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Copper-catalyzed *in situ* oxidative-coupling for one-pot synthesis of 5-aryl-1,4-disubstituted 1,2,3-triazoles under mild conditions†

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A new reaction system with CuCl as catalyst, TEA as base and O₂/chloramine-T as oxidant was developed for one-pot *in situ* oxidative-coupling to synthesize 5-aryl-1,4-disubstituted 1,2,3-triazoles in this paper. A variety of 5-arylated-1,2,3-triazole compounds could be efficiently prepared directly from the readily accessible organic azides, terminal alkynes and arylboronic acids. Advantages of the method include use of low-cost catalyst, clean oxidant, less-toxic additive, and low reaction temperature. Importantly, due to avoiding harsh strong basic reagents and high temperatures, the presented method can offer mild conditions for multi-component synthesis of 5-aryl-1,2,3-triazoles from the designed structurally complicated alkynyl or azide donors bearing natural product motifs and sensitive functional groups.

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Introduction

1,2,3-Triazoles have not only demonstrated extensive anti-cancer, anti-inflammatory, and antibacterial activities,^{1,2} but also been widely used as promising potential building blocks for energetic materials, lubricants, dyes and light stabilizers in materials science.^{3,4} The increasing interest in the applications of 1,2,3-triazoles calls for concise and convenient synthesis methods for preparing structurally diverse 1,2,3-triazole derivatives. Copper-catalyzed cycloadditions of azide and terminal alkynes (CuAAC) reported in 2002, have given easy access to 1,4-disubstituted 1,2,3-triazoles.^{5,6} Since then, a huge number of efforts have been made for improving catalytic systems for CuAAC reaction toward high efficiency, mild conditions and application for a wide scope of substrates.^{7,8} In contrast, only a few of reaction systems have been reported to access to 5-aryl-1,4-disubstituted 1,2,3-triazoles.^{9–16} Traditionally, the reaction of aryl alkyne and azide gives 1,4- and 1,5-substituted isomers under heating conditions.⁷ Fokin group reported a Ru-catalysis approach for constructing 5-aryl-1,4-disubstituted 1,2,3-triazoles from the cycloaddition of diphenylacetylene and benzy-lazide in the presence of Cp*RuCl(PPh₃)₂.⁹ More recently, a C–H activation method for synthesis of 5-aryl-1,4-disubstituted 1,2,3-triazoles from pre-prepared 1,4-disubstituted 1,2,3-triazole and

aryl halides was reported by Ackermann group in the presence of Pd catalyst and tetrabutylammonium acetate in PEG20000.¹¹ Other reported arylation methods including uses of bromo-benzene^{15,16} and aryl tosylate¹⁰ also showed effective for incorporations of aryl groups on C-5 of 1,2,3-triazoles. However, most of these methods are involved expensive noble metal catalysts, complex ligands, harsh reaction conditions or high temperatures.

On the other hand, a multi-component one-pot reaction strategy based on *in situ* capture of triazole compounds has been developed in our and other groups.^{17–21} By utilizing the nucleophilicity of *in situ* formed copper triazolides, a range of electrophilic groups such as acyl, allyl, iodine, bromine *etc.* could be introduced into the C-5 position of various complex 1,2,3-triazoles derivatives under mild conditions.^{17,18,19a} Furthermore, the oxidative coupling reactions based on the copper triazolides were also found to be feasible synthetic route for incorporations of different nucleophilic groups *e.g.* phosphate and fluoroalkyl onto the C-5 position of 1,2,3-triazoles.^{19c,d} Different from the reaction with electrophilic reagents, however, the oxidative coupling reaction of copper triazolides with nucleophilic reagents often suffer from undesirable efficiency and selectivity, obsessed by the self-oxidative couplings to give bis-triazoles, 1,4-diynes, 5-alkynyl triazoles and other by-products.²² To address the problems, careful optimizations of oxidants, and choice of ligands are suggested, and strong basic reagents for deprotonation were necessary in some cases before achieving desirable yields, but which inevitably leads to tedious manipulations and harsh reaction environments.

In this paper, we reported a simple copper-catalyzed O₂/chloramine-T system to effectively promote the three-component reaction of organic azide, terminal alkyne and

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arylboronic acid for one-pot synthesis of 5-aryl-1,4-disubstituted 1,2,3-triazoles under mild conditions (Fig. 1D). In comparison with the literature methods,^{11,20,21} our method avoids the uses of noble metal catalysts, high reaction temperatures as well as strong basic reagents, thus permitting to apply not only for simple organic compounds, but also for complex bioactive molecules such as ribose and estrone derivatives.

Results and discussion

The initial attempt was carried out in the air at room temperature in the presence of CH_2Cl_2 with 10 mol% Cu(I) salt and 2 equivalents of Et_3N (entries 1 and 2 in Table 1). Only 24% yield of 5-aryl-1,4-disubstituted 1,2,3-triazole **4a** was obtained after 24 hours with CuI as the catalyst. Then, we studied the influence of Cu salt. A little higher 39% yield of 5-aryl-1,4-disubstituted 1,2,3-triazole **4a** could be given when CuI was replaced by CuCl, but considerable by-products were also obtained including protonated 1,4-disubstituted triazole and phenylethynyl triazole. Different bases including DIPEA, pyridine, DIPA, DBU, Na_2CO_3 , NaOH were next screened for the reaction, but all of them were unable to increasing the yield of target compound. Solvent effects were also investigated. The reaction in toluene demonstrated the highest yield 54% than in other solvents such as DMSO, CH_3CN , dioxane, MeOH and CH_3Cl . There are a large number of additives have been used for promoting oxidative reactions²³ Based on the literatures, we further investigated the detailed effects of oxidant additives for the one-pot reaction to prepare 5-aryl-1,4-disubstituted 1,2,3-triazole **4a** with CuCl as the catalyst, triethylamine (TEA) as the base and toluene as the solvent (entry 13 to entry 20 in Table 1). The first group of additives such as DDQ, *m*-CPBA caused the oxidation of Cu(I) to Cu(II), thus losing the catalytic capacity for CuAAC reaction with no any triazole-type products obtained. The second group including di-*t*-butyl peroxide (DTBP), NIS, NBS, Oxone and $\text{K}_2\text{Cr}_2\text{O}_7$ reduced the reaction efficiency of

CuAAC reaction, with 11–23% yields of **4a**. Interestingly, the third group of additives, selectfluor and chloramine-T were found to promote the reaction to give **4a** with 56% and 68% yield respectively. With the air/chloramine-T oxidant system, a higher 84% yield was given at 50 °C reaction temperature. Since oxygen in the air might play a role of oxidant for the one-pot reaction, we attempted to replace air atmosphere by pure oxygen. Gratefully, a desirable 90% yield of **4a** was finally obtained (entry 24 in Table 1).

With the optimized conditions in hand, we investigated the substrate scope of the one-pot reaction by using variant organic azides, terminal alkynes and arylboronic acids. Firstly, aryl alkynes with electron-withdrawing substituents (such as -F, -Cl and -Br) and electron-donating substituents (such as - CH_3 , - OCH_3), reacted smoothly with benzyl azides **2a** and arylboronic acids **3a** to give target product 5-aryl-1,2,3-triazoles **4a** to **4e** with the yields from 80%~90% (entry 1 to entry 5 in Table 2). Secondly, various alkyl azides (**2a** to **2g**) bearing different substituted groups such as - NO_2 , -F, - OCH_3 , reacted smoothly with benzyl azides **2a** and arylboronic acids **3a** to give target product 5-aryl-1,2,3-triazoles **4l** to **4t** with the yields from 68%~80% (entry 12 to entry 20 in Table 2). Among these azides, azide **2g** that contained 2,5-difluorobenzyl motifs that occurs in the clinic drug rufinamide²⁴ could react smoothly with terminal alkynes and arylboronic acids to give 2,5-difluorobenzyl 5-aryl-1,2,3-triazoles **4s** and **4t**, implying the potential applications of the method for drug screening. Besides of benzyl azides, naphthylmethyl azide can also effectively react with various alkynes and arylboronic acids to provide 5-aryl-1,2,3-triazoles with a yield as high as 89% (entry 6 to entry 11 in Table 2). Other azides including phenyl ether **2c**, naphthyl **2d** and phenylethyl azide **2f** were also the effective substrates of the reaction to prepare diverse 5-aryl-1,2,3-triazoles. In addition, we tested alkyl alkyne **1g** for the three-component reaction, and the target product **4x** could be obtained in the yield of 64% (entry 24 in Table 2). Finally, we investigated different phenylboronic acids with electron-donating substituents (-Me) and electron-withdrawing substituents (-F and -Br) for the reaction. 5-*p*-Methylphenyl-1,4-disubstituted 1,2,3-triazole **4u** was obtained with 87%, 5-*p*-fluorophenyl-1,4-disubstituted 1,2,3-triazole **4v** was obtained with 67%, and 5-*p*-bromophenyl-1,4-disubstituted 1,2,3-triazole **4w** was obtained with 64%. Therefore, the current method has shown a wide scope of substrates including variant alkynes, azides and arylboronic acids.

Inspired by the results shown in Table 2, we then studied the potential applications of this reaction to synthesize compounds with more complex structures, by using azides and aromatic alkynes containing natural product skeleton (Scheme 1). Glucosinolates containing 1,2,3-triazole motif represent a class of broad-spectrum antibacterial agents.^{25,26} Here, we proved that 5-aryl-1,2,3-triazole nucleoside can be directly synthesized from glucosyl alkyne, aryl azide and phenylboronic acid in one pot, and the target compound **4y** was obtained with a yield of 61%. During the reaction, the glucose motif remained intact without isomerization of glycosidic bond. Another example is the azido-containing estrone motif, which contains ketone groups sensitive to strong basic conditions and possibly suffer side-reactions

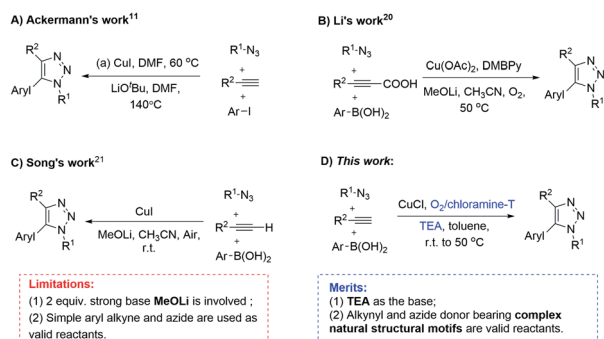
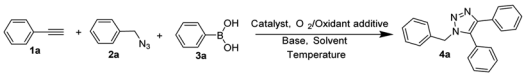


Fig. 1 The reactions for multi-component synthesis of 5-aryl-1,2,3-triazoles. (A) Synthesis of 5-aryl-1,2,3-triazoles from iodobenzenes, azides and alkynes developed in Ackermann's lab. (B) Synthesis of 5-aryl-1,2,3-triazoles from propiolic acids, azides, and arylboronic acids developed in Li's lab. (C) Synthesis of 5-aryl-1,2,3-triazoles from arylboronic acids, organic azides and alkynes developed in Song's lab. (D) Synthesis of 5-aryl-1,2,3-triazoles from arylboronic acids, organic azides and alkynes developed in the current work.

Table 1 Optimization of reaction conditions



Entry ^a	Temperature	Catalyst	Oxidant additive	Base	Solvent	Product ^b (%)
1	rt	CuI	—	Et ₃ N	DCM ^d	24
2	rt	CuCl	—	Et ₃ N	DCM	39
3	rt	CuCl	—	DIPEA ^d	DCM	27
4	rt	CuCl	—	Pyridine	DCM	15
5	rt	CuCl	—	DIPA ^d	DCM	31
6	rt	CuCl	—	NaHCO ₃	DCM	12
7	rt	CuCl	—	DBU ^d	DCM	20
8	rt	CuCl	—	NaOH	DCM	—
9	rt	CuCl	—	Et ₃ N	DMSO ^d	14
10	rt	CuCl	—	Et ₃ N	CH ₃ CN	11
11	rt	CuCl	—	Et ₃ N	CHCl ₃	30
12	rt	CuCl	—	Et ₃ N	Toluene	32
13	rt	CuCl	Selectfluor	Et ₃ N	Toluene	56
14	rt	CuCl	DDQ ^d	Et ₃ N	Toluene	—
15	rt	CuCl	NBS ^d	Et ₃ N	Toluene	15
16	rt	CuCl	<i>m</i> -CPBA ^d	Et ₃ N	Toluene	—
17	rt	CuCl	DTBP ^d	Et ₃ N	Toluene	11
18	rt	CuCl	NIS ^d	Et ₃ N	Toluene	15
19	rt	CuCl	Oxone	Et ₃ N	Toluene	23
20	rt	CuCl	K ₂ Cr ₂ O ₇	Et ₃ N	Toluene	20
21	rt	CuCl	Chloramine-T	Et ₃ N	Toluene	68
22	40	CuCl	Chloramine-T	Et ₃ N	Toluene	77
23	50	CuCl	Chloramine-T	Et ₃ N	Toluene	84
24 ^c	50	CuCl	Chloramine-T	Et ₃ N	Toluene	90

^a 0.15 mmol azide, 0.6 mmol arylboronic acid, 0.17 mmol terminal alkyne, 0.015 mmol CuX were used as substrates in the presence of 2.0 equivalent of base and 1.0 equivalent of the oxidant. ^b Isolated yields. ^c Oxygen environment was added. ^d DCM (dichloromethane). DIPEA (*N,N*-diisopropylethylamine). DIPA (diisopropanolamine). DBU (1,8-diazabicyclo[5.4.0]undec-7-ene). DMSO (dimethyl sulfoxide). DDQ (2,3-dichloro-5,6-dicyano-1,4-benzoquinone). NBS (*N*-bromosuccinimide). *m*-CPBA (3-chloroperbenzoic acid). DTBP (di-*tert*-butyl peroxide). NIS (*N*-iodosuccinimide).

in the presence of strong oxidative reagents.^{27,28} While in the current reaction system, it can also be used as an effective substrate to provide the target 5-aryl-1,2,3-triazole **4z** in the yield of 74% and no any side-reactions related to estrone motifs were detected. In the reported reaction conditions for the preparations of 5-aryl 1,2,3-triazole (Fig. 1A to C), ether over 100 °C reaction temperatures or strong basic reagents like lithium *tert*-butoxide or lithium methoxide were used, which could be hardly used for acetyl protected glucoses, base-sensitive ketones and other complicated substrates bearing base-sensitive functional groups. In contrast, the method presented in this paper can be proceeded well at 50 °C with weak organic base TEA, catalytic amount of CuCl and oxygen-chloramine-T oxidant system, thus offering the mildest conditions for one-pot preparation of 5-aryl-1,4-disubstituted 1,2,3-triazoles.

The possible role of chloramine-T during the *in situ* oxidative coupling reaction was also investigated by control experiments. In replace of oxygen atmosphere with nitrogen atmosphere, only 5-H-1,2,3-triazole product could be obtained (eqn (1) in Scheme 2), which indicated the oxygen was the essential oxidant for the reaction. Increasing the amount of chloramine-T did not enhance the yield of 5-aryl-1,2,3-triazoles, suggesting chloramine-T may actually act as an additive for promoting

aerobic coupling reaction. Additional control experiments were also conducted, including the reaction of 5-H-1,2,3-triazole with arylboronic acids and the reaction of diaryl alkyne with azide under the current conditions, both of which could not lead to the generation of target 5-aryl-1,2,3-triazoles (eqn (2) and (3) in Scheme 2). Trapping the reaction intermediates by nucleophilic allyl bromide demonstrated the existence of triazolide in the current reaction procedure (eqn (4) in Scheme 2). On the basis of the above experimental results and the known oxidative coupling mechanism of triazolide copper(I),^{3e} a plausible mechanism of the *in situ* multi-component oxidative coupling reaction for synthesis of 5-aryl-1,2,3-triazoles was proposed as shown in Scheme 2. Briefly, the reaction proceeded through a tandem click-coupling and oxidative coupling reaction, the Cu-catalyzed click-coupling of an azide with alkyne (**1a** to **5'**), followed by aerobic oxidative coupling of **5'** with arylboronic acids (**5'** to **4a**). Copper(I) acetylide intermediate **6** is formed from terminal alkyne **1a** in the presence of TEA as the base, the intermediate **6** react with benzyl azide **2a** via the CuAAC reaction pathway to give triazolide copper **5'**. Under these oxidative conditions, transmetalation of intermediate **5'** with phenylboronic acids, generating **8** should be reasonable,^{20,21} and the transmetalation must take place before the protonation of **5'**.



Table 2 Substrate scope of the reaction





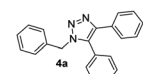



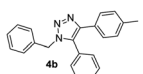



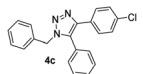



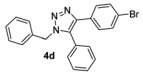



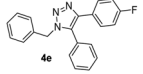



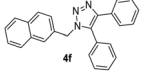



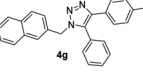



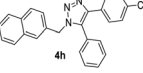



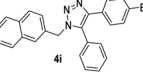



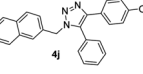


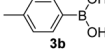
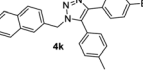

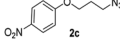

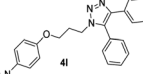

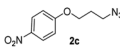

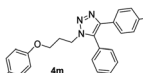

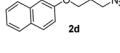

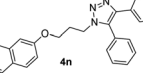

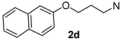
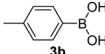
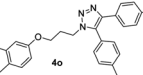



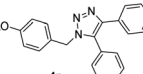
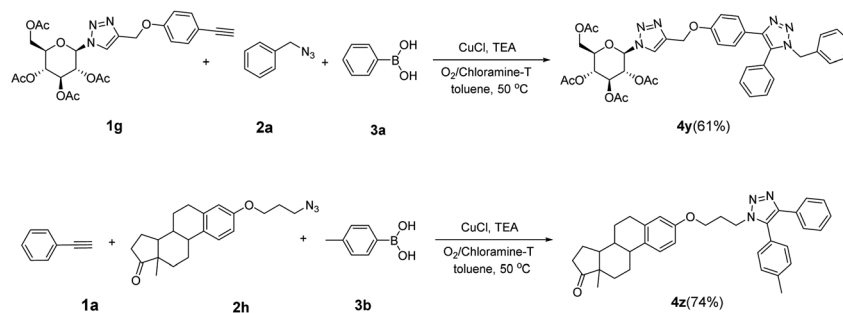
<div>$\text{R}^1\text{-N}_3 + \text{R}^2\text{-C}\equiv\text{C} + \text{Ar-B(OH)}_2 \xrightarrow[\text{Et}_3\text{N, toluene, 50 }^\circ\text{C}]{\text{CuCl, O}_2/\text{chloramine-T}} \text{Product}$</div>					
<div></div>					
Entry ^a	Alkyne	Azide	Arylboronic acid	Product	Yield ^b
1					90
2					80
3					88
4					85
5					86
6					83
7					76
8					89
9					87
10					72
11					87
12					75
13					80
14					72
15					69
16					78

Table 2 (Contd.)

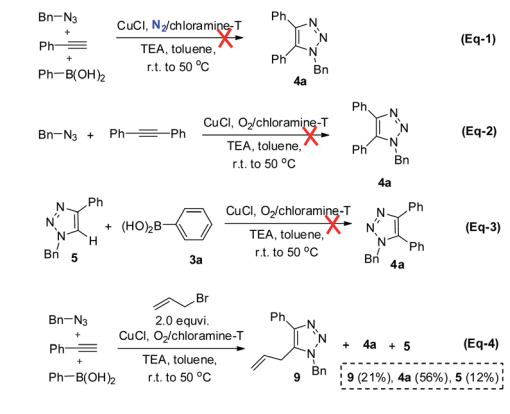
$R^1-N_3 + R^2 \equiv + Ar-B(OH)_2 \xrightarrow[Et_3N, \text{ toluene, } 50^\circ C]{CuCl, O_2/\text{chloramine-T}} \begin{matrix} R^2 \\ \\ N=N \\ \\ R^1 \end{matrix} \begin{matrix} R^2 \\ \\ N=N \\ \\ Aryl \end{matrix}$					
Entry ^a	Alkyne	Azide	Arylboronic acid	Product	Yield ^b
17					76
18					68
19					70
20					75
21					87
22					67
23					64
24					64

^a 0.15 mmol azide, 0.6 mmol arylboronic acid, 0.17 mmol terminal alkyne, 0.015 mmol CuCl, 0.15 mmol chloramine T and 0.15 mmol triethylamine were used as substrates. ^b Isolated yield.



Scheme 1 Applications of the one-pot reaction for syntheses of complex molecules.





Scheme 2 Control experiments and plausible reaction mechanism.

However, the detailed mechanism of chloramine-T-activated aerobic oxidative coupling reaction, such as the intermediates of potential reactions of chloramine-T with O₂ is still not clear at present.

Conclusions

In summary, we reported a new reaction system for one-pot synthesis of 5-aryl-1,4-disubstituted 1,2,3-triazoles with low-cost CuCl as catalyst, clean oxygen as oxidant and less-toxic chloramine-T as additive in this paper. A wide scope of substituted aryl alkynes, alkynyl alkynes, benzyl and alkyne azides, substituted arylboronic acids can be used as the effective reaction substrates for the reaction to prepare structurally diverse 5-aryl-1,2,3-triazoles in modest to good yields. Importantly, the presented reaction system avoids the uses of strong basic reagents and high temperature, and thus can be used not only for simple molecules but also for the structurally complicated alkynyl or azide donors bearing natural product motifs and sensitive functional groups. Therefore, it presented the latest mild conditions for multicomponent synthesis of 5-aryl-1,2,3-triazoles. The applications of this method in designing more complex bioactive compounds are undergoing in our lab.

Data availability

Source data are provided with this paper. Methods and additional results are provided in the ESI.†

Conflicts of interest

The authors declare no conflicts of interest.

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Notes and references

- (a) H. C. Kolb and K. B. Sharpless, *Drug Discov. Today.*, 2003, **8**, 1128–1137; (b) D. Dheer, V. Singh and R. Shankar, *Bioorg. Chem.*, 2017, **71**, 30–54; (c) E. Bonandi, M. S. Christodoulou, G. Fumagalli, D. Perdicchia, G. Rastelli and D. Passarella, *Drug Discov. Today.*, 2017, **22**, 1572–1581; (d) P. Thirumurugan, D. Matosiuk and K. Jozwiak, *Chem. Rev.*, 2013, **113**, 4905–4979.
- (a) D. Dheer, C. Behera, D. Singh, M. Abdullaha, G. Chashoo, S. B. Bharate, P. N. Gupta and R. Shankar, *Eur. J. Med. Chem.*, 2020, **207**, 112813; (b) Z. Xu, S. Zhao and Y. Liu, *Eur. J. Med. Chem.*, 2019, **183**, 111700; (c) F. Pagliai, T. Pirali, E. D. Grosso, R. D. Brisco, G. C. Tron, G. Sorba and A. A. Genazzani, *J. Med. Chem.*, 2006, **49**, 467–470; (d) N. Ahmed, N. K. Konduru, S. Ahmad and M. Owais, *Eur. J. Med. Chem.*, 2014, **82**, 552–564; (e) T. Ostrowski, P. Januszczak, M. Cieslak, J. Kazmierczak-Baransk, B. Nawrot, E. Bartoszak-Adamska and J. Zeidler, *Bioorg. Med. Chem.*, 2011, **19**, 4386–4398; (f) D. Goyard, A. S. Chajistamatiou, A. I. Sotiropoulou, E. D. Chrysina, J.-P. Praly and S. Vidal, *Chem. –Eur. J.*, 2014, **20**, 5423–5432.
- (a) J. E. Moses and A. D. Moorhouse, *Chem. Soc. Rev.*, 2007, **36**, 1249–1262; (b) F. Ahmed and H. Xiong, *Dyes Pigments*, 2021, **185**, 108905; (c) S. Kantheti, R. Narayana and K. V. S. N. Raju, *RSC Adv.*, 2015, **5**, 3687–3708; (d) L. D. Rodrigues, D. Sunil, D. Chaithra and P. Bhagavath, *J. Mol. Liq.*, 2020, **297**, 111909; (e) D. Fournier, R. Hoogenboom and U. S. Schubert, *Chem. Soc. Rev.*, 2007, **36**, 1369–1380.
- (a) J. Niskanen, M. N. Tousignant, A. J. Peltekoff and B. H. Lessard, *Polymer*, 2021, **212**, 123144; (b) M. Pulst, J. Balko, Y. Golitsyn, D. Reichert, K. Busse and J. Kressler, *Phys. Chem. Chem. Phys.*, 2016, **18**, 6153–6163; (c) E. Güzel, *RSC Adv.*, 2019, **9**, 10854–10864.
- V. V. Rostovtsev, L. G. Green, V. V. Fokin and K. B. Sharpless, *Angew. Chem., Int. Ed.*, 2002, **41**, 2596–2599.
- C. W. Tornøe, C. Christensen and M. Meldal, *J. Org. Chem.*, 2002, **67**, 3057–3064.
- C. W. Tornøe and M. Meldal, *Chem. Rev.*, 2008, **108**, 2952–3015.
- (a) S. Neumann, M. Biewend, S. Rana and W. H. Binder, *Macromol. Rapid Commun.*, 2019, **41**, 1900359; (b)



- M. Meldal and F. Diness, *Trends in Chemistry*, 2020, **2**, 569–584.
- 9 L. Zhang, X. Chen, P. Xue, H. H. Y. Sun, I. D. Williams, K. B. Sharpless, V. V. Fokin and G. Jia, *J. Am. Chem. Soc.*, 2005, **127**, 15998–15999.
- 10 L. Ackermann, A. Althammer and S. Fenner, *Angew. Chem., Int. Ed.*, 2009, **48**, 201–204.
- 11 L. Ackermann and R. Vicente, *Org. Lett.*, 2009, **11**, 4922–4925.
- 12 L. Ackermann, H. K. Potukuchi, D. Landsberg and R. Vicente, *Org. Lett.*, 2008, **39**, 3081–3084.
- 13 R. Chen, L. Zeng, Z. Lai and S. Cui, *Adv. Syn. Catal.*, 2019, **361**, 989–994.
- 14 L. Li, T. Shang, X. Ma, H. Guo, A. Zhu and G. Zhang, *Synlett*, 2015, **26**, 695–699.
- 15 S. Chuprakov, N. Chernyak, A. S. Dudnik and V. Gevorgyan, *Org. Lett.*, 2007, **9**, 2333–2336.
- 16 F. Wei, H. Li, C. Song, Y. Ma, L. Zhou, C.-H. Tung and Z. Xu, *Org. Lett.*, 2015, **17**, 2860–2863.
- 17 Y.-M. Wu, J. Deng, Y. Li and Q.-Y. Chen, *Synthesis*, 2005, **8**, 1314–1318.
- 18 (a) F. Wu, W. Zhou, K. Chen, W. Chen, M. Liu and H. Wu, *Adv. Synth. Catal.*, 2018, **360**, 2435–2439; (b) F. Cui, J. Chen, Z. Mo, S. Su, Y. Chen, X. Ma, H. Tang, H. Wang, Y. Pan and Y. Xu, *Org. Lett.*, 2018, **20**, 925–929; (c) W. Wang, F. Wei, Y. Ma, C. Tung and Z. Xu, *Org. Lett.*, 2016, **18**, 4158–4161; (d) X. Deng, J. Liang, B. B. Allison, C. Dvorak, H. McAllister, B. M. Savall and N. S. Mani, *J. Org. Chem.*, 2015, **80**, 11003–11012; (e) R. Yan, K. Sander, E. Galante, V. Rajkumar, A. Badar, M. Robson, E. El-Emir, M. F. Lythgoe, R. B. Pedley and E. Arstad, *J. Am. Chem. Soc.*, 2013, **135**, 703–709; (f) J. C. Morris, J. Chiche, C. Grellier, M. Lopez, L. F. Bornaghi, A. Maresca, C. T. Supuran, J. Pouyssegur and S.-A. Poulsen, *J. Med. Chem.*, 2011, **54**, 6905–6918; (g) W. Wang, X. Peng, F. Wei, C.-H. Tung and Z. Xu, *Angew. Chem., Int. Ed.*, 2016, **55**, 649–653; (h) B. Wang, N. Liu, W. Chen, D. Huang, X. Wang and Y. Hu, *Adv. Synth. Catal.*, 2015, **357**, 401–407; (i) Z. Zhang, Q. Zhou, F. Ye, Y. Xia, G. Wu, M. L. Hossain, Y. Zhang and J. Wang, *Adv. Synth. Catal.*, 2015, **357**, 2277–2286; (j) W. S. Brotherton, R. J. Clark and L. Zhu, *J. Org. Chem.*, 2012, **77**, 6443–6455; (k) X. Jian and Q. Song, *Org. Chem. Front.*, 2017, **4**, 938–942.
- 19 (a) L. Li, G. Zhang, A. Zhu and L. Zhang, *J. Org. Chem.*, 2008, **73**, 3630–3633; (b) L. Li, S. Ding, Y. Yang, A. Zhu, X. Fan, M. Cui, C. Chen and G. Zhang, *Chem. –Eur. J.*, 2017, **23**, 1166–1172; (c) L. Li, G. Hao, A. Zhu, X. Fan, G. Zhang and L. Zhang, *Chem. –Eur. J.*, 2013, **19**, 14403–14406; (d) A. Zhu, X. Xing, S. Wang, D. Yuan, G. Zhu, M. Geng, Y. Guo, G. Zhang and L. Li, *Green Chem.*, 2019, **21**, 3407–3412.
- 20 X.-X. Wang, Y. Xin, Y. Li, W.-J. Xia, B. Zhou, R.-R. Ye and Y.-M. Li, *J. Org. Chem.*, 2020, **85**, 3576–3586.
- 21 X. Yu, J. Xu, Y. Zhou and Q. Song, *Org. Chem. Front.*, 2018, **5**, 2463–2467.
- 22 (a) B. Schulze and U. S. Schubert, *Chem. Soc. Rev.*, 2014, **43**, 2522–2571; (b) J. E. Hein and V. V. Fokin, *Chem. Soc. Rev.*, 2010, **39**, 1302–1315.
- 23 (a) L. D. S. Yadav, V. P. Srivasta and R. Patel, *Synlett*, 2010, 1047–1050; (b) Y. Yang, J. Lan and J. You, *Chem. Rev.*, 2017, **117**, 8787–8863.
- 24 (a) L. A. Sorbera, P. A. Leeson, X. Rabasseda and J. Castaner, *Drugs Future*, 2000, **25**, 1145; (b) M. A. Rogawski, *Epilepsy Res.*, 2006, **69**, 273–294; (c) C. E. Stafstrom, *Neuropsychiatr. Dis. Treat.*, 2009, **5**, 547–551.
- 25 (a) J. C. Morris, J. Chiche, C. Grellier, M. Lopez, L. F. Bornaghi, A. Maresca, C. T. Supuran, J. Pouyssegur and S.-A. Poulsen, *J. Med. Chem.*, 2011, **54**, 6905–6918; (b) J.-B. He, H.-F. He, L. Zhao, L. Zhang, G.-Y. You, L.-L. Feng, J. Wan and H.-W. He, *Bioorg. Med. Chem.*, 2015, **23**, 1395–1401.
- 26 (a) K. T. Andrews, G. M. Fisher, S. D. M. Sumanadasa, T. Skinner-Adams, J. Moeker, M. Lopez and S.-A. Poulsen, *Bioorg. Med. Chem. Lett.*, 2013, **23**, 6114–6117; (b) N. Ahmed, N. K. Konduru, S. Ahmad and M. Owais, *Eur. J. Med. Chem.*, 2014, **82**, 552–564; (c) V. R. Sirivolu, S. K. V. Vernekar, T. Ilina, N. S. Myshakina, M. A. Parniak and Z. Q. Wang, *J. Med. Chem.*, 2013, **56**, 8765–8780.
- 27 (a) B. Ildikó, K. Csilla, O. A. Boglárka, K. Gábor, R. Réka, Ö.-L. Csilla and M. Erzsébet, *Molecules*, 2018, **23**, 821; (b) A. Gupta, B. S. Kumar and A. S. Negi, *J. Steroid Biochem. Mol. Biol.*, 2013, **137**, 242–270.
- 28 (a) P. C. Meltzer, D. Butler, J. R. Deschamps and B. K. Madras, *J. Med. Chem.*, 2006, **49**, 1325–1345; (b) J. R. Hanson, *Nat. Prod. Rep.*, 2007, **24**, 1342–1349.

