



A Metal-Free Three-Component Reaction for the Regioselective Synthesis of 1,4,5-Trisubstituted 1,2,3-Triazoles**

Joice Thomas, Jubi John, Nikita Parekh, and Wim Dehaen*

Abstract: A metal-free three-component reaction to synthesize 1,4,5-trisubstituted 1,2,3-triazoles from readily available building blocks, such as aldehydes, nitroalkanes, and organic azides, is described. The process is enabled by an organocatalyzed Knoevenagel condensation of the formyl group with the nitro compound, which is followed by the 1,3-dipolar cycloaddition of the azide to the activated alkene. The reaction features an excellent substrate scope, and the products are obtained with high yield and regioselectivity. This method can be utilized for the synthesis of fused triazole heterocycles and materials with several triazole moieties.

Substituted 1,2,3-triazoles are among the most important heterocyclic compounds and have found a broad spectrum of applications in areas ranging from medicinal chemistry to material science.^[1] The amide–triazole bioequivalence of these heterocycles has been utilized for the development of many privileged medicinal scaffolds that exhibit, for instance, anti-HIV, anticancer, and antibacterial activities.^[2] Because of their reliability, regioselective triazole-forming reactions have gained much attention, particularly those that are based on copper(I)- and ruthenium(II)-mediated azide–alkyne cycloadditions reactions.^[3,4] However, these methods are mostly restricted to terminal alkynes, and the toxicity of the heavy metals makes these strategies not ideal for some biological applications.^[5] Therefore, the development of new efficient methods that are devoid of these deficiencies would be of great importance.

Recently, organocatalytic triazole formation has been used as a powerful, albeit less developed, alternative to metal-catalyzed click reactions (Figure 1).^[6] The first example was reported by Ramachary et al., who investigated the synthesis of functionalized NH-1,2,3-triazoles from γ -activated enones and organic azides under proline catalysis.^[6a,b] Recently, the groups of Wang and Bressy independently developed a regioselective approach for the synthesis of 1,4,5-trisubstituted 1,2,3-triazoles through enamide–azide cycloadditions of β -keto esters or nitriles to azides in the presence of a catalytic amount of a secondary amine.^[6b–d,f,g] However, major limi-

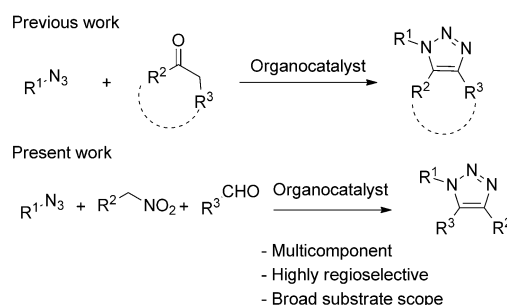


Figure 1. Organocatalytic routes to substituted 1,2,3-triazoles.

tations of these approaches are the narrow substrate scope and the restriction to ketone or cyclic enone substrates.

Despite these advances in organocatalytic triazole synthesis, some challenging issues still remain: 1) A regioselective synthesis of 1,4,5-trisubstituted 1,2,3-triazoles with considerable molecular complexity and diversity to enable structure–activity relationship studies of drug-like compounds and 2) an economically viable procedure to synthesize densely functionalized triazoles from inexpensive commercially available building blocks have not been developed. Perhaps the most promising and powerful method to reach these goals is to rely on new multicomponent reactions (MCRs).^[7] Ideally, MCRs should be versatile so that any combination of functional groups can be integrated into the final products. In view of realizing such transformations, we were prompted to consider a three-component reaction (3CR) to construct fully functionalized triazole scaffolds from readily available building blocks, such as aldehydes, nitroalkanes, and organic azides (Figure 1). We hypothesized that nitroalkene dipolarophiles prepared in situ by a Knoevenagel condensation of the corresponding aldehydes and substituted nitroalkanes may undergo a regioselective intermolecular Huisgen cycloaddition reaction with organic azides to form 1,4,5-trisubstituted 1,2,3-triazoles after aromatization by spontaneous loss of HNO_2 in an atom-economic approach.^[8]

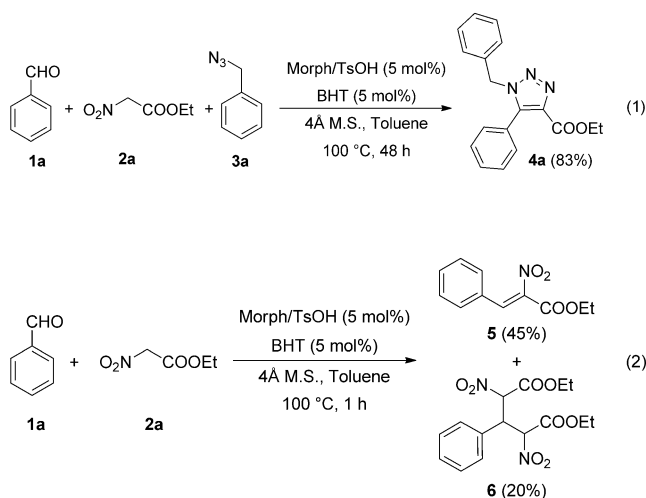
The reaction conditions were optimized with benzaldehyde (**1a**), ethyl nitroacetate (**2a**), and benzyl azide (**3a**) as the model substrates.^[9] Therefore, the optimized reaction conditions of the one-pot 3CR were found to entail the use of **1a**, **2a**, and **3a** in a molar ratio of 1.3:1:1, morpholinium *para*-toluenesulfonate (Morph/TsOH, 5 mol %) as the catalyst, and 2,6-di-*tert*-butyl-4-methylphenol (BHT; 5 mol %) as an additive over 4 Å molecular sieves in toluene (2 M) at 100 °C in a sealed tube under argon atmosphere. The desired product

[*] Dr. J. Thomas, Dr. J. John, N. Parekh, Prof. Dr. W. Dehaen
Molecular Design and Synthesis
Department of Chemistry, KU Leuven
Celestijnenlaan 200F, 3001 Leuven (Belgium)
E-mail: wim.dehaen@chem.kuleuven.be

[**] We thank the University of Leuven and the FWO-Vlaanderen for financial support. The Erasmus Exchange program “Experts II” is acknowledged for a fellowship to N.P.

Supporting information for this article is available on the WWW under <http://dx.doi.org/10.1002/anie.201403453>.

4a was isolated in 83 % yield with a regioselectivity of > 99 % [Eq. (1)].



To get insight into the mechanism of the reaction, several experiments were done. When **1a** and **2a** were reacted in the presence of the Morph/TsOH catalyst (5 mol %) for a period of one hour, nitroalkene **5** was obtained in 45 % yield, together with the expected Michael adduct, 1,3-dinitroalkane **6**, in 20 % yield [Eq. (2)]. Then, two separate experiments were conducted with the isolated dipolarophile **5** and benzyl azide **3a** both in the absence and in the presence of the catalyst over a period of 48 hours. Interestingly, both reactions led to the desired product **4a** in 84 % and 86 % yield, respectively, and exhibited the same regioselectivity as a reaction under the optimized conditions. This observation convincingly demonstrated that the organocatalyst plays no role in determining the high regioselectivity of the final cycloaddition step. Based on these studies, the probable catalytic pathway of this MCR involves the initial formation of an activated iminium intermediate from benzaldehyde (**1a**) and the morpholine salt.^[10] This intermediate is then attacked by ethyl nitroacetate (**2a**) to afford nitroalkene **5**, together with the regeneration of the catalyst. A condensation reaction catalyzed by *para*-toluenesulfonic acid could constitute another reaction pathway. However, some of these Knoevenagel adducts will be consumed

by further Michael addition reactions with nitroalkenes to generate the undesired dinitroglutaric ester **6**.^[11] We presume that this species is in equilibrium with the Knoevenagel product **5**, and that the formation of triazole **4** can displace this equilibrium, so that this transformation is an example of thermodynamically controlled dynamic covalent chemistry.^[12] Thus, the yield of the 3CR is superior to that of the 2CR Knoevenagel condensation itself, and isolation of the nitroalkene prior to the cycloaddition^[8] is not needed, and even disadvantageous for the overall yield. The high regioselectivity of this reaction is clearly due to the presence of a strongly electron-withdrawing nitro group on the dipolarophile **5**, which lowers the energy of the lowest unoccupied molecular orbital (LUMO) and causes the β carbon atom to be the most electrophilic.^[13] Thus, dipolar reaction partners are expected to attack the partially positively charged β position of the nitroalkene dipolarophile in a Huisgen cycloaddition to form a cyclic triazoline intermediate, which would then eliminate nitrous acid to regioselectively yield a triazole with the carboxy and the phenyl group at the C4 and the C5 position, respectively.^[8]

With the optimized reaction conditions in hand, we first studied the scope and limitations of this transformation with

Table 1: Substrate scope of the triazole synthesis.^[a]

1	2	3	Reaction Conditions	4
$R^3\text{-CHO}$	$R^2\text{-CH}_2\text{NO}_2$	$R^1\text{-N}_3$	Morph/TsOH (5 mol %), BHT (5 mol %), 4 Å M.S., Toluene, 100 °C, 48 h	$R^1\text{-N}_3\text{-N}_2\text{-N}_2\text{-R}^2$
4a (83%), R = Ph	4b (67%) ^[b] , R = <i>p</i> -OMe-C ₆ H ₄	4c (80%) ^[b] , R = <i>o</i> -OMe-C ₆ H ₄	4d (61%), R = <i>o</i> -Me-C ₆ H ₄	4e (58%), R = <i>p</i> -F-C ₆ H ₄
4f (66%), R = <i>p</i> -Br-C ₆ H ₄	4g (78%), R = <i>p</i> -CHO-C ₆ H ₄	4h (85%), R = <i>p</i> -COOMe-C ₆ H ₄	4i (76%) ^[c]	4j (56%) ^[d]
4k (76%)	4l (50%)	4m (77%), R = COPh	4n (64%), R = SO ₂ Ph	4o (43%), R = CONHMe
4p (46%)	4q (26%), R = PO(OEt) ₂	4r (64%) ^[e] , R = Br	4s (62%) ^[e] , R = Me	4t (59%) ^[e] , R = H
4u (49%) ^[e] , R = Ph	4v (43%) ^[e] , R = CH ₂ -2-thienyl	4w (51%) ^[e] , R = CH ₂ -C ₆ H ₄ - <i>p</i> -OMe	4x (37%) ^[e] , R = (CH ₂) ₂ CO ₂ Me	4y (35%) ^[e] , R = (CH ₂) ₄ CH ₃
4z (37%) ^[e] , R = (CH ₂) ₃ CH ₃	4aa (41%) ^[e] , R = (CH ₂) ₃ OH	4ab (78%), R = <i>p</i> -OMe-C ₆ H ₄	4ac (42%), R = <i>p</i> -COOEt-C ₆ H ₄	4ad (60%), R = Ph
4ae (80%), R = <i>n</i> -pentyl	4af (78%), R = CH ₂ CO ₂ Me	4ag (66%) ^[c]		

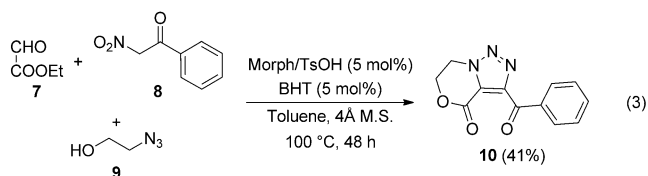
[a] Reaction conditions: **1** (1.3 equiv), **2** (1.0 equiv), **3** (1.0 equiv), Morph/TsOH (5 mol %), BHT (5 mol %), 4 Å M.S. (50 mg), toluene (0.2 mL), 100 °C, 48 h. Yields of isolated products are given. [b] 4 % of the other regioisomer was observed. [c] BHT (30 mol %). [d] Thiophene-2-carbaldehyde (2.0 equiv). [e] **2** (2.6 equiv), 72 h. M.S. = molecular sieves.

a wide range of aromatic and aliphatic aldehydes (Table 1). Both electron-donating functional groups, such as methoxy (**4b** and **4c**) and methyl (**4d**) substituents, and electron-withdrawing groups, such as halogens (**4e** and **4f**), aldehyde (**4g**), and ester (**4h**) moieties, on the aromatic rings were compatible with this transformation, and the corresponding products were obtained in good to excellent yields. The use of electron-poor aldehydes led to the formation of a single regioisomer, whereas the use of electron-rich aldehydes resulted in a small, but noticeable amount (4%) of the other regioisomer, which bears the ester group derived from ethyl nitroacetate on the C5 position of the triazole ring. These observations revealed that electron-donating groups reduce the electrophilicity at the β carbon atom of the corresponding dipolarophile, leading to a small amount of the other regioisomer. Fortunately, this minor regioisomer is effectively removed by column chromatography. The reaction was also not affected by the steric hindrance impaired by methoxy (**4c**) or methyl (**4d**) groups at the *ortho* position of the aromatic aldehydes. Notably, a readily available fluorescent material, pyrene-1-carboxaldehyde, performed well in this transformation, affording the triazole **4i** in 76% yield, but a larger amount of BHT (30 mol%) had to be employed. Otherwise, the reaction afforded desired product **4i** in only 43% yield. The reaction of the heterocyclic substrate thiophene-2-carbaldehyde also proceeded with reduced efficiency under the optimized conditions. Fortunately, when the reaction was repeated with two equivalents of thiophene-2-carbaldehyde, the yield of the corresponding bis(heteroaryl) product **4j** improved to 56%. Furthermore, ethyl glyoxalate was also found to be a suitable coupling partner, which led to the expected compound **4k** in 77% yield. The reaction with an aliphatic aldehyde afforded compound **4l** in 50% yield. An expected obstacle with the aliphatic aldehyde was the undesired aldol condensation, which also proceeded under the reaction conditions.

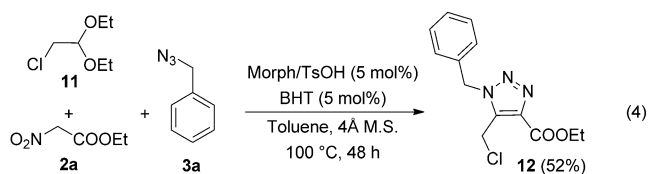
We then examined the scope of this MCR with respect to the nitroalkane coupling partner. Differently functionalized nitroalkanes, such as benzonitromethane, phenylsulfonylnitromethane, and nitroacetamide, were compatible with these conditions and afforded the expected compounds once again with excellent regioselectivity. To extend the applicability of this transformation and to demonstrate its broad scope, we synthesized 1,2,3-triazolyl-4-phosphonate **4q** using this strategy. To the best of our knowledge, a metal-free synthesis of 1,2,3-triazolyl phosphonates has not yet been described.^[14] We believe that the lower yield of this reaction is due to the hydrolysis of the phosphonate group under the present reaction circumstances. We next studied the use of non-activated nitroalkanes (**4r–4aa**) in this transformation, and after some optimization, we found that this multicomponent reaction proceeded more effectively with an excess amount of the nitro compound (2.6 equiv) and required a reaction time of 72 hours. Several aliphatic and aromatic groups were introduced at the C4 position of the triazole heterocycle. To our delight, the reaction with bromonitromethane furnished 1,5-disubstituted 4-bromotriazole **4r** in 64% yield, showing that HNO_2 is eliminated rather than HBr , which would be equally plausible.^[15] Generally, copper- or iridium-catalyzed

cycloaddition reactions of azides and bromoalkynes have been employed to synthesize 1,5-disubstituted 4-bromotriazoles, but the lack of structural diversity in the alkynyl building blocks has limited the application of this method.^[16] The reaction with nitromethane constitutes an additional example of a metal-free multicomponent reaction for the regioselective synthesis of 1,5-disubstituted 1,2,3-triazoles.^[17] Furthermore, the reactivity of several azides was evaluated. For aromatic azides, an electron-donating *para*-methoxy group resulted in the isolation of the desired cycloadduct **4ab** in good yield; however, azides with an electron-withdrawing ester group or a phenyl substituent provided the corresponding products in diminished yields in comparison with benzyl azide (**4ac** and **4ad**). This may partially be explained by the lower thermal stability of aryl azides. Not surprisingly, aliphatic azides were converted into the corresponding products with higher efficiency than the aromatic azides (**4ae–4ag**).

Interestingly, the reaction with ethyl glyoxalate (**7**), benzonitromethane (**8**), and 2-azidoethanol (**9**) under optimized conditions led to the formation of the novel heterocycle-fused 1,2,3-triazole **10**, which entails a six-membered lactone fused to the 1- and 5-positions of the triazole ring system [Eq. (3)].



In a preliminary investigation, we have established that this three-component reaction is also applicable to acetal-protected aldehydes, thus giving access to triazole heterocycles that cannot be synthesized by other methods. For example, under the standard conditions, diethyl chloroacetal **11** yielded the desired product **12** in 52% yield with good regioselectivity [Eq. (4)].



Bifunctional building blocks with the same functional groups gave bis(triazole) derivatives after multiple MCRs (Figure 2). Our initial experiments focused on the bifunctional substrate terephthalaldehyde, which gave the novel bis(triazole) compound **13** in acceptable yield (40%) on treatment with **2a** and **3a** (2 equiv each) under the optimized reaction conditions. Furthermore, two diazide building blocks, 1,2-bis(azidomethyl)benzene and 1,4-bis(azidomethyl)benzene, were treated with an excess of **1a** and **2a** to

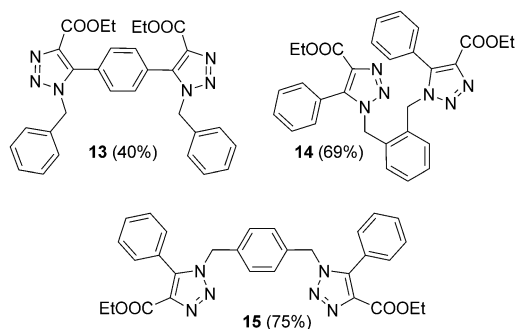
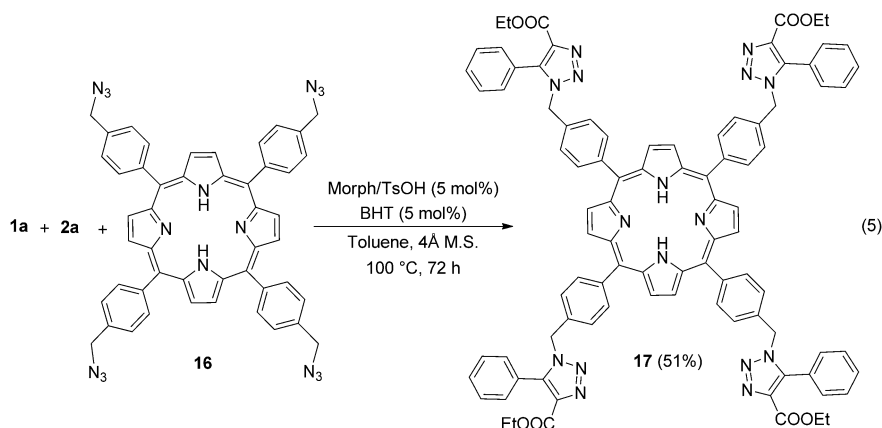


Figure 2. Multicomponent synthesis of bis(triazole) derivatives.

furnish the desired products **14** and **15** in 69% and 75% yield, respectively.

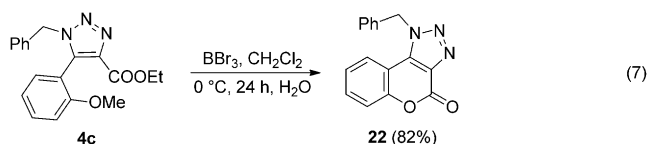
The versatility of these multiple MCRs was further exemplified by synthesizing compound **17**, a metal-free tetraarylporphyrin functionalized with four fully substituted 1,2,3-triazole groups [Eq. (5)]. In earlier work, we had seen



that unless the porphyrin is metalated (with Zn) prior to the copper-catalyzed click reaction, we obtained a Cu^{II} metalated porphyrinate.^[18] Close inspection of the ¹H NMR data of the crude reaction mixture revealed the presence of 4% of the other regioisomer. Ultimately, **17** was isolated as a single regioisomer in good yield by column chromatography followed by precipitation of the isolated compound in an excess of heptane.

Inspired by the success of the above reactions, our efforts were focused on the reaction of salicylaldehyde (**18**), ethyl nitroacetate (**2a**), and organic azides to generate coumarin-fused triazole derivatives [Eq. (6)].^[9] Surprisingly, the products arising from these transformations, heterobicycles **20** and

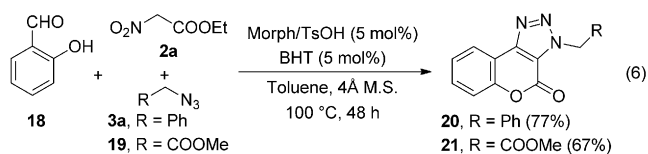
21, could be shown to be the other regioisomer (with the carbonyl group of the lactone ring connected to the 5-position of the triazole) with respect to the preceding examples. Initial evidence was obtained from the ¹H NMR spectra of these compounds and the unusual downfield shifts of the peaks corresponding to the methylene groups that originate from the organic azides compared to other trisubstituted 1,2,3-triazoles. To obtain concrete evidence for the regiochemistry of this product, we synthesized the regioisomer of **20**, triazole **22** (with the carbonyl group of the lactone ring connected to the 4-position of the triazole), by BBr₃ mediated cleavage of the ether moiety of triazole derivative **4c** followed by lactonization [Eq. (7)]. An upfield shift of the peaks corre-



sponding to the benzylic hydrogen atoms in the ¹H NMR spectrum of **22** relative to those of **20** confirmed the regiochemistry of the coumarin-fused triazole derivatives. We speculate that with the dipolarophile 3-nitrocoumarin, steric effects surpass electronic preferences, to give exclusively the opposite regioisomer.^[13]

In conclusion, we have developed a versatile organocatalytic three-component reaction that generates fully substituted 1,2,3-triazoles decorated with useful functional groups, which can be used for further manipulation and diversification. This method features metal-free conditions and high regioselectivity, and it provides an easy

access to diversely functionalized 1,2,3-triazoles that are inaccessible by other means. Many functional groups, such as aldehydes, ketones, esters, sulfones, halides, amides, and phosphonates, are well tolerated under these reaction circumstances. A rapid search for the products reported herein showed that less than 20% of them have been previously described. Furthermore, most of the reported syntheses have the disadvantage of requiring heavy metals and less available unsymmetric internal alkynes; therefore, our method is very convenient. Further elaboration of this chemistry to other new reactions and the development of applications of these transformations in the medicinal as well as the supramolecular sciences are currently actively pursued within our group.



Received: March 18, 2014

Revised: May 12, 2014

Published online: July 2, 2014

Keywords: dipolar cycloaddition · multicomponent reactions · organocatalysis · regioselectivity · triazole

- [1] For selected reviews on the application of 1,2,3-triazoles, see: a) "Special issue on click chemistry", *Chem. Soc. Rev.* **2010**, 39, 1221–1408; b) T. Muller, S. Bräse, *Angew. Chem.* **2011**, 123, 12046–12047; *Angew. Chem. Int. Ed.* **2011**, 50, 11844–11845; c) C. Chu, R. Liu, *Chem. Soc. Rev.* **2011**, 40, 2177–2188; d) Y. H. Lau, P. J. Rutledge, M. Watkinson, M. H. Todd, *Chem. Soc. Rev.* **2011**, 40, 2848–2866; e) D. Astruc, L. Liang, A. Rapakousiou, J. Ruiz, *Acc. Chem. Res.* **2012**, 45, 630–640.
- [2] a) R. Alvarez, S. Velazquez, A. San-Felix, S. Aquaro, E. De Clercq, C.-F. Perno, A. Karlsson, J. Balzarini, M. J. Camarasa, *J. Med. Chem.* **1994**, 37, 4185–4194; b) R. S. Bohacek, C. McMartin, W. C. Guida, *Med. Res. Rev.* **1996**, 16, 3–50; c) M. J. Soltis, H. J. Yeh, K. A. Cole, N. Whittaker, R. P. Wersto, E. C. Kohn, *Drug Metab. Dispos.* **1996**, 24, 799–806; d) R. Kharb, P. C. Sharma, M. S. Yar, *J. Enzyme Inhib. Med. Chem.* **2011**, 26, 1–21; e) C. Sheng, W. Zhang, *Curr. Med. Chem.* **2011**, 18, 733–766; f) S. G. Agalave, S. R. Maujan, V. S. Pore, *Chem. Asian J.* **2011**, 6, 2696–2718; g) P. Thirumurugan, D. Matosiuk, K. Jozwiak, *Chem. Rev.* **2013**, 113, 4905–4979.
- [3] a) V. V. Rostovtsev, L. G. Green, V. V. Fokin, K. B. Sharpless, *Angew. Chem.* **2002**, 114, 2708–2711; *Angew. Chem. Int. Ed.* **2002**, 41, 2596–2599; b) C. W. Tornøe, C. Christensen, M. Meldal, *J. Org. Chem.* **2002**, 67, 3057–3064; c) P. Appukkuttan, W. Dehaen, V. V. Fokin, E. Van der Eycken, *Org. Lett.* **2004**, 6, 4223–4225; d) M. Meldal, C. W. Tornøe, *Chem. Rev.* **2008**, 108, 2952–3015.
- [4] a) L. Zhang, X. G. Chen, P. Xue, H. H. Y. Sun, I. D. Williams, K. B. Sharpless, V. V. Fokin, G. C. Jia, *J. Am. Chem. Soc.* **2005**, 127, 15998–15999; b) L. K. Rasmussen, B. C. Boren, V. V. Fokin, *Org. Lett.* **2007**, 9, 5337–5339.
- [5] a) L. M. Gaetke, C. K. Chow, *Toxicology* **2003**, 189, 147–163; b) A. J. Link, D. A. Tirrell, *J. Am. Chem. Soc.* **2003**, 125, 11164–11165; c) A. J. Link, M. K. S. Vink, N. J. Agard, J. A. Prescher, C. R. Bertozzi, D. A. Tirrell, *Proc. Natl. Acad. Sci. USA* **2006**, 103, 10180–10185; d) J. A. Johnson, J. M. Baskin, C. R. Bertozzi, J. T. Koberstein, N. J. Turro, *Chem. Commun.* **2008**, 3064–3066.
- [6] For examples of organocatalytic [3+2] cycloaddition reactions, see: a) D. B. Ramachary, K. Ramakumar, V. V. Narayana, *Chem. Eur. J.* **2008**, 14, 9143–9147; b) L. J. T. Danence, Y. Gao, M. Li, Y. Huang, J. Wang, *Chem. Eur. J.* **2011**, 17, 3584–3587; c) M. Belkheira, D. E. Abed, J.-M. Pons, C. Bressy, *Chem. Eur. J.* **2011**, 17, 12917–12921; d) L. Wang, S. Y. Peng, L. J. T. Danence, Y. Gao, J. Wang, *Chem. Eur. J.* **2012**, 18, 6088–6093; e) N. Seus, L. C. Goncalves, A. M. Deobald, L. Savegnago, D. Alves, M. W. Paixao, *Tetrahedron* **2012**, 68, 10456–10463; f) D. K. J. Yeung, T. Gao, J. Huang, S. Sun, H. Guo, J. Wang, *Green Chem.* **2013**, 15, 2384–2388; g) W. Li, Q. Jia, Z. Du, J. Wang, *Chem. Commun.* **2013**, 49, 10187–10189; h) D. B. Ramachary, A. B. Shashank, *Chem. Eur. J.* **2013**, 19, 13175–13181; i) N. Seus, B. Goldani, E. J. Lenardão, L. Savegnago, M. W. Paixão, D. Alves, *Eur. J. Org. Chem.* **2014**, 1059–1065.
- [7] A. Dömling, W. Wang, K. Wang, *Chem. Rev.* **2012**, 112, 3083–3135.
- [8] a) J. C. Piet, G. Le Hetet, P. Cailleux, H. Benhaoua, R. Carrie, *Bull. Soc. Chim. Belg.* **1996**, 105, 33–44; b) T. Wang, X.-C. Hu, X.-J. Huang, X.-S. Li, J.-W. Xie, *J. Braz. Chem. Soc.* **2012**, 23, 1119–1123; c) P. S. S. Lacerda, A. M. G. Silva, A. C. Tome, M. G. P. M. S. Neves, A. M. S. Silva, J. A. S. Cavaleiro, A. L. Llamas-Saiz, *Angew. Chem.* **2006**, 118, 5613–5617; *Angew. Chem. Int. Ed.* **2006**, 45, 5487–5491.
- [9] See the Supporting Information.
- [10] a) D. W. C. MacMillan, *Nature* **2008**, 455, 304–308; b) B. List, *Angew. Chem.* **2010**, 122, 1774–1779; *Angew. Chem. Int. Ed.* **2010**, 49, 1730–1734; c) S.-K. Xiang, B. Zhang, L.-H. Zhang, Y. Cui, N. Jiao, *Chem. Commun.* **2011**, 47, 8097–8099; d) P. Renzi, M. Bella, *Chem. Commun.* **2012**, 48, 6881–6896.
- [11] R. Ballini, S. Gabrielli, A. Palmieri, *Eur. J. Org. Chem.* **2014**, DOI: 10.1002/ejoc.201301531.
- [12] a) P. T. Corbett, L. Vial, K. R. West, J.-L. Wietor, J. K. M. Sanders, S. Otto, *Chem. Rev.* **2006**, 106, 3652; b) J.-M. Lehn, *Chem. Soc. Rev.* **2007**, 36, 151; c) J. Thomas, G. Reekmans, P. Adriaenssens, L. Van Meervelt, M. Smet, W. Maes, W. Dehaen, L. Dobrzanska, *Angew. Chem.* **2013**, 125, 10427–10430; *Angew. Chem. Int. Ed.* **2013**, 52, 10237–10240.
- [13] a) R. Huisgen, G. Szeimies, L. Möbius, *Chem. Ber.* **1967**, 100, 2494–2507; b) A. Padwa, in *Comprehensive Organic Synthesis*, Vol. 4 (Ed.: B. M. Trost), Pergamon, Oxford, **1991**, pp. 1069–1109; c) J. E. Hein, V. V. Fokin, *Chem. Soc. Rev.* **2010**, 39, 1302–1315.
- [14] a) J.-M. Kee, B. Villani, L. R. Carpenter, T. W. Muir, *J. Am. Chem. Soc.* **2010**, 132, 14327–14329; b) L. Li, G. Hao, A. Zhu, X. Fan, G. Zhang, L. Zhang, *Chem. Eur. J.* **2013**, 19, 14403–14406.
- [15] A referee suggested that this may be due to the *cis* arrangement of the H and Br substituents in the intermediary triazoline adduct.
- [16] a) B. H. M. Kuipers, G. C. T. Dijkmans, S. Grootuys, P. J. L. M. Quaedflieg, R. H. Blaauw, F. L. van Delft, F. P. J. T. Rutjes, *Synlett* **2005**, 3059–3062; b) E. Rasolofonjatovo, S. Theeramunkong, A. Bouriaud, S. Kolodych, M. Chaumontet, F. Taran, *Org. Lett.* **2013**, 15, 4698–4701.
- [17] a) S. W. Kwok, J. R. Fotsing, R. J. Fraser, V. O. Rodionov, V. V. Fokin, *Org. Lett.* **2010**, 12, 4217–4219; b) M. E. Meza-Aviña, M. K. Patel, C. B. Lee, T. J. Dietz, M. P. Croatt, *Org. Lett.* **2011**, 13, 2984–2987; c) F. Kloss, U. Köhn, B. O. Jahn, M. D. Hager, H. Görls, U. S. Schubert, *Chem. Asian J.* **2011**, 6, 2816–2824; d) G. Cheng, X. Zeng, J. Shen, X. Wang, X. Cui, *Angew. Chem.* **2013**, 125, 13507–13510; *Angew. Chem. Int. Ed.* **2013**, 52, 13265–13268; e) A. Kayet, T. Pathak, *J. Org. Chem.* **2013**, 78, 9865–9875.
- [18] N. T. Nguyen, G. Mamardashvili, M. Gruzdev, N. Mamardashvili, W. Dehaen, *Supramol. Chem.* **2013**, 25, 180–188.