Tetrahedron 81 (2021) 131911

Contents lists available at ScienceDirect

Tetrahedron

journal homepage: www.elsevier.com/locate/tet

Efficient copper-catalyzed tandem oxidative iodination and alkyne-azide cycloaddition in the presence of glycine-type ligands

Donghe Yuan, Shilei Wang, Gongming Zhu**, Anlian Zhu, Lingjun Li*

Collaborative Innovation Center of Henan Province for Green Manufacturing of Fine Chemicals, Key Laboratory of Green Chemical Media and Reactions, Ministry of Education, Henan Key Laboratory of Organic Functional Molecule and Drug Innovation, School of Chemistry and Chemical Engineering, Henan Normal University, Xinxiang, Henan, 453007, PR China

ARTICLE INFO

Article history:
Received 6 October 2020
Received in revised form
20 December 2020
Accepted 23 December 2020
Available online 8 January 2021

Keywords:
5-iodo-1,2,3-triazole
CuAAC reaction
Oxidation iodination
Glycine-type ligands

ABSTRACT

Tandem oxidative iodination and alkyne-azide cycloaddition reaction has provided one of the most widely used methods for preparation of 5-iodo-1,2,3-triazoles. However, stoichiometric copper salts are involved in this type of reaction in order to enhance the reaction effectiveness, which caused some problems related to toxic metal contaminations and less sustainability. In this paper, we described that a copper-catalyzed (10 mol%) tandem oxidative iodination and alkyne-azide cycloaddition could be completed in the presence of the newly-found glycine-type ligands with low-cost NaI as the iodine resource. In the novel reaction system, a wide range of terminal alkyne, organic azide and inexpensive iodide could react effectively in one pot to give structurally diverse 5-iodo-1,4-subsitutied 1,2,3-triazoles. Natural product derivatives and alkynyl pyridines that hardly react under traditional conditions could also be transferred smoothly to the target products for the first time.

5-Iodo-1,2,3-triazoles represent a kind of intriguing fully-substituted 1,2,3-triazoles, not only because of their flexibility to transfer into variant 5-substituted 1,2,3-triazoles using metal-coupling reactions [1], but also the unique properties of 5-iodo-1,2,3-triazoles in the structural modifications of bioactive molecules [2], supramolecular recognitions [3] and radioactive labeling [4]. Current methods for syntheses of 5-iodo-1,2,3-triazoles can be classified into four types based on the different starting materials (Fig. 1): (1) multi-component syntheses of 5-iodo-1,2,3-triazoles from terminal alkynes, organic azides and electrophonic iodine/iodide reagents [1–8]; (2) cycloadditions of 1-iodo-alkyne or its precursors and organic azides [9,10]; (3) transformations from 5-NH_2-1,2,3-triazoles by diazotization/iodination reactions [11]; (4) direct iodination or metal-iodine exchange of triazoles [12,13]. The multi-component reaction is the most convenient strategy benefiting from easily accessible and stable starting materials, one-pot operations with step economy and very mild reaction conditions. However, it should be pointed out that the reported methods of multi-component syntheses of 5-iodo-1,2,3-triazoles generally involved stoichiometric copper salts such as CuI [6], $CuCl_2$ [4] and $Cu(ClO_5)_2$ [7], etc. in most cases. High ratios of copper salts are disadvantageous to the complex reactants like biological molecules [14,15], and also may cause the heavy metal residues in the products [16]. To address these problem, more efficient reaction systems that can promote the syntheses of 5-iodo-1,2,3-triazoles in the catalytic amount of copper would be highly appreciated.

In this paper, we reported that a copper-catalyzed (10 mol%) tandem oxidative iodination and alkyne-azide cycloaddition could be completed in the presence the newly-found glycine-type ligands with low-cost NaI as the iodine resource. Through the effective copper-catalyzed multi-component reactions, not only simple aryl or alkyl alkynes and azides could react effectively to give various 1,4-disubstituted 5-iodo-1,2,3-triazoles in good yields, but also structurally complicated alkynes bearing natural product motifs and low-reactivity alkynyl pyridines could give the desirable products smoothly.

The reaction between phenylacetylene and benzyl azide was applied as the model (Table 1). In the presence of 10 mol% CuI as the catalyst, 1.2 equivalent NaI as the iodine resource, we firstly attempted the different oxidants for the multi-component reaction (Entries 1 to 6 in Table 1). Our previously used oxidant NBS and selectfluor proved less efficient to give 5-iodo-1,2,3-triazole under the current conditions. A wider screening of ordinary organic oxidant including mCPBA, DDQ, tBuOOH, Chloramine-T, then

* Corresponding author.
** Corresponding author.
E-mail addresses: zhugm1201@163.com (G. Zhu), lingjunlee@htu.cn (L. Li).

https://doi.org/10.1016/j.tet.2020.131911
0040-4020/

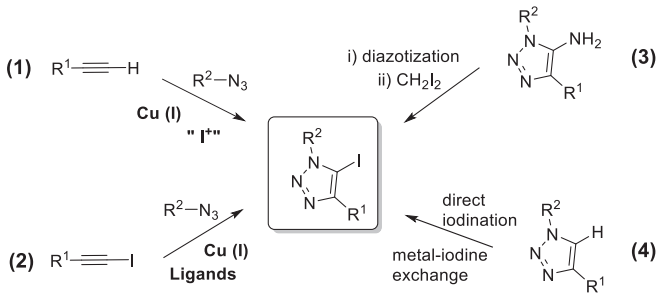
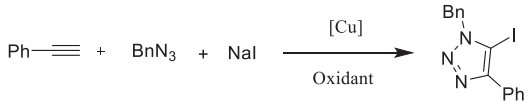


Fig. 1. Synthetic methods of 5-iodo-1,2,3-triazoles.

Table 1
Optimization of the reaction conditions for the synthesis of 5-iodo-1,2,3-triazoles.



Entry [a]	Catalyst (10 mol%)	Oxidant (1.2 eq)	Base (1.2 eq)	Solvent	Product[b] (%)
1	CuCl	selectfluor	Et_3N	DCM	25
2	CuI	NBS	Et_3N	DCM	10
3	CuI	mCPBA	Et_3N	DCM	35
4	CuI	Chloramine-T	Et_3N	DCM	60
5	CuI	DDQ	Et_3N	DCM	16
6	CuI	^tBuOOH	Et_3N	DCM	14
7	CuI	Chloramine-T	pyridine	DCM	36
8	CuI	Chloramine-T	DIPEA	DCM	63
9	CuI	Chloramine-T	DBU	DCM	32
10	CuI	Chloramine-T	DIPA	DCM	25
11	CuI	Chloramine-T	NaOH	DCM	30
12	CuI	Chloramine-T	DIPEA	DMF	42
13	CuI	Chloramine-T	DIPEA	THF	68
14	CuI	Chloramine-T	DIPEA	MeCN	30
15	CuI	Chloramine-T	DIPEA	CH_2Cl_2	48
16	CuI	Chloramine-T	DIPEA	DMSO	25
17	CuI	Chloramine-T	DIPEA	CH_3OH	46
18	CuI	Chloramine-T	DIPEA	Dioxane	32
19	CuI	Chloramine-T	DIPEA	$CHCl_3$	41
20	**TBTA**/CuI	Chloramine-T	DIPEA	THF	56
21	**Phen**/CuI	Chloramine-T	DIPEA	THF	20
22	**L1**/CuI	Chloramine-T	DIPEA	THF	60
23	**L2**/CuI	Chloramine-T	DIPEA	THF	64
24	**L3**/CuI	Chloramine-T	DIPEA	THF	66
25	**L4**/CuI	Chloramine-T	DIPEA	THF	76
25[c]	**L4**/CuI	Chloramine-T	DIPEA	THF	78
26[d]	**L4**/CuI	Chloramine-T	DIPEA	THF	86
27[d]	CuI	Chloramine-T	DIPEA	THF	74

[a] Otherwise noted, reactions were performed using azide (0.10 mmol), alkyne (0.12 mmol), iodide source (0.12 mmol), oxidant (0.12 mmol), copper catalyst (0.01 mmol), ligand (0.01 mmol), solvent (2 mL) at room temperature under N_2 atmosphere.
[b] Isolated yield.
[c] Study at 40 °C.
[d] Study at 50 °C.

showed Chloramine-T as the best one, by which 60% yield of target compound could be obtained. Secondly, we investigated the effects of bases on the reaction (Entries 7 to 11 in Table 1), and DIPEA shown a little better than TEA to give 63% yield of 5-iodo-1,2,3-triazole. Inorganic base and other organic bases were adverse for the reaction with yields of target compound less than 36%. Thirdly, we tried to optimize the solvents for the reaction (Entries 12 to 20 in Table 1). Among the ten solvents, THF was best one with 68% yield of 5-iodo-1,2,3-triazole.

Traditional glycine derivatives, such as N,N-dimethylglycine and N-methylglycine, have already been employed in copper(I)-catalyzed organic reactions, such as Goldberg reaction [17], Ullmann coupling reaction [18,19], amine and halides coupling reactions [20,21], aryl halides and terminal alkynes coupling reaction [22]. One the other hand, fine modifications on the amino acid derivatives could offer the new ligands for more challenging C–H activation transformations [23]. Inspired by these works, we synthesized four glycine-type ligands as shown in Fig. 2, and attempted them for promoting the multi-component synthesis of 5-iodo-1,2,3-triazoles. The effects of ligands on the multicomponent reactions were investigated as shown in Entry 21 to.

Entry 28 in Table 1. TBTA [24] and 1,10-phenanthroline (Phen) [25] which were the classic ligands for CAAC reaction indicated slightly and strongly inhibitory respectively for the production of 5-iodo-1,2,3-triazole (Entry 20 and Entry 21 in Table 1). In contrast, the glycine-type ligands didn't show strongly inhibitory (Entry 22 to Entry 24 in Table 1). 5-iodo-1,2,3-triazoles. Interestingly, ligand **L4** had a promoting effect on the reaction to give the target product with 76% yield at room temperature. Increasing reaction temperature to 50 °C could further to enhance the yield to 86%. In order to clarify the roles of L4 in the reaction, another control experiment was conducted in the absence of ligang L4 under the same conditions (Entry 27 in Table 1). However, a lower yield (74%) of 5-iodo-1,2,3-triazole was obtained. A possible explanation is that the high reaction temperature with the oxidant (here is Chloramine-T) might cause a partial oxidation of Cu(I) to Cu (II), thus losing some catalytic ability for the CuAAC reaction. To our best knowledge, the glycine-type ligands are the first class of ligands that may selectively promote the multicomponent preparations of 5-iodo-1,2,3-triazoles from alkynes and azides.

The scope of the substrates was then investigated with the new catalytic system. Alkynes and azides bearing various substituents reacted smoothly with NaI under the optimized reaction conditions (Table 2). Phenylacetylenes with electron-withdrawing and electron-donating substituents reacted to give the corresponding 5-iodo-1,2,3-triazoles (Entries 1–7 in Table 2) 71–88% yield. Benzyl azides with electron-withdrawing and electron-donating groups were also effective substrates for the reaction, in which the corresponding 5-iodo-1,2,3-triazoles could be obtained in yields of 67–84% (Entries 10–13). Alkyl azides were also effective in this reaction to give 5-iodo-1,2,3-triazoles in 74% (**3o**) and 73% (**3p**) yield respectively. These results suggested that this reaction was very useful for the preparation 5-iodo-1,2,3-triazole derivatives of small organic molecules. Inspired by the successful applications of the proposed reaction to a wider scope of substrates, we next investigated the potential of the reactions for the synthesis of more structurally complex or low-reactivity compounds (Scheme 1). Estrone derivatives bearing the 1,2,3-triazole motifs represented a class of promising bioactive and functional molecules [26]. Here an example is the azide-bearing estrone motifs **1h**, which could act as an effective substrate to provide the target 5-I-1,2,3-triazoles **3q** in 76% yield. Besides, the yield of **3r** could up to 87% when 3-alkynyl pyridine **1j** as substrate.

A possible reaction pathway was suggested as shown in Scheme 1. Chloramine-T acts as a mild oxidant to oxidize the iodide of NaI to electrophilic "I^+". In Route-A, the iodination might occur on the reaction intermediate copper triazolide (II). While in Route-B, the iodination might occur directly on alkyne to produce iodoalkyne

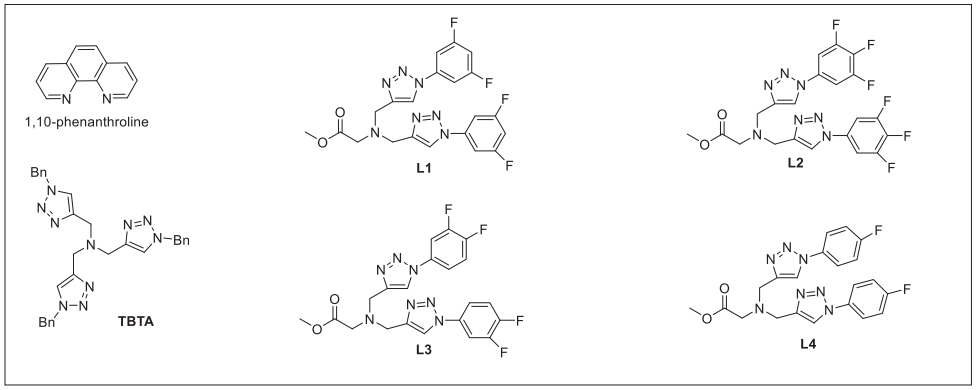
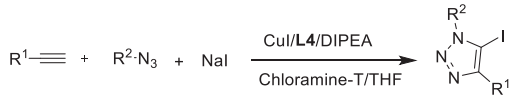


Fig. 2. The structure of ligands.

Table 2
Preparations of various 5-iodo-1,2,3-triazoles.[a]



Entry	Alkyne	Azide	Product	Isolated yields
1	**1a**	BnN_3 **2a**	**3a**	86
2	**1b**	BnN_3 **2a**	**3b**	80
3	**1c**	BnN_3 **2a**	**3c**	83
4	**1d**	BnN_3 **2a**	**3d**	88
5	**1e**	BnN_3 **2a**	**3e**	82
6	**1f**	BnN_3 **2a**	**3f**	71
7	**1g**	BnN_3 **2a**	**3g**	73
8	**1h**	BnN_3 **2a**	**3h**	89
9	**1i**	BnN_3 **2a**	**3i**	71
10	**1a**	**2b**	**3j**	67
11	**1a**	**2c**	**3k**	84
12	**1a**	**2d**	**3l**	70
13	**1a**	**2e**	**3m**	71

(*continued on next page*)

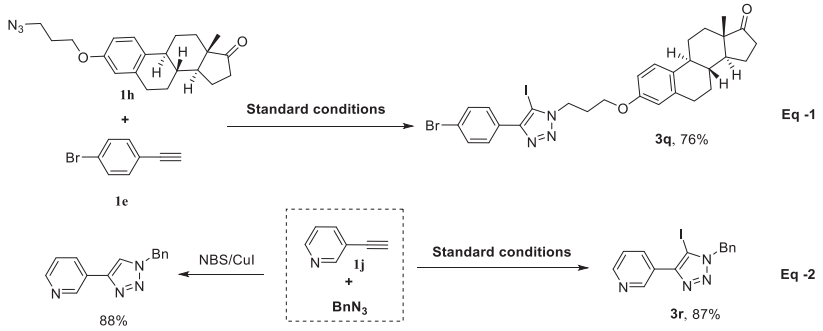
Table 2 (*continued*)

Entry	Alkyne	Azide	Product	Isolated yields
14	**1e**	**2c**	**3n**	72
15	**1e**	**2f**	**3o**	74
16	**1e**	**2g**	**3p**	73

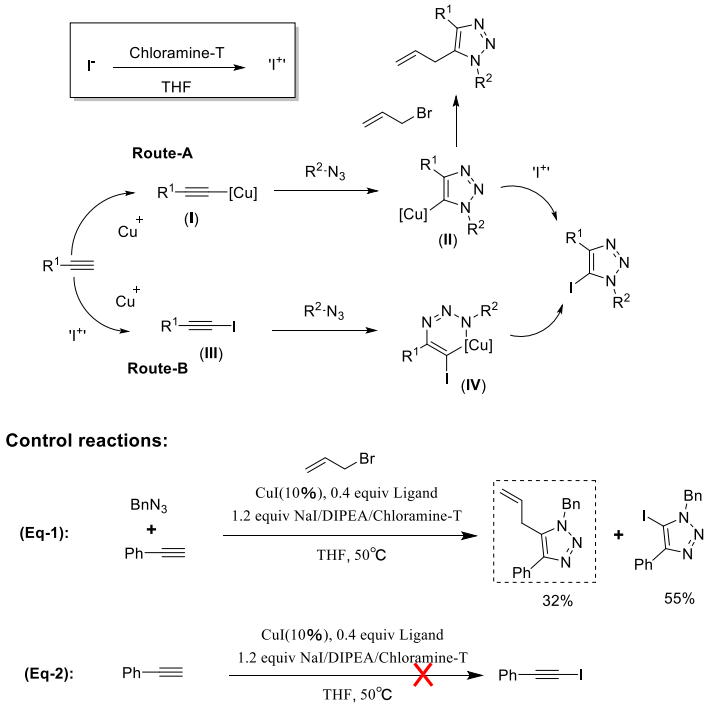
[a] The reactions were conducted under N_2 atmosphere at 50 °C temperature.

(III) and then the proceed CuAAC reaction. To further investigate the two pathway, two control experiments were conducted as shown in Scheme 2. No iodoalkyne (III) could be effectively prepared under the current reaction conditions. Besides, the trapping experiment yielded 5-alkyl-1,2,3-triaozles, which suggested potential existences of copper triazolide (II). As to possible interaction mode of the ligand L4, we carried out DFT theoretical calculations and the result indicated that the copper binding of ligand **L4** is similar to TBTA [22] in a tridentate model. The similar binding models implied that **L4** could stabilize the copper (I) species like TBTA to some extent avoiding their oxidation to copper (II) and loss catalytic properties for CuAAC reactions. The carboxyl group of **L4** could effectively coordinate with Cu(I) where the distance of Cu—O was 2.350 Å, which was dramatic longer than the distance of Cu—N on triazolyl arms (2.035 Å) in the complex of TBTA:Cu(I) as shown in Fig. 3. The structure of complex of **L4** and copper (I) species thus might be looser in the reaction in contrast to TBTA, which would be helpful to the attack of "I^+" for giving 5-iodo-1,2,3-triazole.

In conclusion, a novel copper(I)-catalyzed multi-component reaction of 5-iodo-1,2,3-triazoles was developed in this work. In the presence of catalytic CuI and **L4**, a wide range of terminal alkyne, organic azide and inexpensive iodide could react effectively in one pot to give structurally diverse 5-iodo-1,4-subsitutied 1,2,3-triazoles. Natural product derivatives and low-reactivity alkynyl pyridines could also be transferred smoothly to the target products. Besides, the stabilization effects of glycine-type ligands on Cu(I) catalysts were discussed, which suggested a new approach to optimize reaction system toward the multicomponent preparations of other 5-substituted 1,2,3-triazoles from terminal alkynes and organic azides.



Scheme 1. Applications in complicated and low-activity reactants.



Scheme 2. Possible reaction mechanism and control experiments.

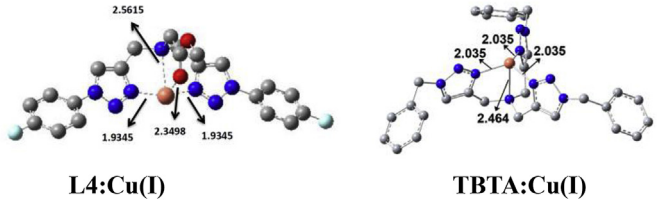


Fig. 3. The DFT theoretical calculations for possible binding model of **L4**:Cu(I).

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgements

We are grateful for financial support from the National Natural Science Foundation of China (nos. 21801257, 21778015 and 22077027), the 111 Project (No. D17007 to L. L.) and a start-up fund from Henan Normal University (qd 18018).

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.tet.2020.131911.

References

[1] (a) C. Spiteri, J.E. Moses, Angew. Chem. Int. Ed. 49 (2010) 31–33;
(b) B.T. Worrell, J.E. Hein, V.V. Fokin, Angew. Chem. Int. Ed. 124 (2012) 11961–11964.
[2] (a) J.C. Morris, J. Chiche, C. Grellier, M. Lopez, L.F. Bornaghi, A. Maresca, C.T. Supuran, J. Pouyssegur, S.A. Poulsen, J. Med. Chem. 54 (2011) 6905;
(b) J. He, L. Feng, J. Li, R. Tao, F. Wang, X. Liao, Q. Sun, Q. Long, Y. Ren, J. Wan, H. He, Bioorg. Med. Chem. 20 (2012) 1665;
(c) K.T. Andrews, G.M. Fisher, S.D.M. Sumanadasa, T. Skinner-Adams, J. Moeker, M. Lopez, S.A. Poulsen, Bioorg. Med. Chem. Lett 23 (2013) 6114;
(d) N. Ahmed, N.K. Konduru, S. Ahmad, M. Owais, Eur. J. Med. Chem. 82 (2014) 552;
(e) J.B. He, H.F. He, L. Zhao, L. Zhang, G.Y. You, L.L. Feng, J. Wan, H.W. He,

Bioorg. Med. Chem. 23 (2015) 1395.
[3] (a) M.J. Langton, S.W. Robinson, I. Marques, V. Fvlix, P.D. Beer, Nat. Chem. 6 (2014) 1039–1043;
(b) F. Kniep, L. Rout, S.M. Walter, H.K.V. Bensch, S.H. Jungbauer, E. Herdtweck, S.M. Huber, Chem. Commun. 48 (2012) 9299–9301.
[4] (a) R. Yan, E. El-Emir, V. Rajkumar, M. Robson, A.P. Jathoul, R.B. Pedley, E. Åastad, Angew. Chem. Int. Ed. 50 (2011) 6793–6795;
(b) R. Yan, K. Sander, E. Galante, V. Rajkumar, A. Badar, M. Robson, E. El-Emir, M.F. Lythgoe, R.B. Pedley, E. Astad, J. Am. Chem. Soc. 135 (2013) 703–709.
[5] J. Deng, Y.M. Wu, Q.Y. Chen, Synthesis 16 (2005) 2730–2738.
[6] L. Li, G. Zhang, A. Zhu, L. Zhang, J. Org. Chem. 73 (2008) 3630–3633.
[7] W.S. Brotherton, R.J. Clark, L. Zhu, J. Org. Chem. 77 (2012) 6443–6455.
[8] L. Li, S. Ding, Y. Yang, A. Zhu, X. Fan, M. Cui, C. Chen, G. Zhang, Chem. Eur J. 23 (2016) 1166.
[9] J.E. Hein, J.C. Tripp, L.B. Krasnova, K.B. Sharpless, V.V. Fokin, Angew. Chem. Int. 48 (2009) 8018–8021.
[10] J. García-Álvarez, J. Díez, J. Gimeno, Green Chem. 12 (2010) 2127–2130.
[11] N. Joubert, R.F. Schinazi, L.A. Agrofoglio, Tetrahedron 61 (2005) 11744.
[12] A. Giraudo, J. Krall, B. Nielsen, T.E. Sørensen, K.T. Kongstad, B. Rolando, D. Boschi, B. Frølund, M.L. Lolli, Eur. J. Med. Chem. 158 (2018) 311–321.
[13] (a) P. Dinér, T. Andersson, J. Kjellén, K. Elbing, S. Hohmann, M. Grøtli, New J. Chem. 33 (2009) 1010–1016;
(b) R. Tepper, B. Schulze, M. Jäger, C. Friebe, D.H. Scharf, H. Görls, U.S. Schubert, J. Org. Chem. 80 (2015) 3139–3150;
(c) N.V. Dubrovina, L. Domke, I.A. Shuklov, A. Spannenberg, R. Franke, A. Villinger, A. Börner, Tetrahedron 69 (2013) 8809–8817;
(d) J.Y.C. Lim, M.J. Cunningham, J.J. Davis, P.D. Beer, Chem. Commun. 51 (2015) 14640–14643.
[14] V. Hong, S.I. Presolski, C. Ma, M.G. Finn, Angew. Chem. Int. Ed. 48 (2009) 9879–9883.
[15] M. Yang, A.S. Jalloh, W. Wei, J. Zhao, P. Wu, P.R. Chen, Nat. Commun. 5 (2014) 4981.
[16] S. Neumann, M. Biewend, S. Rana, W.H. Binder, Macromol. Rapid Commun. 41 (2020) 1900359.
[17] W. Deng, Y.F. Wang, Y. Zou, L. Liu, Q.X. Guo, Tetrahedron Lett. 45 (2004) 2311–2315.
[18] D. Ma, Q. Cai, Org. Lett. 5 (2003) 3799–3802.
[19] H. Zhang, D. Ma, W. Cao, Synlett (2007) 243–246.
[20] H. Zhang, D. Ma, W. Cao, Synlett (2007) 243–246.
[21] W. Deng, L. Liu, C. Zhang, M. Liu, Q.X. Guo, Tetrahedron Lett. 46 (2005) 7295–7298.
[22] D. Ma, F. Liu, Chem. Commun. (2004) 1934–1935.
[23] Y. Lu, D.H. Wang, K.M. Engle, J.Q. Yu, J. Am. Chem. Soc. 132 (2010) 5916–5921.
[24] T.R. Chan, R. Hilgraf, K.B. Sharpless, V.V. Fokin, Org. Lett. 6 (2004) 2853–2855.
[25] W.G. Lewis, F.G. Magallon, V.V. Fokin, M.G. Finn, J. Am. Chem. Soc. 126 (2004) 9152–9153.
[26] (a) B. Bodnár, E. Mernyák, J. Szabó, J. Wölfling, G. Schneider, I. Zupkó, Z. Kupihár, L. Kovács, Bioorg. Med. Chem. Lett 27 (2017) 1938–1942;
(b) B. Bodnár, E. Mernyák, J. Wölfling, G. Schneider, B.E. Herman, M. Szécsi, I. Sinka, I. Zupkó, Z. Kupihár, L. Kovács, Molecules 21 (2016) 1212;
(c) M. Frutos, M.C. de la Torre, Inorg. Chem. 54 (2015) 11174–11185;
(d) P. Ramírez-López, M.C. de la Torre, M. Asenjo, J. Ramírez-Castellanos, J. González-Calbet, A. Rodríguez-Gimeno, C. Ramírez de Arellano, M.A. Sierra, Chem. Commun. 47 (2011) 10281–10283.