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Application of two magnetic nanoparticle-supported copper(I) catalysts for the synthesis of triazole derivatives

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Abstract

Catalytic performance of two magnetically recoverable copper(I) complexes is reported for the synthesis of 1,2,3-triazole derivatives. Boronic acids and alkyl halides, in the presence of either catalyst, react with terminal alkynes and NaN_3, forming 1,2,3-triazole derivatives in good yields. Both catalysts are easily recoverable and show a high potential of reusability.

Keywords 1,2,3-Triazole · Click reaction · Nanomagnet · Copper(I)

Introduction

Currently, one important field of catalysis is the design, synthesis and application of nanomagnetic catalysts in organic transformations. From the perspective of green chemistry principles, nanomagnetic catalysts are ideal selections as they enable environmentally friendly and sustainable catalytic processes [1–4]. Furthermore, functionalization of magnetically recoverable nanomaterials provides a bridge between heterogeneous and homogeneous catalysis. These magnetic nanoparticle-supported catalysts have features of both homogeneous and heterogeneous catalysts. For example, they have high activity and selectivity, and they are easy to separate, recover and reuse [5–9].

Electronic supplementary material The online version of this article (https://doi.org/10.1007/s11164-019-03864-7) contains supplementary material, which is available to authorized users.

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Among the metal-based catalytic systems, copper catalysis has received significant attention due to the appealing features of copper such as low cost and low toxicity [10]. As Cu(0), Cu(I), Cu(II), and Cu(III) oxidation states are easily accessible, both radical and two-electron bond-forming pathways are possible through copper catalysis [11]. Because of these qualities, copper catalysis is frequently used to enhance the ease and practicality of the synthetic processes. Copper catalysts have shown great performance in varied organic transformations including C–N, C–O, C–S, and C–C bond forming reactions [10], asymmetric coupling reactions [12], C–H functionalization [13], synthesis of N-heterocyclic compounds [14], and aerobic organic reactions [11]. Compared with other catalysts based on Ru, Ag, Ir, Ni, Zn, and Ln metals, Cu(I) catalysts are the ones most used in promoting the azide-alkyne cycloaddition reaction [15, 16].

Formation of 1,2,3-triazoles through Cu(I)-catalyzed azide-alkyne cycloaddition (CuAAC) has attracted much attention in recent years. This reaction between organic azides and terminal alkynes enables the construction of 1,4-disubstituted triazoles and is classified as a ‘click reaction’. The reaction has various advantages. These include no or mild heating requirements, a wide substrate scope, benign reaction conditions and easy workup and purification procedures that give high yields of products [17].

The 1,2,3-triazole derivatives are commonly utilized in drug development and in the preparation of functional materials [14, 18]. These versatile heterocycles are used as antibacterial and antiviral agents, and as a ligation tool in polymer and materials science [18–27]. Due to this importance, the synthesis and chemistry of 1,2,3-triazole are well-documented [28–40].

We are interested in the design, synthesis and applications of nanomagnetic catalysts [41–43]. Because of the abovementioned merits of Cu(I)-catalysis in organic transformations and the importance of 1,2,3-triazoles, we were interested to test nanomagnetic catalysts in the synthesis of 1,2,3-triazoles. Although many copper catalysts have been used in the synthesis of 1,2,3-triazoles, genuine Cu(I) catalysts are more reactive. The copper component may be a problem if traces remain under physiological conditions [44]. Copper(I)-complexed magnetic nanoparticle catalysts provide a solution to this problem as these catalysts can provide stable Cu(I)-catalysts which can be easily removed from the reaction mixture and reused. Furthermore, nanocatalysts exhibit higher catalytic activity than conventional catalysts, due to enhanced surface area [16]. This is one reason why application of nanomagnetic catalysts in the preparation of triazoles have become an active area of research [29, 31, 36, 45–47]. Here, we report the performance of two highly efficient Cu(I)-nanomagnetic catalysts in the synthesis of 1,2,3-triazoles. These catalysts were tested in two very direct methods (both one pot) of making 1,2,3-traizoles—the reaction between NaN_3, alkynes and boronic acids, and the reaction between NaN_3, alkynes and alkyl halides. The structures of the two catalysts are shown in Fig. 1. We have previously reported the synthesis and characterization of these two catalysts [42, 43].

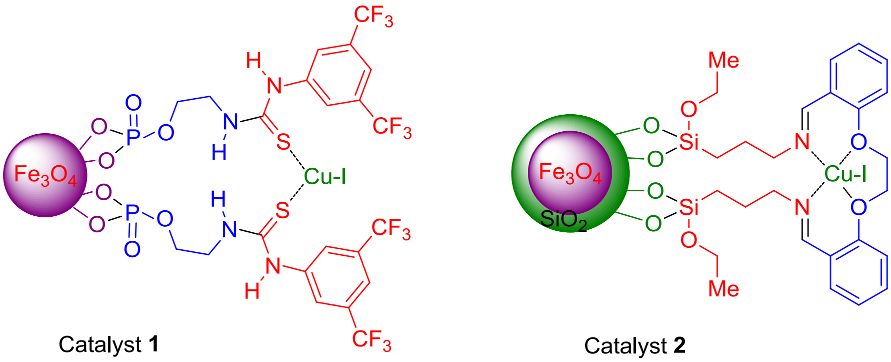


Fig. 1 The structures of Cu(I)-complexed magnetic nanoparticle catalysts **1** and **2**

Experimental

General Method A. Synthesis of 3a–3i

Catalyst **1** or **2** (20 mg) was added to a mixture of alkyne (1.0 mmol), NaN_3 (3.0 mmol) and arylboronic acid (1.0 mmol) in 2.0 mL of EtOH/H_2O. The resulting mixture was stirred at room temperature for the specified period of time (Table 2). The catalyst was separated from the reaction mixture with a permanent magnet. The catalyst was washed with distilled water (15 mL × 5) and MeOH (15 mL × 5) for future use. The reaction mixture was evaporated. The residue was dissolved in ethyl acetate (30 mL) and washed with water (10 mL). The organic layer was separated, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure to give crude **3**. Crude **3** was purified by column chromatography.

General method B. Synthesis of 4a–4h

Similar to general method A with the following modifications. Amount of catalyst **2** used in the reaction was 50.0 mg. The reaction was stirred for the time specified in Table 4. After the catalyst was removed, water (5.0 mL) was added and the reaction mixture was extracted with EtOAc (2.0 × 10 mL). The organic layer was dried over anhydrous Na_2SO_4 and the solvent was evaporated under reduced pressure to give crude **4**. Crude **4** was recrystallized from CH_2Cl_2, n-hexane, to yield the purified product.

3-(1-(4-(*tert*-Butyl)phenyl)-1*H*-1,2,3-triazol-4-yl)propan-1-ol (3b)

General method A was used for the preparation of **3b**. Column chromatography was carried out using 60% ethyl acetate in dichloromethane. Isolated yield: 43%; m.p. = 83–85 °C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ: 7.65–7.51 (m, 5H), 3.80 (s, br, 2H), 2.93 (s, br, 2H), 2.10–2.03 (m, 3H), 1.36 (s, 9H); **^{13}C NMR** (100 MHz, $CDCl_3$) *δ*: 152.1, 133.8, 126.8, 124.9, 120.4, 62.1, 34.9, 31.9, 29.8; HRMS (ESI+) m/z $(M+H)^+$ calcd for $C_{15}H_{22}N_3O$, 260.1759; measured, 260.1761.

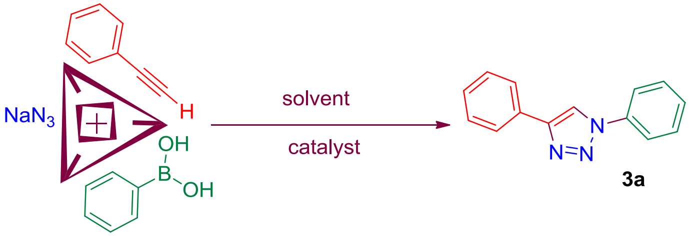
4-Phenyl-1-(phenyl-1-(p-tolyl)-1H-1,2,3-triazole (3h) [48, 49]

General method A was used for the preparation of **3h**. Column chromatography was carried out using 60% ethyl acetate in petroleum ether. Isolated yield: 81%; m.p. = 158–160 °C; **^{1}H NMR** (300 MHz, DMSO-d_6) *δ*: 9.24 (s, br, 1H), 8.05–7.71 (m, 4H), 7.60–7.30 (m, 5H), 2.37 (s, 3H); **^{13}C NMR** (100 MHz, DMSO-d_6) *δ*: 148.2, 139.3, 131.2, 130.0, 129.1, 126.6, 120.8, 120.4, 21.5.

Results and discussion

We selected the reaction of phenylboronic acid, NaN_3 and phenylacetylene to find the best reaction conditions for the synthesis of 1,2,3-triazoles. In light of previous results [42, 43] selected amounts of catalysts and solvents were screened at room temperature (Table 1). Both catalysts **1** and **2** successfully formed **3a**. The best conditions are when the reaction (1 mmol scale) is performed in the solvent mixture of EtOH and water (1:1) with 20 mg of catalysts. In the case of catalyst

Table 1 Screening for optimal reaction conditions for the synthesis of **3a**[a]



Entry	Catalyst (mg)	Solvent	Catalyst **1**		Catalyst **2**	
			Time (h)	Yield (%)[b]	Time (h)	Yield (%)[b]
1	20	H_2O	4	90	10	70
2	20	EtOH	4	60	10	70
3	**20**	**EtOH/H_2O (1:1)**	**4**	**95**	**10**	**98**
4	10	EtOH/H_2O (1:1)	4	60	10	60

[a] Reaction conditions: Phenylboronic acid (1.00 mmol, 0.122 g), NaN_3 (3.00 mmol, 0.195 g), phenylacetylene (1.00 mmol, 0.102 g), solvent: 2.00 mL. rt

[b] Isolated yield

1, the reaction completes in 4 h and in the case of catalyst **2**, the model reaction completes in 10 h.

We used the optimized reaction conditions to study the scope and limitations of these catalysts. Various 1,2,3-triazole derivatives were prepared via the three-component cross-coupling click reaction between arylboronic acids, NaN_3 and alkynes in the presence of nanomagnetic catalysts **1** and **2** (Table 2). The reaction was successful with both electron donating (Table 2, entries 2, 6 and 8–9) and electron withdrawing groups (Table 2, entry 7) on arylboronic acids. Both aromatic (Table 2, entries 1, 3–9) and aliphatic (Table 2, entry 2) alkynes can be transformed into **3**. The presence of unprotected alcohol or the fluorine atom on alkynes (Table 2, entries 2–4) affected the performance of catalyst **2**. However, even in these cases, catalyst **1** still gave high yields of cycloadducts **3**.

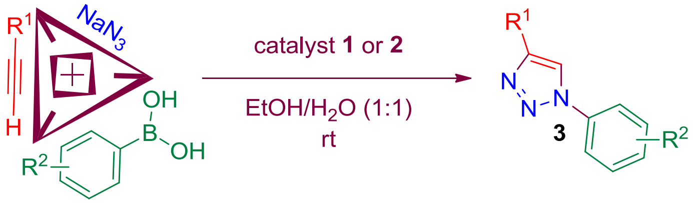
Next, we decided to compare the two catalysts in the preparation of 1,2,3-triazoles from aryl halides, NaN_3 and alkynes. Reaction optimization and substrate scope have already been reported with catalyst **1** [42]. We carried out same reaction optimization strategy with catalyst **2** (Table 3). The best results were obtained when the reaction (1 mmol scale) was performed in the presence of 50 mg of the catalyst and using water as the green solvent (Table 3, entry 3).

We tested the scope and versatility of the method towards the synthesis of 1,2,3-triazoles. Yields of **4** obtained from catalyst **2** were compared with our previously reported yields of **4** while using catalyst **1** (Table 4) [42]. The reaction was successful with aromatic (Table 4, entries 1–7) and aliphatic (Table 4, entry 8) alkyl halides. The reaction gave product **4** with aromatic (Table 4, entries 1, 3–5 and 8) and aliphatic alkynes (Table 4, entries 2 and 6–7) and tolerated both electron donating (Table 4, entries 3 and 5) and electron withdrawing alkynes (Table 4, entry 7). All products were obtained in high yields.

We explored the recovery and reusability of catalysts **1** and **2** in the synthesis of **3a** and **4a** (Table 5). After each run, the nanomagnetic catalysts were separated from the reaction mixture via an external magnet. The catalysts were thoroughly washed with H_2O and MeOH. After drying, the catalysts were used in the next run. Even after five cycles, both catalysts were able to catalyze the formation of **3a** and **4a** and the products were obtained in high yields. Therefore, we conclude that both catalysts have good recyclability in the formation of 1,2,3-triazoles from either arylboronic acids or alkyl halides.

The expected mechanism operative here involves formation of aryl azides from arylboronic acids and alkyl halides. Although the conversion of arylboronic acids to aryl azides via a Cu(I)-catalyzed process in the presence of sodium azide is known [50, 51], the mechanistic details are unknown [49, 52, 53] The conversion of alkyl halides to alkyl azides is an S_N2 process [50]. Once formed, aryl or alkyl azides undergo the usual Cu(I)-catalyzed cycloaddition, giving products **3** and **4** [54].

Table 2 Synthesis of 1,2,3-triazoles from arylboronic acids in the presence of catalysts **1** and **2**[a]



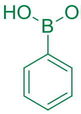
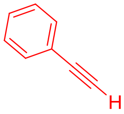
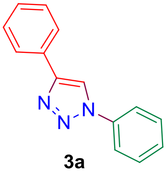
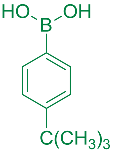
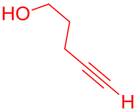
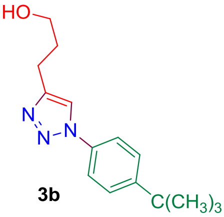
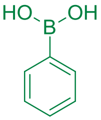
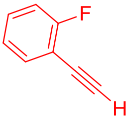
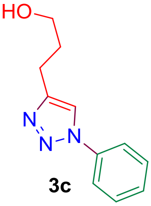
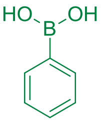
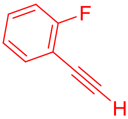
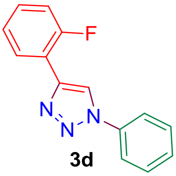
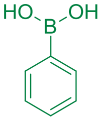
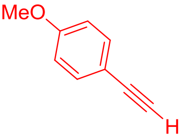
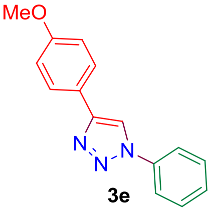
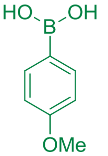
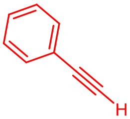
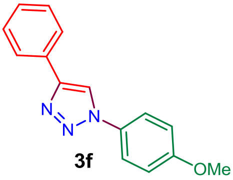
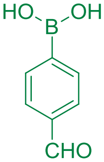
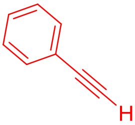
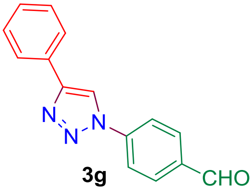
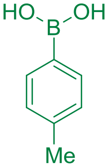
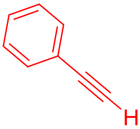
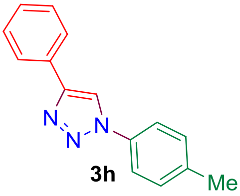
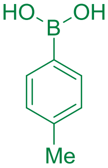
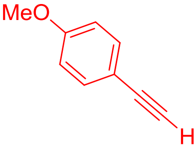
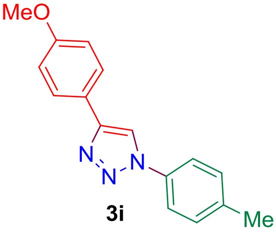
Entry	Arylboronic acid	Alkyne	Product	Catalyst **1** Time (h)/ Yield (%)[b]	Catalyst **2** Time (h)/ Yield(%)[b]
1			 **3a**	4/95	10/98
2			 **3b**	4/85	7/43
3			 **3c**	4/82	10/78
4			 **3d**	5/81	12/50
5			 **3e**	3/93	12/90

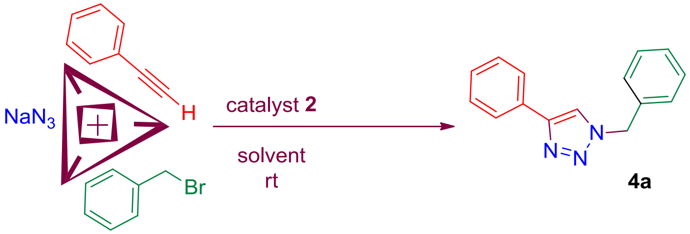
Table 2 (continued)

Entry	Arylboronic acid	Alkyne	Product	Catalyst **1** Time (h)/ Yield (%)^b	Catalyst **2** Time (h)/ Yield(%)^b
6			 **3f**	2/90	10/92
7			 **3g**	3/93	10/85
8			 **3h**	4/92	8/81
9			 **3i**	3/90	6/83

[a]Reaction conditions: Boronic acids (1.00 mmol), NaN_3 (3.00 mmol, 0.195 g), alkynes (1.00 mmol), solvent: 2.00 mL. 20 mg catalyst **1** or **2**, rt

[b]Isolated yield

Table 3 Screening for optimal reaction conditions for the synthesis of **4a**[a]



Entry	Catalyst (mg)	Solvent	Catalyst **2**	
			Time (h)	Yield (%)[b]
1	10	–	5	5
2	50	–	5	5
3	20	H_2O	5	60
4	**50**	$\mathbf{H_2O}$	**5**	**90**
5	10	EtOH	5	20
6	10	MeOH	5	25
7	20	CH_3CN	5	10

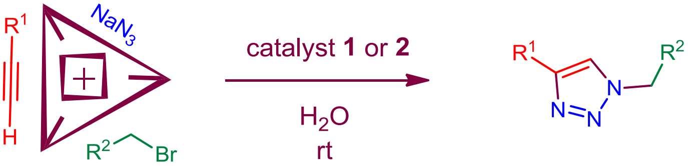
[a] Reaction conditions: Benzyl bromide (1.00 mmol, 0.171 g), NaN_3 (3.00 mmol, 0.195 g), phenylacetylene (1.00 mmol, 0.102 g), solvent: 2.00 mL. rt

[b] Isolated yield

Conclusions

In summary, catalytic performance of two magnetically recoverable copper(I) complexes was investigated in the synthesis of 1,2,3-triazoles via reactions between arylboronic acids or alkyl halides, terminal alkynes and NaN_3. Both catalysts show excellent catalytic activity and recyclability. All desired compounds, prepared through benign reaction conditions, were obtained in high yields.

Table 4 Synthesis of 1,2,3-triazoles from aryl halides in the presence of catalysts **1** and **2**[a]



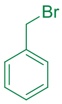
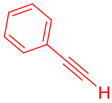
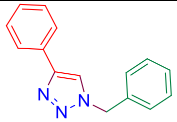
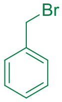
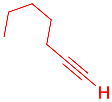
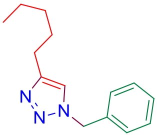
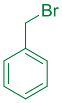
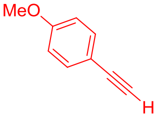
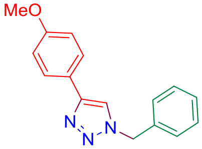
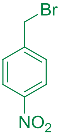
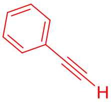
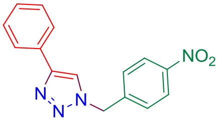
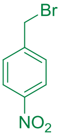
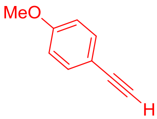
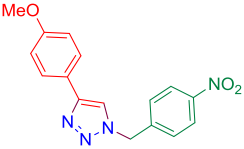
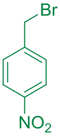
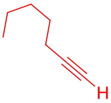
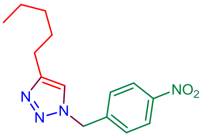
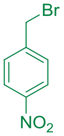
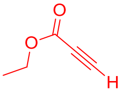
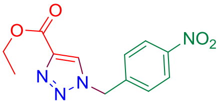
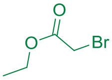
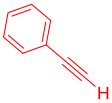
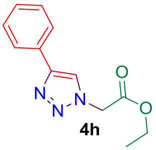
Entry	Alkyl halide	Alkyne	Product	Catalyst **1** Time (h)/ Yield (%)[b]	Catalyst **2** Time (h)/ Yield(%)[c]
1			 **4a**	0.5/92	5/90
2			 **4b**	1/90	5/90
3			 **4c**	1/90	5/93
4			 **4d**	0.5/90	5/86
5			 **4e**	0.5/85	5/92
6			 **4f**	1.5/92	5/91

Table 4 (continued)

Entry	Alkyl halide	Alkyne	Product	Catalyst **1** Time (h)/ Yield (%)[b]	Catalyst **2** Time (h)/ Yield(%)[c]
7			 **4g**	1.5/89	5/88
8			 **4h**	1/89	5/88

[a]Reaction conditions: Alkyl halides (1.00 mmol), NaN_3 (3.00 mmol, 0.195 g), alkynes (1.00 mmol), solvent: 2.00 mL. 50.0 mg catalyst **2**, rt

[b]Isolated yield

[c]Previously reported yields [42]

Table 5 Recyclability of catalysts **1** and **2** in the preparation of **3a** and **4a**

		Cycle 1	Cycle 2	Cycle 3	Cycle 4	Cycle 5
3a	Yield (%)[a] catalyst **1/2**	95/98	91/93	87/90	85/82	85/82
	Time (h) catalyst **1/2**	4/10	4/10	4/10	6/11	6/11
4a	Yield (%)[a] catalyst **1/2**	92/90	89/87	85/85	84/85	82/80
	Time (h) catalyst **1/2**	0.5/5	0.5/5	0.5/5	0.75/7	0.75/7

[a]Isolated yields

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References

1. D. Wang, D. Astruc, Chem. Rev. **114**, 6949 (2014)
2. R. Mrówczyński, A. Nan, J. Liebscher, RSC Adv. **4**, 5927 (2014)
3. T. Cheng, D. Zhang, H. Li, G. Liu, Green Chem. **16**, 3401 (2014)
4. D. Zhang, C. Zhou, Z. Sun, L.-Z. Wu, C.-H. Tung, T. Zhang, Nanoscale **4**, 6244 (2012)
5. S. Shylesh, V. Schünemann, W.R. Thiel, Angew. Chem. Int. Ed. **49**, 3428 (2010)
6. B. Karimi, F. Mansouri, H.M. Mirzaei, ChemCatChem **7**, 1736 (2015)
7. C.W. Lim, I.S. Lee, Nano Today **5**, 412 (2010)
8. V. Polshettiwar, R. Luque, A. Fihri, H. Zhu, M. Bouhrara, J.-M. Basset, Chem. Rev. **111**, 3036 (2011)
9. M. Mokhtary, J. Iran. Chem. Soc. **13**, 1827 (2016)
10. S. Bhunia, G.G. Pawar, S.V. Kumar, Y. Jiang, D. Ma, Angew. Chem. Int. Ed. **56**, 16136 (2017)

11. S.E. Allen, R.R. Walvoord, R. Padilla-Salinas, M.C. Kozlowski, Chem. Rev. **113**, 6234 (2013)
12. F. Zhou, Q. Cai, Beilstein J. Org. Chem. **11**, 2600 (2015)
13. X.-X. Guo, D.-W. Gu, Z. Wu, W. Zhang, Chem. Rev. **115**, 1622 (2015)
14. J. Huo, H. Hu, M. Zhang, X. Hu, M. Chen, D. Chen, J. Liu, G. Xiao, Y. Wang, Z. Wen, RSC Adv. **7**, 2281 (2017)
15. C. Wang, D. Ikhlef, S. Kahlal, J.-Y. Saillard, D. Astruc, Coord. Chem. Rev. **316**, 1 (2016)
16. A. Tăbăcaru, B. Furdui, I.O. Ghinea, G. Cârâc, R.M. Dinică, Inorg. Chim. Acta **455**, 329 (2017)
17. M.S. Singh, S. Chowdhury, S. Koley, Tetrahedron **72**, 5257 (2016)
18. J.M. Altimari, S.C. Hockey, H.I. Boshoff, A. Sajid, L.C. Henderson, ChemMedChem **10**, 787 (2015)
19. A. Anand, M.V. Kulkarni, S.D. Joshi, S.R. Dixit, Bioorg. Med. Chem. Lett. **26**, 4709 (2016)
20. M. Nasrollahzadeh, S.M. Sajadi, Y. Mirzaei, J. Colloid Interface Sci. **468**, 156 (2016)
21. L. Türker, Def. Technol. **12**, 1 (2016)
22. N. Pribut, C.G.L. Veale, A.E. Basson, W.A.L. van Otterlo, S.C. Pelly, Bioorg. Med. Chem. Lett. **26**, 3700 (2016)
23. J.-F. Lutz, Angew. Chem. Int. Ed. **46**, 1018 (2007)
24. J.E. Moses, A.D. Moorhouse, Chem. Soc. Rev. **36**, 1249 (2007)
25. S. Sainas, A.C. Pippione, A. Giraudo, K. Martina, F. Bosca, B. Rolando, A. Barge, A. Ducime, A. Federico, S.J. Grossert, R.L. White, D. Boschi, M.L. Lolli, J. Heterocycl. Chem. **56**, 501 (2019)
26. Z. Fallah, H.N. Isfahani, M. Tajbakhsh, H. Tashakkorian, A. Amouei, Cellulose **25**, 639 (2018)
27. Z. Fallah, H.N. Isfahani, M. Tajbakhsh, Process Saf. Environ. **124**, 251 (2019)
28. M. Meldal, C.W. Tornøe, Chem. Rev. **108**, 2952 (2008)
29. M.K. Barman, A.K. Sinha, S. Nembenna, Green Chem. **18**, 2534 (2016)
30. M. Liu, O. Reiser, Org. Lett. **13**, 1102 (2011)
31. K. Bahrami, M. Sheikh Arabi, New J. Chem. **40**, 3447 (2016)
32. M. Gholinejad, N. Jeddi, A.C.S. Sustain, Chem. Eng. **2**, 2658 (2014)
33. L.S. Campbell-Verduyn, L. Mirfeizi, R.A. Dierckx, P.H. Elsinga, B.L. Feringa, Chem. Commun. **2009**, 2139–2141 (2009)
34. S. Lal, S. Díez-González, J. Org. Chem. **76**, 2367 (2011)
35. D. Nandi, A. Taher, R.U. Islam, M. Choudhary, S. Siwal, K. Mallick, Sci. Rep. UK **6**, 33025 (2016)
36. R. Sasikala, S.K. Rani, D. Easwaramoorthy, K. Karthikeyan, RSC Adv. **5**, 56507 (2015)
37. J. Markalain Barta, S. Diez-Gonzalez, Molecules **18**, 8919 (2013)
38. A. Kafle, S.T. Handy, Tetrahedron **73**, 7024 (2017)
39. V.H. Reddy, Y.V.R. Reddy, B. Sridhar, B.V.S. Reddy, Adv. Synth. Catal. **358**, 1088 (2016)
40. K.M. Faraz, V. Garima, A. Wasim, M. Akranth, A.M. Mumtaz, A. Mymoona, H. Asif, H.S. Misbahul, S. Mohammad, H.S. Rashiduddin, Int. J. Drug Dev. Res. **9**, 22 (2017)
41. M. Aghayee, M.A. Zolfigol, H. Keypour, M. Yarie, L. Mohammadi, Appl. Organomet. Chem. **30**, 612 (2016)
42. L. Mohammadi, M.A. Zolfigol, A. Khazaei, M. Yarie, S. Ansari, S. Azizian, M. Khosravi, Appl. Organomet. Chem. **32**, e3933 (2018)
43. L. Mohammadi, M.A. Zolfigol, M. Ebrahiminia, K.P. Roberts, S. Ansari, T. Azadbakht, S.R. Hussaini, Catal. Commun. **102**, 44 (2017)
44. L. Liang, D. Astruc, Coordin. Chem. Rev. **255**, 2933 (2011)
45. R. Hudson, C.-J. Li, A. Moores, Green Chem. **14**, 622 (2012)
46. R.B. Nasir Baig, R.S. Varma, Green Chem. **14**, 625 (2012)
47. R. Bonyasi, M. Gholinejad, F. Saadati, C. Nájera, New J. Chem. **42**, 3078 (2018)
48. B. Kaboudin, Y. Abedi, T. Yokomatsu, Org. Biomol. Chem. **10**, 4543 (2012)
49. B. Kaboudin, R. Mostafalu, T. Yokomatsu, Green Chem. **15**, 2266 (2013)
50. A.K. Feldman, B. Colasson, V.V. Fokin, Org. Lett. **6**, 3897 (2004)
51. W. Zhu, D. Ma, Chem. Commun. **2004**, 888–889 (2004)
52. A. Garg, A.A. Ali, K. Damarla, A. Kumar, D. Sarma, Tetrahedron Lett. **59**, 4031 (2018)
53. K.D. Grimes, A. Gupte, C.C. Aldrich, Synthesis **2010**, 1441 (2010)
54. B.T. Worrell, J.A. Malik, V.V. Fokin, Science **340**, 457 (2013)