatalysts (**1**–**6**, 10 μM) were thus measured in the presence of seven benzotriazole derivatives bearing a range of nitrogen substituents (25 mM, 2500 equiv of each) under oxygen-free conditions in degassed acetonitrile. The results of this "quenching evaluation" screen are shown in Figure 3b, while more detailed information is provided in the Supporting Information.



Photocatalyst							
1	19%	14%	10%	40%	26%	21%	50%
2	1%	1%	0%	0%	2%	0%	0%
3	5%	1%	0%	4%	6%	1%	4%
4	9%	4%	0%	11%	0%	0%	2%
5	6%	6%	7%	13%	7%	69%	18%
6	99%	97%	98%	0%	0%	80%	65%

Figure 3. a) Conceptual outline of the "quenching evaluation" screening stage. b) Results of the "quenching evaluation" screening stage with benzotriazole derivatives ($F \leq 25\%$ in red, $F \geq 70\%$ in green).

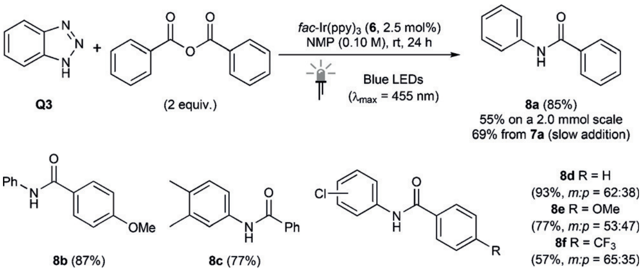
Among the insights provided by this screen is the observation that the original lead compound **Q3** is a less-efficient and overall more-limited quencher than several of the N-substituted variants, with a significant decrease in the emission intensity noted only with catalyst **1**. By contrast, the iridium(III) complex *fac*-Ir(ppy)$_3$ (**6**) was found to be the optimum photocatalyst for most substrates bearing an electron-withdrawing carbonyl or sulfonyl group at the 1-position. The activity of complex **6**, which has the highest excited state oxidation potential of all six tested photocatalysts, is highly suggestive of an oxidative quenching pathway. Electron-withdrawing nitrogen substituents may facilitate such a mechanism by reducing the reduction potentials of these compounds by stabilizing the ring-opened diazonium form of the benzotriazole.[22] The quenching of catalyst **1** by 1*H*-benzotriazole (**Q3**) could instead proceed through a different triplet–triplet energy-transfer pathway involving the 2*H* isomeric form, which has a triplet-state energy comparable to that of **1** (E_T(2*H*-benzotriazole) = 60 kcal mol^{-1}, E_T(**1**) = 61 kcal mol^{-1}).[11,23]

Having obtained an overview of the quenching abilities of benzotriazole derivatives, the next stage of the process involves the development of new visible-light-promoted transformations, which exploit the insights provided by "mechanism-based" screening. As clearly demonstrated in the "quenching evaluation" screen, benzotriazole derivatives which bear electron-withdrawing N-substituents, act as efficient oxidative quenchers of reducing photocatalysts. Upon single-electron reduction, the resulting radical anions would be expected to extrude a dinitrogen molecule and deliver aryl radical anions in a similar fashion to that observed with widely employed aryldiazonium salt quenchers.[5h] Subsequent hydrogen-atom abstraction from the solvent or another species present in the reaction mixture would then deliver the corresponding protected aniline in an overall de-nitrogenation process.

Selecting a substrate/catalyst combination shown by the screen to result in efficient quenching, 1-(benzoyl)benzotriazole (**7a**) was irradiated with visible light from blue LEDs (5 W, $\lambda_{max} = 455$ nm) in a proof-of-concept experiment in the presence of *fac*-Ir(ppy)$_3$ (**6**, 5 mol%) in acetonitrile. After 13 h at room temperature, the corresponding anilide **8a** was generated in 28% GC yield, while control reactions in the absence of light or **6** did not result in product formation (<2% GC yield). As expected from the screening results, conducting the reaction with any of the other five photo-

© 2016 Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim

catalysts in place of **6** was similarly unproductive ($<2\,\%$ GC yield). The other six benzotriazole derivatives employed in the "quenching evaluation" were also treated under the same conditions with *fac*-Ir(ppy)$_3$ (**6**). While most of the results were in accordance with the screen, 1-sulfonyl-substituted derivatives 1-(phenylsulfonyl)benzotriazole and 1-(methanesulfonyl) benzotriazole, however, did not react despite their apparent activity as quenchers of photocatalyst **6**. This observation illustrates that the quenching process is only one step in this specific reaction and that a particular photocatalyst or substrate may not be suitable for other steps in the catalytic cycle or indeed be stable under the reaction conditions. An optimization study led to an improvement in efficiency upon switching solvent to *N*-methyl-2-pyrrolidone (NMP) and either adding the pre-formed 1-(benzoyl)benzotriazole slowly or generating it in situ from 1*H*-benzotriazole (**Q3**) and benzoyl anhydride (see the Supporting Information for more details).[24] Under these conditions, anilide **8a** was generated in 85% isolated yield, while a range of derivatives bearing substituents on the benzotriazole or benzoyl fragments were also successfully transformed (Scheme 1).



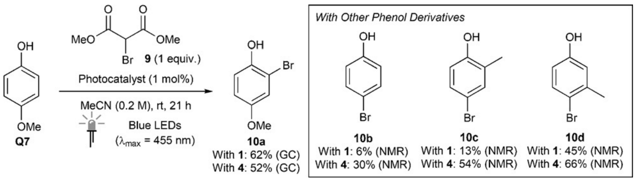
Scheme 1. Visible-light-promoted de-nitrogenation of benzotriazoles.

As discussed above, visible-light-promoted reactions involving phenols acting as quenchers are surprisingly scarce considering that these compounds have been previously shown to act as reductive quenchers of some photocatalysts.[19] To obtain an overview of the quenching ability of various phenols, the same "quenching evaluation" procedure was conducted with a selection of eight structurally diverse phenols (see the Supporting Information). As expected from the literature, the trends in the quenching abilities observed in the screen strongly support the involvement of reductive quenching mechanisms for most substrates with the combination of highly oxidizing photocatalysts and electron-rich phenols resulting in efficient quenching. An interesting anomaly to this general trend, however, was the efficient quenching observed with 2-naphthol and *fac*-Ir(ppy)$_3$ (**6**), which has the lowest excited-state reduction potential of all six tested complexes. In this case, a triplet–triplet energy transfer pathway is likely operative (E_T(2-naphthol) = 54 kcal mol^{-1} and E_T(**6**) = 58 kcal mol^{-1}). Such detailed insight demonstrates the power of this second "quenching evaluation" screen to reveal individual quenching characteristics of specific compounds in a fast and straightforward manner.

Armed with these results, we next sought to rationally design a proof-of-concept transformation involving phenols as direct quenchers. Upon single-electron oxidation by an excited photocatalyst, the resulting radical cation could react further in a halogen-transfer pathway to generate bromophenol compounds useful as feedstocks for organic synthesis.[25] An analogous visible-light-promoted phenol bromination has been previously developed although this process does not involve direct quenching by phenols.[21a] Taking a substrate and catalyst combination shown by the screen to result in efficient quenching, 4-methoxyphenol (**Q7**) was treated with iridium(III) complex **1** (1 mol%) in the presence of dimethyl bromomalonate (**9**, 1 equiv) in acetonitrile under irradiation with visible light from blue LEDs (5 W, $\lambda_\mathrm{max} = 455$ nm). After 21 h at room temperature, the mono-brominated product **10a** was obtained as a single regioisomer in 62% GC yield while control reactions in the absence of light or **1** resulted in only recovered starting material ($<1\,\%$ GC yield). An intriguing disparity between the screening data and the reaction outcomes was observed, however, upon performing the process with [Ir(ppy)$_2$(dtbbpy)]PF$_6$ (**4**) as the catalyst. Whereas the excited state of this comparatively less-oxidising complex was not quenched by **Q7** in the screen, the bromination reaction conducted with this catalyst delivered the product **10a** in a substantial 52% GC yield. This result would seem to imply that an alternative mechanistic pathway is operating in this case, with quenching occurring not with the phenol substrate but with bromomalonate **9**. Indeed, a full Stern–Volmer luminescence-quenching analysis with both catalysts **1** and **4** supported this scenario with complex **1** being quenched only by **Q7** and catalyst **4** being quenched only by the bromomalonate (see the Supporting Information).[24,26] These results clearly illustrate how "mechanism-based" screening can aid understanding during the development of a new photocatalytic reaction by providing insightful mechanistic information at the beginning of a study.

In this case, the possibility of two different photocatalytic pathways allows an informed selection of the catalyst to be made depending on the phenol substrate. For electron-rich phenols, such as **Q7**, direct reductive quenching with catalyst **1** is the more efficient process, while the alternative, likely oxidative quenching pathway accessible with catalyst **4**, is seemingly more effective for substrates such as phenol, which is itself a poor quencher of **1** (Scheme 2). Interestingly, the reactions with phenol, *o*-cresol, and *m*-cresol proceed with very high selectivities for the *para*-functionalized products (p:o/$m > 20$:1) and thus may prove synthetically useful as routes towards *para*-halogenated aromatic compounds.[27,28]

In summary, we have demonstrated that the application of "mechanism-based" screening can help to accelerate the discovery of new chemical reactivity. Using luminescence spectroscopy, direct experimental data on the quenching step



Scheme 2. Visible-light-promoted bromination of phenols.

© 2016 Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim

in photocatalysis was obtained and two new substrate classes, benzotriazoles and phenols, were identified. Mechanistic insights obtained during screening also aided the design and optimization of new specific transformations involving each of them. The method is fast, operationally simple, and versatile, and provides direct experimental data without requiring foreknowledge of redox potentials, triplet-state energies, or other thermodynamic or kinetic parameters. Looking beyond photocatalysis, we believe that "mechanism-based" screening methodologies could be useful and complementary tools to accelerate discovery in many areas of organic chemistry.

Acknowledgements

The authors thank Prof. B. J. Ravoo (WWU Münster) for use of fluorescence and UV/Vis spectrometers and technical assistance, Dr. habil. C. A. Strassert, T. Gensch, Dr. L. Candish, Dr. E. A. Standley, Dr. B. Maji (all WWU Münster) and H. Osaki (Nagoya University, Japan) for helpful discussions. This work was supported by the Deutsche Forschungsgemeinschaft (Leibniz Award) and the Alexander von Humboldt Foundation (M.N.H).

Keywords: benzotriazoles · luminescence · phenols · photocatalysis · screening

How to cite: *Angew. Chem. Int. Ed.* **2016**, *55*, 4361–4366
Angew. Chem. **2016**, *128*, 4434–4439

---

[1] Reviews: a) K. D. Collins, T. Gensch, F. Glorius, *Nat. Chem.* **2014**, *6*, 859; b) L. Weber, K. Illgen, D. M. Almstetter, *Synlett* **1999**, 366.

[2] Prominent recent examples of discovery-focused screening: 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. Buitrago Santanilla et al., *Science* **2015**, *347*, 49; d) E. Wolf, E. Richmond, J. Moran, *Chem. Sci.* **2015**, *6*, 2501.

[3] 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. A. Müller, A. Pfaltz, *Angew. Chem. Int. Ed.* **2008**, *47*, 3363; *Angew. Chem.* **2008**, *120*, 3411; e) I. Fleischer, A. Pfaltz, *Chem. Eur. J.* **2010**, *16*, 95; f) C. Ebner, C. A. Müller, C. Markert, A. Pfaltz, *J. Am. Chem. Soc.* **2011**, *133*, 4710; g) F. Bächle, J. Duschmalé, C. Ebner, A. Pfaltz, H. Wennemers, *Angew. Chem. Int. Ed.* **2013**, *52*, 12619; *Angew. Chem.* **2013**, *125*, 12851; h) F. Bächle, I. Fleischer, A. Pfaltz, *Adv. Synth. Catal.* **2015**, *357*, 2247.

[4] Selected examples: a) C. Hinderling, P. Chen, *Angew. Chem. Int. Ed.* **1999**, *38*, 2253; *Angew. Chem.* **1999**, *111*, 2393; b) B. Dominguez, N. S. Hodnett, G. C. Lloyd-Jones, *Angew. Chem. Int. Ed.* **2001**, *40*, 4289; *Angew. Chem.* **2001**, *113*, 4419; c) 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; report using thermography as a means of evaluating catalyst efficiency d) S. J. Taylor, J. P. Morken, *Science* **1998**, *280*, 267.

[5] Selected Reviews on visible-light photoredox catalysis: 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) F. Teplý, *Collect. Czech. Chem. Commun.* **2011**, *76*, 859; d) J. M. R. Narayanam, C. R. J. Stephenson, *Chem. Soc. Rev.* **2011**, *40*, 102; e) J. Xuan, W.-J. Xiao, *Angew. Chem. Int. Ed.* **2012**, *51*, 6828; *Angew. Chem.* **2012**, *124*, 6934; f) L. Shi, W. Xia, *Chem. Soc. Rev.* **2012**, *41*, 7687; g) S. Fukuzumi, K. Ohkubo, *Chem. Sci.* **2013**, *4*, 561; h) D. P. Hari, B. König, *Angew. Chem. Int. Ed.* **2013**, *52*, 4734; *Angew. Chem.* **2013**, *125*, 4832; i) Y. Xi, H. Yi, A. Lei, *Org. Biomol. Chem.* **2013**, *11*, 2387; j) C. K. Prier, D. A. Rankic, D. W. C. MacMillan, *Chem. Rev.* **2013**, *113*, 5322; k) M. Reckenthäler, A. G. Griesbeck, *Adv. Synth. Catal.* **2013**, *355*, 2727; l) M. N. Hopkinson, B. Sahoo, J.-L. Li, F. Glorius, *Chem. Eur. J.* **2014**, *20*, 3874; m) D. M. Schultz, T. P. Yoon, *Science* **2014**, *343*, 1239176; n) T. Koike, M. Akita, *Top. Catal.* **2014**, *57*, 967; o) D. A. Nicewicz, T. M. Nguyen, *ACS Catal.* **2014**, *4*, 355; p) E. Meggers, *Chem. Commun.* **2015**, *51*, 3290.

[6] G. Ciamician, *Science* **1912**, *36*, 385.

[7] J. W. Tucker, C. R. J. Stephenson, *J. Org. Chem.* **2012**, *77*, 1617.

[8] J. R. Lakowicz, *Principles of Fluorescence Spectroscopy*, Springer, New York, **2006**.

[9] Luminescence enhancement or quenching has been used as analytical tool in "reaction-based" screening methods. Selected examples: a) J. P. Stambuli, S. R. Stauffer, K. H. Shaughnessy, J. F. Hartwig, *J. Am. Chem. Soc.* **2001**, *123*, 2677; b) W. G. Lewis, F. G. Magallon, V. V. Fokin, M. G. Finn, *J. Am. Chem. Soc.* **2004**, *126*, 9152; c) D. A. DiRocco, K. Dykstra, S. Krska, P. Vachal, D. V. Conway, M. Tudge, *Angew. Chem. Int. Ed.* **2014**, *53*, 4802; *Angew. Chem.* **2014**, *126*, 4902. A report using a fluorescence-quenching assay to identify reaction partners: d) B. Xia, B. Gerard, D. M. Solano, J. Wan, G. Jones II, J. A. Porco, Jr., *Org. Lett.* **2011**, *13*, 1346.

[10] While these thermodynamic considerations are critical for determining whether quenching is likely for any system, kinetic factors affecting electron or energy transfer must also be favorable. These effects, as well as those arising from variations in reaction media, are often overlooked and can be difficult to predict. See ref. [7].

[11] M. S. Lowry, J. I. Goldsmith, J. D. Slinker, R. Rohl, R. A. Pascal, Jr., G. G. Malliaras, S. Bernhard, *Chem. Mater.* **2005**, *17*, 5712.

[12] Z. Lu, T. P. Yoon, *Angew. Chem. Int. Ed.* **2012**, *51*, 10329; *Angew. Chem.* **2012**, *124*, 10475.

[13] J. Hu, J. Wang, T. H. Nguyen, N. Zheng, *Beilstein J. Org. Chem.* **2013**, *9*, 1977.

[14] Selected examples: a) A. Gieseler, E. Steckhan, O. Wiest, F. Knoch, *J. Org. Chem.* **1991**, *56*, 1405; b) S. Lerch, L.-N. Unkel, M. Brasholz, *Angew. Chem. Int. Ed.* **2014**, *53*, 6558; *Angew. Chem.* **2014**, *126*, 6676.

[15] Selected examples: a) T. Hirao, J. Shiori, N. Okahata, *Bull. Chem. Soc. Jpn.* **2004**, *77*, 1763; b) M. A. Cismesia, M. A. Ischay, T. P. Yoon, *Synthesis* **2013**, 2699.

[16] Further details of NMR and UV/Vis studies conducted to rule out possible static quenching by **Q3** or **Q7** are provided in the Supporting Information. Additional investigations at this stage could also include analysis of the excited state lifetime of **1**. Such measurements, however, require access to more specialized equipment not widely available in chemistry laboratories.

[17] a) C. Graebe, F. Ullmann, *Justus Liebigs Ann. Chem.* **1896**, *291*, 16; b) A. R. Katritzky, B. Yang, R. Abonia, R. Insuasty, *J. Chem. Res. Synop.* **1996**, *12*, 540. Review on N-substituted benzotriazoles: c) A. R. Katritzky, X. Lan, J. Z. Yang, O. V. Denisko, *Chem. Rev.* **1998**, *98*, 409.

[18] H. Wang, S. Yu, *Org. Lett.* **2015**, *17*, 4272.

[19] a) C. Bronner, O. S. Wenger, *J. Phys. Chem. Lett.* **2012**, *3*, 70; b) K. Miedlar, P. K. Das, *J. Am. Chem. Soc.* **1982**, *104*, 7462.

[20] J. Stubbe, W. A. van der Donk, *Chem. Rev.* **1998**, *98*, 705.

[21] a) Y. Zhao, Z. Li, C. Yang, R. Lin, W. Xia, *Beilstein J. Org. Chem.* **2014**, *10*, 622; b) T. R. Blum, Y. Zhu, S. A. Nordeen, T. P. Yoon, *Angew. Chem. Int. Ed.* **2014**, *53*, 11056; *Angew. Chem.* **2014**, *126*,

© 2016 Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim

11236; c) T. Hamada, H. Ishida, S. Usui, Y. Watanabe, K. Tsumura, K. Ohkubo, *J. Chem. Soc. Chem. Commun.* **1993**, 909.

[22] 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.

[23] J. Catalán, P. Pérez, *Chem. Phys. Lett.* **2005**, *404*, 304.

[24] For a discussion of the reaction mechanism including results of Stern–Volmer luminescence quenching studies and reaction quantum yield determination, see the Supporting Information.

[25] Selected examples: a) G. S. Coumbarides, M. Dingjan, J. Eames, N. Weerasooriya, *Bull. Chem. Soc. Jpn.* **2001**, *74*, 179; b) R. H. Mitchell, Y.-H. Lai, R. V. Williams, *J. Org. Chem.* **1979**, *44*, 4733; c) U. Bora, G. Bose, M. K. Chaudhuri, S. S. Dhar, R. Gopinath, A. T. Khan, B. K. Patel, *Org. Lett.* **2000**, *2*, 247.

[26] C.-J. Wallentin, J. D. Nguyen, B. Finkbeiner, C. R. J. Stephenson, *J. Am. Chem. Soc.* **2012**, *134*, 8875.

[27] N. A. Romero, K. A. Margrey, N. E. Tay, D. A. Nicewicz, *Science* **2015**, *349*, 1326.

[28] For details of the optimized phenol bromination process using 3 equiv. of dimethyl bromomalonate, see the Supporting Information.

Received: January 28, 2016
Revised: February 16, 2016

© 2016 Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim