Letter

# Regioselective Synthesis of 2-Substituted Indoles from Benzotriazoles and Alkynes by Photoinitiated Denitrogenation

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# Regioselective Synthesis of 2-Substituted Indoles from Benzotriazoles and Alkynes by Photoinitiated Denitrogenation

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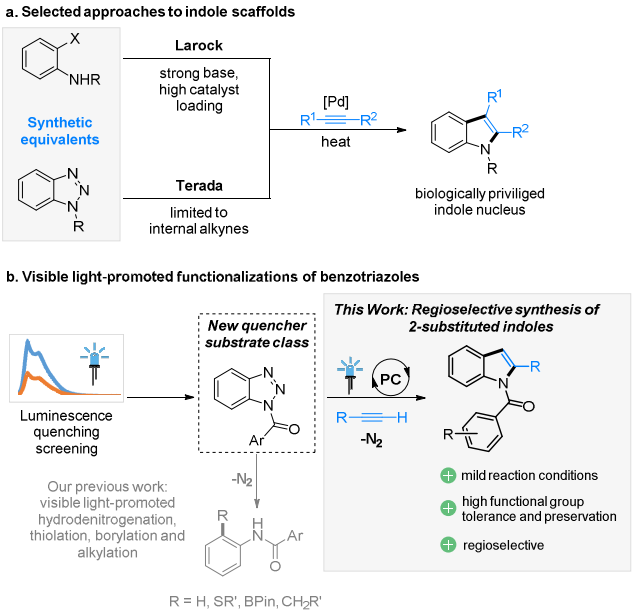
**ABSTRACT:** Herein, we describe a photoinitiated and regioselective synthesis of 2-substituted indoles under mild reaction conditions. This biologically privileged scaffold was accessed in good yields from *N*-aroylbenzotriazoles — a quencher class previously identified using our mechanism-based luminescence screening — and terminal alkynes in the presence of a photocatalyst and blue light irradiation. This straightforward protocol displays a broad substrate scope and functional group tolerance. Furthermore, the mildness and robustness of the reaction were assessed by the application of an additive-based robustness screen. The determination of the reaction quantum yield and Stern-Volmer studies support the proposed photoinitiated radical chain mechanism.

KEYWORDS: photocatalysis, robustness screen, regioselective, indoles, benzotriazoles, mechanism-based screening

The discovery of new transformations and reactivity modes is the overall aim of organic chemists. To this end, chemists have a wide range of tools at their disposal, from rational design based on chemical understanding to the application of screening methodologies.[1] We recently published a mechanism-based screening method,[2] which focuses on accelerating discoveries in the field of photocatalysis.[3] This screening approach focusses on a single key mechanistic step, the interaction of an excited photocatalyst with a substrate. By narrowing one's sight and focusing only on one fundamental step of the overall catalytic cycle, the obtained insights are helpful for the development and optimization of a reaction. Application of this screening approach led to the discovery of *N*-aroylbenzotriazoles (**1**) as a new quencher substrate class for photocatalytic reactions. Using this new oxidative quencher, four novel visible light-promoted functionalizations delivering *ortho*-thiolated, -borylated, -alkylated and hydrodenitrogenated *N*-arylbenzamides were developed (Scheme 1, b).[4] We sought to move beyond *ortho*-functionalizations and envisaged transformations in which the remaining nitrogen atom is used for the construction of heterocyclic systems. Inspired by König and coworkers' report on a photoinitiated synthesis of benzothiophenes from *ortho*-methylthioarene diazonium salts,[5] we recognized that benzotriazoles as synthetically otherwise non-accessible *ortho*-aminodiazonium precursors might be cheap, easy-to-handle and stable starting materials for the synthesis of indole scaffolds.[6]

Indoles are important structural motifs which are embedded in many natural and synthetic molecules, and are often described as privileged in terms of biological activity.[7] 2-Arylindoles have recently been shown to possess significant antibacterial and fungicidal activity,[8] and represent important intermediates in the synthesis of complex molecules.[9] Therefore, the need for synthetic routes to indoles and 2-arylindoles is of great interest for organic and medicinal chemists.




**Scheme 1. a) Examples for the synthesis of substituted indoles. b) This work: Utilizing benzotriazoles for the regioselective synthesis of 2-substituted indoles.**

Consequently, several synthetic strategies have been developed over the years.[10] Most of these strategies employ aniline derivatives as starting materials, like in the classical Bischler-Möhlau[11] or Larock indole synthesis (Scheme 1, a).[12] Alternatively, Terada and coworkers' have shown that benzotriazoles could be used as synthetic aniline equivalents in combination with terminal alkynes for the synthesis of 2,3-diarylated indoles.[13] This denitrogenative approach, however, suffers from harsh reaction conditions limiting the scope to internal alkynes.

Building on our strategy to use *N*-aroylbenzotriazoles as masked *ortho*-aminodiazonium compounds,[6e] we sought to access 2-substituted indoles under mild conditions.

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

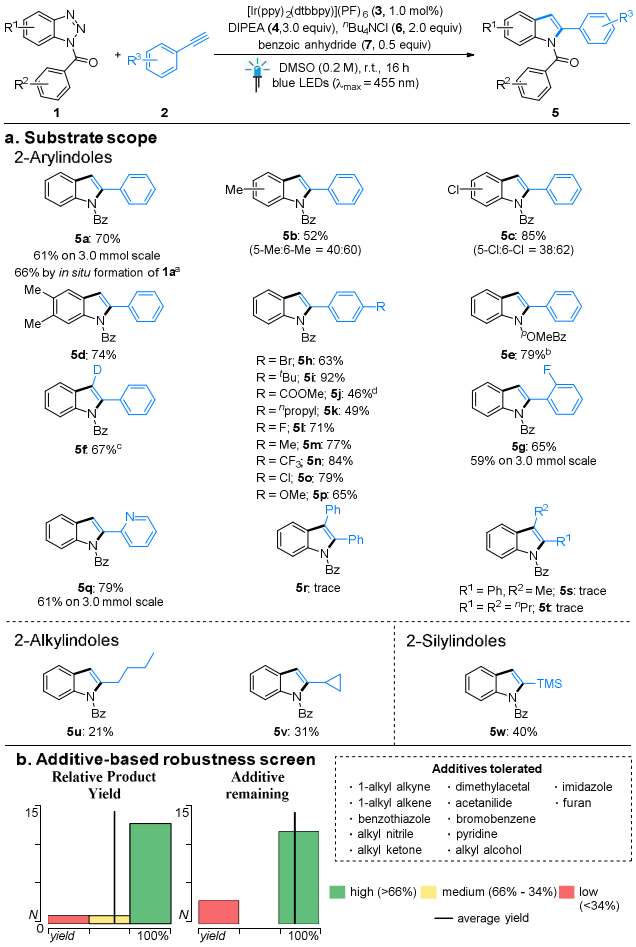

| Entry | Ratio 1a : 2 | Equiv 4 | Additive (equiv) | Yield 5a[b] |
|---|---|---|---|---|
| 1 | 1 : 10 | 3 | / | 32 |
| 2 | 1 : 10 | 3 | $^{n}$Bu4NBr (1.0) | 47 |
| 3 | 1 : 10 | 3 | $^{n}$Bu4NCl (1.0) | 60 |
| 4 | 1 : 20 | 3 | $^{n}$Bu4NCl (1.0) | 73 |
| 5[c] | 1 : 20 | 3 | $^{n}$Bu4NCl (1.0) | 75 |
| 6[d,e] | 1 : 20 | 3 | $^{n}$Bu4NCl (2.0) | 69 |
| 7[d, e, f] | 1 : 20 | 3 | $^{n}$Bu4NCl (2.0) | 3 |
| 8[d, e, g] | 1 : 20 | 3 | $^{n}$Bu4NCl (2.0) | / |
| 9[d,e] | 1 : 20 | / | $^{n}$Bu4NCl (2.0) | / |

[a]Reaction conditions: *N*-(benzoyl)benzotriazole (**1a**, 1.0 equiv), $[Ir(ppy)_2(dtbbpy)]PF_6$ (**3**, 2.5 mol%), benzoic anhydride (**7**, 2.0 equiv), DMSO (0.2 M), r.t., 15 h, 455 nm irradiation. [b]GC-FID yield. [c]neat; no DMSO. [d]1.0 mol% [Ir]-photocatalyst used. [e]0.5 equiv benzoic anhydride used. [f]no photocatalyst. [g]no light. BA = benzoic anhydride, DIPEA = *N*,*N*-di*iso*propylethylamine. Bz = benzoyl.

The addition of an *o*-aminated aryl radical, obtained after denitrogenation from **1**, to a terminal alkyne and subsequent cyclization might result in the formation of the desired indole nucleus (Scheme 1, b).

Our earlier work on the *o*-functionalization of *N*-aroylbenzotriazoles suggested that higher yields were obtained when an indirect reductive quenching manifold was employed.[4] Furthermore, the addition of benzoic anhydride (**7**) ensured the crucial protection of the benzotriazole in terms of quenching, leading to increased product yields. Therefore, initially, *N*-benzoylbenzotriazole (**1a**), phenylacetylene (**2**), DIPEA (**4**), benzoic anhydride (**7**) and $[Ir(ppy)_2(dtbbpy)](PF_6)$ (**3**, 2.5 mol%, ppy = 2-phenylpyridine, dtbbpy = 4,4′-di-*tert*-butyl-2,2′-bipyridine) were irradiated with blue LEDs ($\lambda_{max}$ = 455 nm) in DMSO (0.1 M) for 15 h at room temperature.[14] We were delighted to observe the formation of the desired product *N*-benzoyl-2-phenylindole (**5a**) in 32% GC-yield (table 1, entry 1). We hypothesized that the use of soluble organic salts might result in the stabilization of the postulated ionic intermediates, thus increasing the yield of the reaction.[15] Indeed, by adding tetrabutylammonium bromide ($^{n}$Bu4Br), **5a** was obtained in 47% yield (entry 2). Further optimization of the counter anion (entry 3) and the equivalents of phenylacetylene, afforded **5a** in 73% yield (entry 4). Interestingly, the reaction also worked when it was performed in the absence of solvent (75% yield, entry 5). Gratifyingly, the catalyst loading could be reduced to 1.0 mol% affording the product in a slightly decreased yield of 69% (entry 6). Control experiments showed that only traces of the product were observed in the absence of a photocatalyst (entry 7),[16] and that the reaction did not proceed in the absence of light or DIPEA (entry 8 and 9).

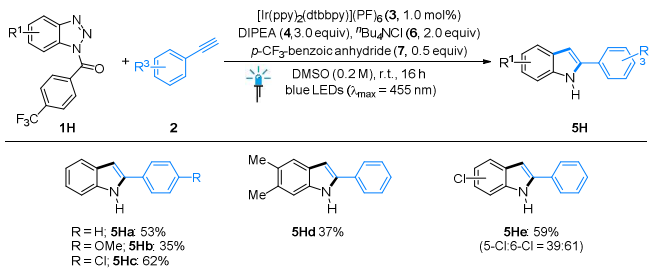
With the optimized reaction conditions in hand we next investigated the scope and limitations of this regioselective synthesis of 2-substituted indoles (Scheme 2, a). *N*-benzoyl-2-phenylindole (**5a**) was isolated in 70% yield. Pleasingly, the reaction also proceeded well on a 3.0 mmol scale delivering **5a** in 61% yield.[17] Alternatively, **1a** could be generated *in situ*, from 1*H*-benzotriazole and **7**, affording **5a** in a slightly lower yield (66%), however, saving one synthetic step. Next, we studied the influence of electronic effects on the benzotriazole ring. The use of 5-methyl or 5-chloro substituted *N*-aroylbenzotriazoles afforded the corresponding 2-arylated indoles in 52% (**5b**) and 85% (**5c**) yield, respectively. Due to Dimroth rearrangement of the starting materials, mixtures of 5- and 6-substituted products were obtained.[18] 5,6-Dimethylbenzotriazole was successfully transformed to the corresponding product **5d** in good yield (74%). Gratifyingly, the insertion of a *p*-methoxy substituent on the protecting group was also well tolerated under the reaction conditions delivering **5e** in 79% isolated yield.




Reactions were performed on a 0.3 mmol scale; isolated yields are given. For more detailed reaction conditions, see the supporting information. [a]*In situ* formation of *N*-benzoylbenzotriazole (**1a**) from 1*H*-benzotriazole (1.0 equiv) and benzoic anhydride (2.0 equiv). See supporting information for experimental details and reference [4]. [b] $^{1}$H-NMR-yield using $CH_2Br_2$. [c] Using 4-methoxybenzoic anhydride. [d]Reaction was performed on a 0.1 mmol scale. Bz = benzoyl, $^{p}$OMeBz = *p*-methoxybenzoyl. See the supporting information for experimental details and results of the additive-based robustness screen.

**Scheme 2. Scope (a) and robustness screen (b).**

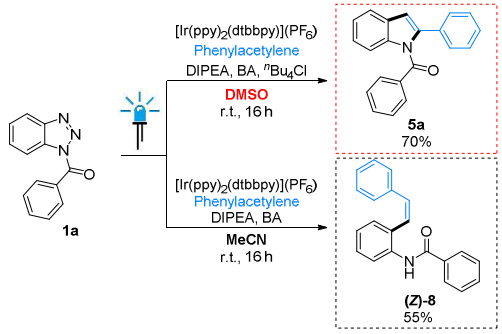
We next examined the effect of modifying the alkyne. The reaction tolerates a wide range of *p*-substituted phenylacetylene derivatives, affording the corresponding products in 48-92% yield (**5h-5p**).




**Scheme 3. Scope using *N*-(4-trifluoromethyl)benzoylbenzotriazoles to obtain deprotected indoles.**

Electron-withdrawing substituents, such as trifluoromethyl or chloro, and electron-donating substituents, e.g. methoxy or $^{t}$Bu, were well tolerated. In addition, terminal deuterated alkynes could also be employed, which represents a general method for the preparation of 2-arylated indoles with a deuterium atom in the C3 position (**5f**, 67%).Pleasingly, the use of 2-ethynylpyridine gave the corresponding product **5q** in 79% yield and in 61% yield on a 3.0 mmol scale. Unfortunately, no product formation was observed when internal alkynes were used (**5r**, **5s** and **5t**). *N*-phenylbenzamide (**13**) was obtained in those cases, thus suggesting that the addition of the aryl radical to the alkyne might not be taking place. Finally, we evaluated whether terminal aliphatic alkynes could also be used to access 2-alkylated indoles under our reaction conditions. Proof of principle experiments were carried out using 1-hexyne and 2-ethynylcyclopropane, affording the corresponding products **5u** and **5v** in diminished yields compared to the arylalkyne derivatives (21% and 31%, respectively). Moreover, the synthesis of 2-silylated indoles was also possible, as shown by the isolation of **5w** in 40% yield. In the latter three experiments, benzanilide **13** was identified as the major product. The robustness and functional group preservation of this denitrogenative indole synthesis was additionally investigated by conducting an additive-based robustness screen. The results are summarized in histograms (Scheme 2, b).[19] We were delighted to see that in most cases the yield of the product was not affected by the presence of an additive, indicating a high robustness of the overall transformation. Furthermore, the reaction is characterized by a high functional group preservation, since the additives were recovered in an average yield of 80%.

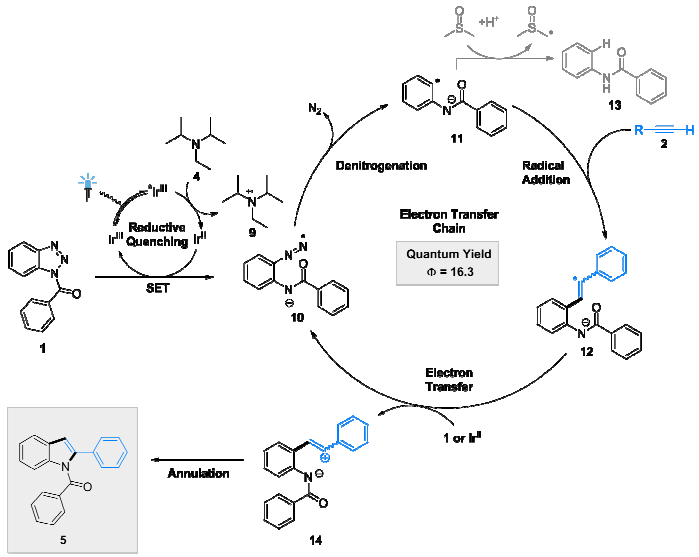
The deprotection of the *N*-benzoyl-2-substituted indole products can be easily achieved by basic treatment with potassium hydroxide in an ethanol/water mixture, delivering the free indoles in high yields (see SI).[20] Alternatively, we observed during our scope investigations that a strongly withdrawing trifluoromethyl group incorporated on the benzoyl fragment leads to the formation of the corresponding deprotected indoles **5Ha-5He** in moderate yields (Scheme 3, 35-62%). This strategy represents a valuable approach for the synthesis of 2-phenyl substituted indoles without the need for additional deprotection steps.




**Scheme 4. Chemodivergent functionalizations of *N*-benzoylbenzotriazole (1a).**

During the optimization studies, we observed a chemodivergent switch when the solvent was changed from DMSO to MeCN (Scheme 4). When the latter was used, (*Z*)-stilbene derivative **8** was obtained in an isolated yield of 55%. These products might be useful for enantioselective halocyclizations using chiral anion phase-transfer catalysis resulting in the formation of halogenated 4*H*-3,1-benzoxazines.[21]

Once the scope and limitations of our methodology were stablished, we began to probe the reaction mechanism. Stern-Volmer analysis, quantum yield determination and other mechanistic experiments were carried out to support the proposed reaction mechanism (Scheme 5).[22] Initially, the excited state photocatalyst, obtained upon blue LED irradiation, is reduced by a single electron transfer (SET) to the reductive quencher **4**,[23] affording the amine radical cation **9** and a highly reducing $Ir^{II}$ photocatalyst. The latter will interact with benzotriazole **1** via a SET, thus regenerating the $Ir^{III}$ photocatalyst and the radical anion **10**. Subsequent nitrogen extrusion from **10** will afford the aryl radical **11**, which can either add to the alkyne **2** to give the stabilized radical intermediate **12** or picks up a hydrogen atom from the solvent




**Scheme 5. Proposed mechanism for the photoinitiated denitrogenative synthesis of 2-substituted indoles.**

resulting in the formation of the undesired side product **13**.[4] Radical intermediate **12** is then predominantly oxidized by another molecule of **1**, as suggested by a reaction quantum yield of 16.3, which indicates a radical chain mechanism. The zwitterionic intermediate **14** cyclizes to give the desired product **5**.[24]

In conclusion, we have successfully developed a protocol for the mild and regioselective construction of biologically important 2-substituted indoles using cheap and stable benzotriazoles. This synthetic strategy displays broad substrate scope, a high functional group tolerance and represents a valuable complement to the synthesis of 2-substituted indoles. The reaction proceeds via a radical chain mechanism as indicated by the determined reaction quantum yield and Stern-Volmer analysis. We have successfully shown that benzotriazoles as quenchers, discovered by our mechanism-based screening technique, can be used as synthetic equivalents of otherwise non-accessible *ortho*-aminoarenediazonium salts in a variety of new photocatalytic reactions.

## ASSOCIATED CONTENT

**Supporting Information**. Experimental details, characterization data, mechanistic experiments and copies of NMR spectra of new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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### Notes

The authors declare no competing financial interest.

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## REFERENCES

(1) Review on screening approaches for reaction discovery: Collins, K. D.; Gensch, T.; Glorius, F. *Nat. Chem.* **2014**, *6*, 859-871.
(2) (a) Hopkinson, M. N.; Gómez-Suárez, A.; Teders, M.; Sahoo, B.; Glorius, F. *Angew. Chem. Int. Ed.* **2016**, *55*, 4361-4366. For selected examples of mechanism-based screening used for reaction optimization or mechanistic elucidation, see: (b) Markert, C.; Pfaltz, A. *Angew. Chem. Int. Ed.* **2004**, *43*, 2498-2500. (c) Hinderling, C.; Chen, P. *Angew. Chem. Int. Ed.* **1999**, *38*, 2253-2256. (d) Wassenaar, J.; Jansen, E.; van Zeist, W.-J.; Bickelhaupt, F. M.; Siegler, M. A.; Spek, A. L.; Reek, J. N. H. *Nat. Chem.* **2010**, *2*, 417-421.
(3) Reviews on visible-light photocatalysis: (a) Zeitler, K. *Angew. Chem., Int. Ed.* **2009**, *48*, 9785-9789. (b) Yoon, T. P.; Ischay, M. A.; Du, J. *Nat. Chem.* **2010**, *2*, 527-532. (c) Narayanam, J. M. R.; Stephenson, C. R. J. *Chem. Soc. Rev.* **2011**, *40*, 102-113. (d) Shi, L.; Xia, W. *Chem. Soc. Rev.* **2012**, *41*, 7687-7697. (e) Xi, Y.; Yi, H.; Lei, A. *Org. Biomol. Chem.* **2013**, *11*, 2387-2403. (f) Prier, C. K.; Rankic, D. A.; MacMillan, D. W. C. *Chem. Rev.* **2013**, *113*, 5322-5363. (g) Hopkinson, M. N.; Sahoo, B.; Li, J.-L.; Glorius, F. *Chem.–Eur. J.* **2014**, *20*, 3874-3886. (h) Meggers, E. *Chem. Commun.* **2015**, *51*, 3290-3301.
(4) Teders, M.; Gómez-Suárez, A.; Pitzer, L.; Hopkinson, M. N.; Glorius, F. *Angew. Chem. Int. Ed.* **2017**,*56*, 902-906.
(5) Hari, D. P.; Hering, T.; König, B. *Org. Lett.* **2012**, *14*, 5334-5337.
(6) Selected examples for benzotriazole ring openings: (a) Su, Y.; Petersen, J. L.; Gregg, T. L.; Shi, X. *Org. Lett.* **2015**, *17*, 1208-1211. (b) Graebe, C.; Ullmann, F. *Liebigs Ann. Chem.* **1896**, *291*, 16-17. (c) Katritzky, A. R.; Yang, B.; Abonia, R.; Insuasty, R. *J. Chem. Res (S)* **1996**, *12*, 540-543. (d) For a review on *N*-substituted benzotriazoles, see: Katritzky, A. R.; Lan, X.; Yang, J. Z.; Denisko, O. V. *Chem. Rev.* **1998**, *98*, 409-548. (e) Wang, Y.; Wu, Y.; Li, Y.; Tang, Y. *Chem. Sci.* **2017**, doi: 10.1039/C7SC00367F.
(7) (a) Kochanowska-Karamyan, A. J.; Hamann, M. T. *Chem. Rev.* **2010**, *110*, 4489-4497. (b) Kaushik, N. K.; Kaushik, N.; Attri, P.; Kumar, N.; Kim, C. H.; Verma, A. K.; Chio, E. H. *Molecules* **2013**, *18*, 6620-6662. (c) Somei, M.; Yamada, F. *Nat. Prod. Rep.* **2005**, *22*, 73-103. (d) Kawasaki, T.; Higuchi, K. *Nat. Prod. Rep.* **2005**, *22*, 761-793.
(8) (a) Lal, S.; Snape, T. J. *Curr. Med. Chem.* **2012**, *19*, 4828-4837. (b) Abdel-Aty, A. M. *Journal of Pesticide Science* **2010**, *35*, 431-535.
(9) Shen, C.; Liu, R.-R.; Fan, R.-J.; Li, Y.-L.; Xu, T.-F.; Gao, J.-R.; Jia Y.-X. *J. Am. Chem. Soc.* **2015**, *137*, 4936-4939.
(10) For reviews on indole syntheses, see: (a) Cacchi, S.; Fabrizi, G. *Chem. Rev.* **2005**, *105*, 2873-2920. (b) Platon, M.; Amardeil, R.: Djakovitch, L.; Hierso, J.-C. *Chem. Soc. Rev.* **2012**, *41*, 3929-3968. For selected examples of transition-metal-catalyzed indole syntheses, see: (c) Phipps, R. J.; Grimster, N. P.; Gaunt, M. J. *J. Am. Chem. Soc.* **2008**, *130*, 8172-8174. (d) Takeda, A.; Kamijo, S.; Yamamoto, Y. *J. Am. Chem. Soc.* **2000**, *122*, 5662-5663. (e) Trost, B. M.; McClory, A. *Angew. Chem. Int. Ed.* **2007**, *46*, 2074-2077. (f) Stuart, D. R.; Bertrand-Laperle, M.; Burgress, K. M. N.; Fagnou, K. *J. Am. Chem. Soc.* **2008**, *130*, 16474-16475. (g) Würtz, S.; Rakshit, S.; Neumann, J. J.; Dröge, T.; Glorius, F. *Angew. Chem. Int. Ed.* **2008**, *47*, 7230. (h) Shi, Z.; Zhang, C.; Li, S.; Pan, D.; Ding, S.; Cui, Y., Jiao, N. *Angew. Chem. Int. Ed.* **2009**, *48*, 4572-4576. (i) Wagaw, S.; Yang, B. H.; Buchwald, S. L. *J. Am. Chem. Soc.* **1999**, *121*, 10251-10263. (j) Hovey, M. T.; Check, C. T.; Sipher, A. F.; Scheidt, K. A. *Angew. Chem. Int. Ed.* **2014**, *53*, 9603-9607.
(11) (a) Bischler, A. *Chem. Ber.* **1892**, *25*, 2860-2879. (b) Bischler, A.; Firemann, P. *Chem. Ber.* **1893**, *26*, 1336-1349.
(12) Larock, R. C.; Yum, E. K. *J. Am. Chem. Soc.* **1991**, *113*, 6689-6690.
(13) Nakamura, I.; Nemoto, T.; Shiraiwa, N.; Terada, M. *Org. Lett.* **2009**, *11*, 1055-1058.
(14) The photocatalyst was selected aided by data obtained from mechanism-based luminescence screening, see (4).
(15) Tetrabutylammonium salts have been used in our group before as additives to increase the product yield: Honeker, R.; Garza-Sanchez, R. A.; Hopkinson, M. N.; Glorius, F. *Chem. Eur. J.* **2016**, *22*, 4395-4399.
(16) UV/vis absorption experiments indicate the formation of an absorbing species, see supporting information.
(17) 18.5 equiv of phenylacetylene were recovered after the reaction, resulting in the effective usage of 1.5 equiv phenylacetylene.
(18) Katritzky, A. R.; Ji, F. B.; Fan, W. Q.; Gallos, J. K.; Greenhill, J. V.; King, R. W.; Steel, P. J. *J. Org. Chem.* **1992**, *57*, 190-195.
(19) (a) Collins, K. D., Glorius, F. *Nat. Chem.* **2013**, *5*, 597-601. (b) Collins, K. D.; Rühling, A.; Glorius, F. *Nat. Protoc.* **2014**, *9*, 1348-1353. For results of the additive-based robustness screen, see SI.
(20) Taylor, E. C.; Katz, A. H.; Salgado-Zamora, H.; McKillop, A. *Tetrahedron Lett.* **1985**, *26*, 5963-5966.
(21) Wang, Y.-M.; Wu, J.; Hoong, C.; Rauniyar, V.; Toste, F. D. *J. Am. Chem. Soc.* **2012**, *134*, 12928-12931.

(22) See the supporting information for further details.
(23) Stern-Volmer luminescence quenching studies identified di*iso*propylethylamine (**4**) as the only quenching species, see SI.
(24) Based on additionally performed experiments, a cascade mechanism seems unlikely, see SI for further details.