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Scalable Synthesis of Benzotriazoles via [3 + 2] Cycloaddition of Azides and Arynes in Flow

Merlin Kleoff,^[a] Lisa Boeser,^[a] Linda Baranyi,^[a] and Philipp Heretsch*^[a]

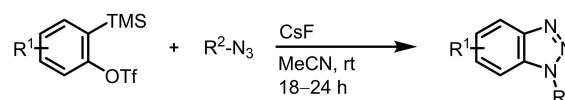
A method for the metal-free synthesis of benzotriazoles in flow is reported. Using azides and in situ generated arynes, benzotriazoles are formed in a [3 + 2] cycloaddition within minutes. Employing different substitution patterns of the azide and aryne coupling partners, a modular access to benzotriazoles is provided. Thermal strain of hazardous azides and accumulation of reactive intermediates is minimized by short reaction times in flow, improving the safety profile of the process. The scalability of the reaction is demonstrated.

The copper(I)-catalyzed [3 + 2] cycloaddition of azides and alkynes (CuAAC) has affected chemistry, biology, and medicinal research alike.^[1] In biological systems, azides and alkynes serve as bioorthogonal linkers allowing conjugation between two molecules by the formation of 1,2,3-triazoles.^[1f,h,2] Owing to the toxicity of copper for living cells, copper-free [3 + 2] cycloadditions are of great interest.^[3] Thus, the metal-free reaction of azides with arynes to substituted 1,2,3-benzotriazoles could allow further applications.^[4,5]

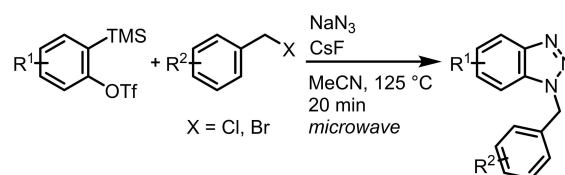
With the appearance of pathogens resistant to commonazole-based pharmaceuticals, benzotriazoles emerged as valuable substitutes and since have been employed for antibacterial, antifungal, and antiviral agents with remarkable potency.^[4c–f,6] Therefore, rapid and scalable access to a broad range of functionalized benzotriazoles could further support medicinal studies.

As described by Larock^[7a] and others,^[7b–f] reaction of *ortho*-trimethylsilyl triflates with fluoride ions generates arynes which undergo [3 + 2] cycloaddition with azides (Scheme 1A). The resulting benzotriazoles were obtained after reaction times of up to 24 hours. To accelerate the reaction, a microwave protocol was developed for the synthesis of benzyl substituted

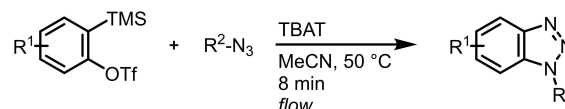
A) [3+2] Cycloaddition of arynes and azides in batch (Larock)



B) Microwave-assisted three component reaction (Biehl)



C) This work: Scalable synthesis of benzotriazoles in flow



Scheme 1. A) Synthesis of benzotriazoles via [3 + 2] cycloaddition of arynes and azides in batch at room temperature. B) Microwave-assisted reaction of arynes with in situ formed benzyl azides. C) Expedient and scalable synthesis of benzotriazoles in flow. TBAT: tetrabutylammonium triphenyldifluorosilylate; Tf: trifluoromethanesulfonyl; TMS: trimethylsilyl.

benzotriazoles but required a reaction temperature of 125 °C (Scheme 1B).^[8]

As heating of organic azides and highly reactive aryne intermediates poses the danger of an explosion, upscaling is problematic.^[9] In recent years, flow chemistry has evolved as an alternative to overcome these limitations.^[10] Given the superior heat and mass transfer in microreactors, various reactions can be significantly accelerated while offering an improved safety and sustainability profile.^[10–12]

We have recently developed a flow platform for the synthesis of natural products and their analogs. Reagents are driven with argon instead of solvent to reduce solvent and reagent waste from drying and equilibration procedures.^[13,14] Using this flow platform, we here describe a scalable method for the efficient preparation of benzotriazoles by [3 + 2] cycloaddition of arynes and azides in flow (Scheme 1C).

At the outset, we screened conditions for the reaction of benzyne precursor **1a** with benzyl azide (**2a**) leading to benzotriazole **3a** (Table 1). To streamline the process and minimize thermal strain of organic azides, we aimed for a short residence time in a heated tube reactor.

Initially, tetrabutylammonium fluoride (TBAF) was used as a fluoride source since the limited solubility of cesium fluoride in

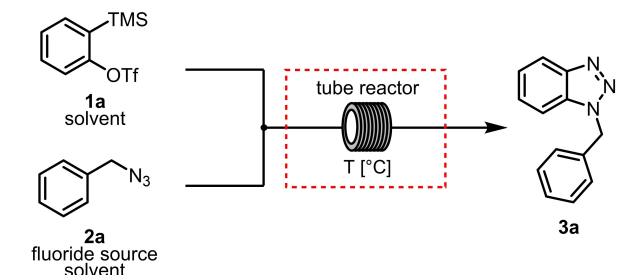
[a] M. Kleoff, L. Boeser, L. Baranyi, Prof. Dr. P. Heretsch
Institut für Chemie und Biochemie
Freie Universität Berlin
Takustraße 3, 14195 Berlin, Germany
E-mail: philipp.heretsch@fu-berlin.de
www.chemie.fu-berlin.de/heretsch

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Table 1. Optimization of the [3+2] cycloaddition of benzyne and benzyl azide in a flow reactor.^[a]



Entry	Fluoride source	Solvent	T [°C]	Yield [%]
1	TBAF	THF	50	30
2	TBAF	PhCF ₃	50	33
3	TBAF	MeCN	50	53
4	KF/18-c-6	MeCN	50	3
5	TBAT	MeCN	50	74
6	TBAT	MeCN	40	68
7	TBAT	MeCN	55	72
8	TBAT	MeCN	60	66
9 ^[b]	TBAT	MeCN	50	64
10 ^[c]	TBAT	MeCN	50	87

[a] Yields of isolated product are given. Reaction conditions: **1a** (0.3 mmol, 0.15 M, 1.5 equiv), **2a** (0.2 mmol, 0.1 M, 1.0 equiv), TBAT (0.32 mmol, 0.16 M, 1.6 equiv); flow rate: 0.4 mL, 8 min. [b] Performed with a residence time of 4 min. [c] Performed with 1.7 equiv. of **1a** and 1.8 equiv. of TBAT. 18-c-6: 1,4,7,10,13,16-hexaoxacyclooctadecane; THF: tetrahydrofuran.

acetonitrile precluded its use in our flow process. At 50 °C and with a residence time of 8 minutes, different solvents (entries 1–3) were screened. While tetrahydrofuran (THF) and benzonitrile resulted in low yields, employing acetonitrile as solvent, **3a** was isolated with a moderate yield of 53%. When potassium fluoride and 18-crown-6 were used, almost no product was obtained (entry 4). Switching to tetrabutylammonium triphenyldifluorosilicate (TBAT) as a fluoride source gave smooth conversion to benzotriazole **3a** and an improved yield of 74% (entry 5). Further investigation of parameters revealed a residence time of 8 min at 40 °C led to an incomplete reaction (68% yield, entry 6). At higher temperatures, complete consumption of starting material was observed, but lower yields were obtained (entries 7 and 8).

Employing higher flow rates and a shorter residence time of 4 minutes at 50 °C, incomplete conversion of starting material was observed along with a lower yield of 64% (entry 9). Eventually, when 1.7 equivalents of benzyne precursor **1a** and 1.8 equivalents of TBAT were used, the yield of benzotriazole **3a** could be increased to 87% (entry 10). In accordance with our previous studies, the reaction could be performed without exclusion of air and moisture.^[13a]

With the optimized flow protocol in hand, the scope of the [3+2] cycloaddition of benzyne with various azides was investigated (Scheme 2). Despite the intriguing properties of ferrocenyl benzotriazoles,^[4d] they have not been prepared from arynes and ferrocenyl azides, thus far.^[13b] This may be attributed



Merlin Kleoff was born in Berlin, Germany, in 1994 and studied chemistry at Freie Universität Berlin where he received his B.Sc. in 2015. During his Master studies, he worked with Prof. Dr. H.-U. Reißig on the preparation of super Lewis basic terpyridine ligands. In 2018, he completed his M.Sc. with a thesis on the synthesis of new ferrocene building blocks in the group of Prof. Dr. B. Sarkar. He then joined the group of Prof. Dr. P. Heretsch for his PhD where he is currently working on synthetic applications of flow chemistry.



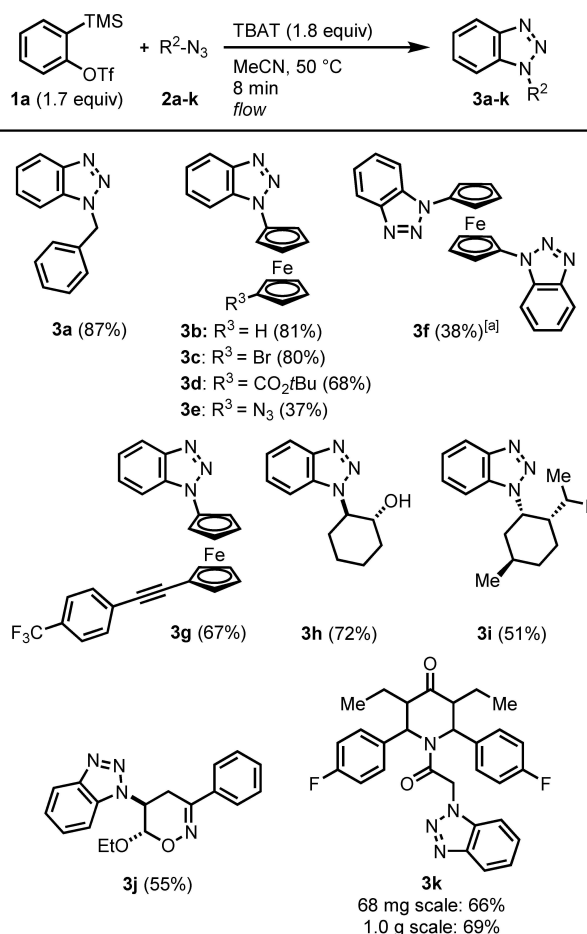
Lisa Boeser was born in Berlin, Germany, in 1998 and studied chemistry at Freie Universität Berlin. She completed her B. Sc. with a thesis on the scalable synthesis of ferrocenyl azides in flow in the group of Prof. Dr. P. Heretsch in 2019. Currently, she is conducting her master studies at Freie Universität Berlin.



Linda Baranyi was born in 1993 in Furth im Wald, Germany. She studied chemistry at the Humboldt-Universität zu Berlin where she received her B.Sc. in 2018. Currently, she is conducting her master studies in chemistry at Freie Universität Berlin.



Philipp Heretsch was born in Lippstadt, Germany, in 1982. He obtained his PhD degree from Universität Leipzig (supervisor: Prof. Dr. A. Giannis) in 2009. After a postdoctoral stay with K.C. Nicolaou at The Scripps Research Institute, La Jolla, California, and at Rice University, Houston, Texas, he was appointed assistant professor at Freie Universität Berlin in 2015. His group is interested in framework manipulation strategies in the context of abeo-steroid and alkaloid synthesis as well as application of flow chemistry in natural product synthesis.



Scheme 2. Scope of benzotriazoles **3a–k** for the reaction of benzyne with organic azides **2**. Yields of isolated product are given. Reaction conditions: **1a** (0.34 mmol, 0.17 M, 1.7 equiv), **2a–k** (0.2 mmol, 0.1 M, 1.0 equiv), TBAT (0.36 mmol, 0.18 M, 1.8 equiv), 50 °C, 8 min. For further details, see the supporting information. [a] Employing **1a** (0.34 mmol, 0.17 M, 3.4 equiv), **2e** (0.1 mmol, 0.05 M, 1.0 equiv), and TBAT (0.36 mmol, 0.18 M, 3.6 equiv).

to the potential explosiveness and thermal lability of ferrocenyl azides, hampering their use in reactions at elevated temperatures.^[15]

Employing our flow protocol, the reaction of azidoferrrocene **2b** provided the corresponding ferrocenyl benzotriazole **3b** in a good yield of 81%. Also, the bromo- (**3c**, 80% yield) and the ester-functionalized ferrocenyl benzotriazoles (**3d**, 68% yield) could be obtained.

1,1'-Diazidoferrrocene **2e** is a valuable building block for redox-switchable catalysts and sensors.^[15,16] Due to the explosiveness of **2e** at temperatures above 56 °C,^[15] synthetic applications are limited, especially on a larger scale. However, in flow, azide **2e** could be used without safety concerns. When 1.7 equivalents of benzyne precursor **1a** were employed, monobenzotriazole **3e** was isolated in a moderate yield of 37%. Using 3.4 equivalents of benzyne precursor **1a** and 3.6 equivalents of TBAT, dibenzotriazole **3f** was obtained in 38% yield. The alkynyl substituted ferrocenyl benzotriazole **3g** was isolated in 67% yield. Although, alcohols can react as nucleophiles with arynes, the [3 + 2] cycloaddition of alcohol

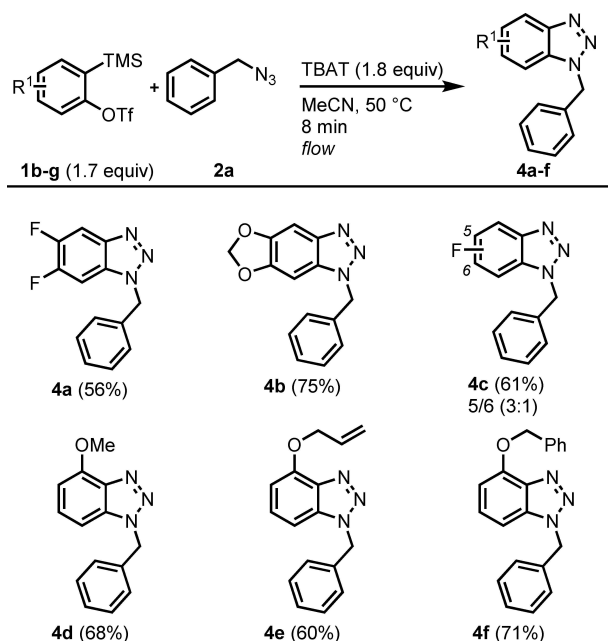
substituted azide **2h** gave benzotriazole **3h** with a good yield of 72%. The enantioenriched benzotriazole **3i** (51% yield) was derived from the corresponding menthyl azide under retention of the stereoconfiguration.

Eventually, heterocyclic azides were tested as substrates. The 5,6-dihydro-2-oxazine **2j** was prepared by aza-Michael addition of 6*H*-1,2-oxazine with sodium azide in protic solvents (see the supporting information).^[17] Cycloaddition with benzyne gave the corresponding benzotriazole **3j** in a yield of 55%.

As benzotriazole substituted piperidone **3k** shows promising antibacterial and antifungal activity,^[6] we aimed for its rapid and scalable synthesis. Employing our method, we prepared **3k** in a yield of 66%. To demonstrate the scalability of our flow protocol, we synthesized **3k** also on a gram scale corresponding to a theoretical productivity of 0.33 g/h in a similar yield of 69% with the same reactor setup.

Finally, we investigated the scope of arynes by using functionalized aryne precursors **1b–g** (Scheme 3). When electron-deficient aryne precursor **1b** was employed, difluorinated benzotriazole **4a** was isolated in 56% yield. The sesamol-derived aryne precursor **1c** reacted smoothly to benzotriazole **4b** in a good yield of 75%. Using fluorinated aryne precursor **1d**, an inseparable mixture of the 5- and 6-fluoro isomers of benzotriazole **4c** (61% yield) was obtained in a 3:1 ratio. In contrast, reaction with *ortho*-substituted precursors **1e–g** selectively gave the 4-functionalized benzotriazoles **4d–f** (60–71% yield), as assigned by nOe spectroscopic analysis.

In conclusion, we have developed a flow protocol for the metal-free synthesis of benzotriazoles by [3 + 2] cycloaddition of azides and in situ generated arynes. Due to the short residence time of 8 minutes, thermal strain is minimized



Scheme 3. Scope of benzotriazoles **4a–f** for the reaction of various arynes **1b–g** with benzyl azide **2a**. Yields of isolated product are given. Reaction conditions: **1b–g** (0.34 mmol, 0.17 M, 1.7 equiv), **2a** (0.2 mmol, 0.1 M, 1.0 equiv), TBAT (0.36 mmol, 0.18 M, 1.8 equiv), 50 °C, residence time: 8 min.

enhancing the safety and efficiency of this protocol. A variety of functionalized azides and arynes have been employed to provide the corresponding benzotriazoles, including the gram-scale preparation of an antibacterial benzotriazole.

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Conflict of Interest

The authors declare no conflict of interest.

Keywords: Arynes · Click chemistry · Cycloaddition · Flow chemistry · Nitrogen heterocycles

- [1] a) H. C. Kolb, M. G. Finn, K. B. Sharpless, *Angew. Chem. Int. Ed.* **2001**, *40*, 2004–2021; *Angew. Chem.* **2001**, *113*, 2056–2075; b) V. V. Rostovtsev, L. G. Green, V. V. Fokin, K. B. Sharpless, *Angew. Chem. Int. Ed.* **2002**, *41*, 2596–2599; *Angew. Chem.* **2002**, *114*, 2708–2711; c) C. W. Tornøe, C. Christensen, M. Meldal, *J. Org. Chem.* **2002**, *67*, 3057–3064; d) M. Meldal, C. W. Tornøe, *Chem. Rev.* **2008**, *108*, 2952–3015; e) D. Schweinfurth, L. Hettmanczyk, L. Suntrup, B. Sarkar, *Z. Allg. Anorg. Chem.* **2017**, *643*, 554–584; f) P. Thirumurugan, D. Matosiuk, K. Jozwiak, *Chem. Rev.* **2013**, *113*, 4905–4979; g) P. L. Golas, K. Matyjaszewski, *Chem. Soc. Rev.* **2010**, *39*, 1338–1354; h) A. H. El-Sagheer, T. Brown, *Chem. Soc. Rev.* **2009**, *39*, 1388–1405.
- [2] a) E. M. Sletten, C. R. Bertozzi, *Angew. Chem. Int. Ed.* **2009**, *48*, 6984–6998; *Angew. Chem.* **2009**, *121*, 7108–7133; b) C. P. Glindemann, A. Backenköhler, M. Strieker, U. Wittstock, P. Klahn, *ChemBioChem* **2019**, *20*, 2341–2345.
- [3] a) J. C. Jewett, C. R. Bertozzi, *Chem. Soc. Rev.* **2010**, *39*, 1272–1279; b) X. Hou, C. Ke, J. F. Stoddart, *Chem. Soc. Rev.* **2016**, *45*, 3766–3780; c) E. Kim, H. Koo, *Chem. Sci.* **2019**, *10*, 7835–7851; d) H. B. Jalani, A. C. Karagöz, S. B. Tsogoeva, *Synthesis* **2017**, *49*, 29–41; e) J. Escorihuela, A. T. M. Marcelis, H. Zuñihof, *Adv. Mater. Interfaces* **2015**, *2*, 1500135.
- [4] For selected reviews concerning benzotriazoles, see: a) A. R. Katritzky, S. Rachwal, *Chem. Rev.* **2010**, *110*, 1564–1610; b) A. R. Katritzky, S. Rachwal, *Chem. Rev.* **2011**, *111*, 7063–7120; c) I. Briguglio, S. Piras, P. Corona, E. Gavini, M. Nieddu, G. Boatto, A. Carta, *Eur. J. Med. Chem.* **2015**, *97*, 612–648; d) Y. Ren, L. Zhang, C.-H. Zhou, R.-X. Geng, *Med. Chem.* **2014**, *4*, 640–662; e) X. M. Peng, G.-X. Cai, C.-H. Zhou, *Curr. Top. Med. Chem.* **2013**, *13*, 1963–2010; f) R. R. Kale, V. Prasad, P. P. Mohapatra, V. K. Tiwari, *Monatsh. Chem.* **2010**, *141*, 1159–1182; g) E. Loukopoulos, G. E. Kostakis, *Coord. Chem. Rev.* **2019**, *395*, 193–229.
- [5] For selected reviews concerning arynes, see: a) A. Bhunia, S. R. Yetra, A. T. Biju, *Chem. Soc. Rev.* **2012**, *41*, 3140–3152; b) J. García-Lopez, M. F. Greaney, *Chem. Soc. Rev.* **2016**, *45*, 6766–6798; c) J. Shi, Y. Li, Y. Li, *Chem. Soc. Rev.* **2017**, *46*, 1707–1719; d) A. V. Dubrovskiy, N. A. Markina, R. C. Larock, *Org. Biomol. Chem.* **2013**, *11*, 191–218; e) R. Karmakar, D. Lee, *Chem. Soc. Rev.* **2016**, *45*, 4459–4470; f) D. B. Werz, A. T. Biju, *Angew. Chem. Int. Ed.* **2020**, *59*, 3385–3398; *Angew. Chem.* **2020**, *132*, 3410–3420; g) H. Takikawa, A. Nishii, T. Sakai, K. Suzuki, *Chem. Soc. Rev.* **2018**, *47*, 8030–8056; h) A. E. Goetz, T. K. Shah, N. K. Garg, *Chem. Commun.* **2015**, *51*, 34–45.
- [6] R. Ramachandran, M. Rani, S. Senthana, Y. T. Jeong, S. Kabilan, *Eur. J. Med. Chem.* **2011**, *46*, 1926–1934.
- [7] For selected examples, see: a) F. Shi, J. P. Waldo, Y. Chen, R. C. Larock, *Org. Lett.* **2008**, *10*, 2409–2412; b) L. Campbell-Verduyn, P. H. Elsinga, L. Mirfeizi, R. A. Dierckx, B. L. Feringa, *Org. Biomol. Chem.* **2008**, *6*, 3461–3463; c) S. Chandrasekhar, M. Seenaiyah, C. L. Rao, C. R. Reddy, *Tetrahedron* **2008**, *64*, 11325–11327; d) D. J. Atkinson, J. Sperry, M. A. Brimble, *Synlett* **2011**, 99–103; e) F. Zhang, J. E. Moses, *Org. Lett.* **2009**, *11*, 1587–1590; f) G. Singh, R. Kumar, J. Swett, B. Zajc, *Org. Lett.* **2013**, *15*, 4086–4089.
- [8] H. Ankati, E. Biehl, *Tetrahedron Lett.* **2009**, *50*, 4677–4682.
- [9] a) S. Bräse, K. Banert (Eds.), *Organic Azides: Synthesis and Applications*, Wiley: Chichester, West Sussex, 2010; b) S. Bräse, C. Gil, K. Knepper, V. Zimmermann, *Angew. Chem. Int. Ed.* **2005**, *44*, 5188–5240; *Angew. Chem.* **2005**, *117*, 5320–5374; c) P. Klahn, H. Erhardt, A. Kotthaus, S. F. Kirsch, *Angew. Chem. Int. Ed.* **2014**, *53*, 7913–7917; *Angew. Chem.* **2014**, *126*, 8047–8051.
- [10] a) M. B. Plutschack, B. Pieber, K. Gilmore, P. H. Seeberger, *Chem. Rev.* **2017**, *117*, 11796–11893; b) M. Movsisyan, E. I. P. Delbeke, J. K. E. T. Berton, C. Battilocchio, S. V. Ley, C. V. Stevens, *Chem. Soc. Rev.* **2016**, *45*, 4892–4928; c) C. J. Mallia, I. R. Baxendale, *Org. Process Res. Dev.* **2016**, *20*, 327–360; d) D. Cambié, C. Bottecchia, N. J. W. Straathof, V. Hessel, T. Noël, *Chem. Rev.* **2016**, *116*, 10276–10341; e) T. Noël, S. L. Buchwald, *Chem. Soc. Rev.* **2011**, *40*, 5010–5029; f) B. Gutmann, D. Cantillo, C. O. Kappe, *Angew. Chem. Int. Ed.* **2015**, *54*, 6688–6728; *Angew. Chem.* **2015**, *127*, 6788–6832; g) C. Empel, R. M. Koenigs, *J. Flow Chem.* **2020**, *10*, 157–160; h) S. T. R. Müller, T. Wirth, *ChemSusChem* **2015**, *8*, 245–250; i) M. Elsherbini, T. Wirth, *Acc. Chem. Res.* **2019**, *52*, 3287–3296.
- [11] C. Wiles, P. Watts, *Green Chem.* **2014**, *14*, 38–54.
- [12] Benzotriazoles have been prepared in flow, for example, from chloronitrobenzenes and amines, see: M. Chen, S. L. Buchwald, *Angew. Chem. Int. Ed.* **2013**, *52*, 4247–4250; *Angew. Chem.* **2013**, *125*, 4341–4344.
- [13] a) J. Schwan, M. Kleoff, B. Hartmayer, P. Heretsch, M. Christmann, *Org. Lett.* **2018**, *20*, 7661–7664; b) M. Kleoff, J. Schwan, L. Boeser, B. Hartmayer, M. Christmann, B. Sarkar, P. Heretsch, *Org. Lett.* **2020**, *22*, 902–907.
- [14] M. Kleoff, J. Schwan, M. Christmann, P. Heretsch, *ChemRxiv* **2020**, DOI: 10.26434/chemrxiv.13266260.v1.
- [15] A. Shafir, M. P. Power, G. D. Whitener, J. Arnold, *Organometallics* **2000**, *19*, 3978–3982.
- [16] a) J. Wei, P. L. Diaconescu, *Acc. Chem. Res.* **2019**, *52*, 415–424; b) F. Zapata, A. Caballero, P. Molina, *Eur. J. Inorg. Chem.* **2016**, 237–241.
- [17] K. Homann, J. Angermann, M. Collas, R. Zimmer, H.-U. Reissig, *J. Prakt. Chem.* **1998**, *340*, 649–655.

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