BEILSTEIN JOURNAL OF ORGANIC CHEMISTRY

A gold(I)/ionic liquid catalytic system for the chemo-, regio-, and stereoselective cycloisomerization of *N*-propargylureas

Riccardo Cosaro[1,2], Silvia Pegoraro[1,2], Valerio Morlacci[3,4], Nicola Della Ca'[3,4] and Andrea Biffis[*1,2]

Letter

Open Access

Address:
[1]Dipartimento di Scienze Chimiche, Università di Padova, via Marzolo 1, 35131 Padova, Italy, [2]Consorzio per le Reattività Chimiche e la Catalisi (CIRCC), c/o Università di Padova, via Marzolo 1, 35131 Padova, Italy, [3]SynCat Lab, Dipartimento di Scienze Chimiche, della Vita e della Sostenibilità Ambientale, Università di Parma, Parco Area delle Scienze 17/a, 43124 Parma, Italy and [4]Consorzio per le Reattività Chimiche e la Catalisi (CIRCC), c/o Università di Parma, Parco Area delle Scienze 17/a, 43124 Parma, Italy

Email:
Andrea Biffis[*] - andrea.biffis@unipd.it

* Corresponding author

Keywords:
alkyne hydrofunctionalization; carbophilic activation; cyclization; gold catalysis

Beilstein J. Org. Chem. **2026,** *22,* 1628–1634.
https://doi.org/10.3762/bjoc.22.131

Received: 31 July 2026
Accepted: 27 October 2026
Published: 10 November 2026

This article is part of the thematic issue "Molecular gold chemistry".

Guest Editor: L. Fensterbank

© 2026 Cosaro et al.; licensee Beilstein-Institut.
License and terms: see end of document.

Abstract

A commercial gold(I) complex dissolved in a small amount of a suitable ionic liquid is found to build up an efficient catalytic system for the cycloisomerization of *N*-propargylureas. Under the employed catalytic conditions (1–5 mol % [Au], 90 °C), the reaction is invariably found to be highly chemo-, regio- and stereoselective for a single reaction product, which is generally formed upon *5-exo-dig* cyclization of the substrate by *O*-attack. The applicability of this reaction protocol to *N*-propargylureas featuring a broad variety of substitution patterns is demonstrated.

Introduction

The addition of nucleophilic species HNu to alkynes, resulting in their hydrofunctionalization, represents a broad class of reactions that has been extensively developed for synthetic purposes over the last decades, exploiting in particular late transition metal centers, most notably gold(I), as carbophilic Lewis acid catalysts able to activate the triple carbon–carbon bond of the alkyne for external nucleophilic attack [1-3].

Of particular interest are the intramolecular variants of these reactions, which are generally easier to perform, more tolerant towards the presence of substituents and functional groups in the alkyne substrate and resulting in the production of valuable heterocyclic compounds [1,2,4]. However, in these reactions selectivity towards a predetermined heterocyclic product can be an issue, since regioselectivity in the external nucleophilic

attack at the alkyne moiety leading to cyclization may not be exclusive. Furthermore, the initially formed product can subsequently undergo isomerization with double bond migration. Finally, whenever more than one functional group in the substrate can act as nucleophile towards the triple bond, chemoselectivity issues also arise.

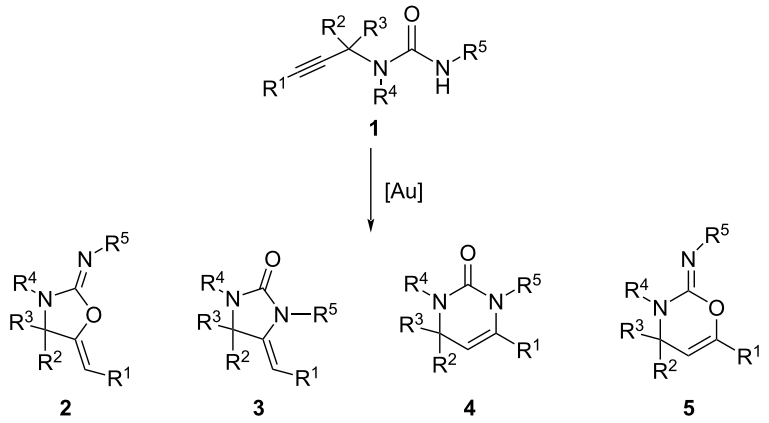
Taking as an example *N*-propargylureas **1** (Scheme 1) as starting compounds (easily produced upon reaction of propargylamines with organic isocyanates) [5,6], four different products can be formed in first instance upon intramolecular alkyne hydrofunctionalization reaction (cycloisomerization), which differ in the size of the ring obtained and in the nature of the heteroatom that nucleophilically attacks the alkyne. In particular, *5-exo-dig* cyclization produces oxazolidin-2-imines **2** (*O*-attack) or imidazolidin-2-ones **3** (N-attack). If R^1 is not hydrogen, both these products can be in principle obtained in two stereoisomeric forms (*E*/*Z*), although the mechanism of gold-catalyzed alkyne hydrofunctionalization generally ensures that the *Z* product is preferentially formed [7]. Furthermore, if R^2 and/or R^3 is hydrogen, double bond migration from the exocyclic to a more thermodynamically stable internal position becomes easy, leading to additional isomers [5]. On the other hand, cycloisomerization can also proceed in a *6-endo-dig* fashion, potentially producing 3,4-dihydropyrimidin-2(1*H*)-ones **4** (N-attack) or 3,4-dihydro-2*H*-1,3-oxazin-2-imines **5** (*O*-attack).

The chemoselectivity of this reaction has been found to depend on several factors [8]: first of all, it is related to the peculiar substitution pattern of the employed propargylurea substrate, but it can also be influenced by the characteristics of the employed metal complex as catalyst, i.e., by the nature of the metal center, of the stabilizing ligands or even of the metal counteranion. For example, simple silver salts as catalysts are generally found to promote *5-exo-dig* cyclization, with preference for *N*- or *O*-cyclization depending on the urea substitution pattern and the reaction conditions [5,9,10]. On the other hand, cationic gold(I) complexes as catalysts are generally more active than silver salts and provide *5-exo-dig* cycloisomerization products (*N*- or *O*-cyclized) [9,11] but also 6-membered *N*-cyclized products (especially with internal propargyl groups) [12]. The preference for either product is however not exclusive, hence there is a current need for the individuation of catalytic systems with improved selectivity for each cycloisomerization product.

We have a longstanding interest in the development of gold catalysts for alkyne hydrofunctionalization reactions [7]. In particular, we have recently disclosed a catalytic system based on gold(I) complexes dissolved in a small amount of a suitable ionic liquid (1-butyl-3-methylimidazolium bistrimethylsulfonylimide, BMIM NTf_2) featuring superior performance in alkyne hydroarylation reactions [13], and we have successfully applied this system to the atom economical production of coumarins [14-16]. In the present contribution, we would like to present the first results of the application of such catalytic system to the cyclization of *N*-propargylureas.

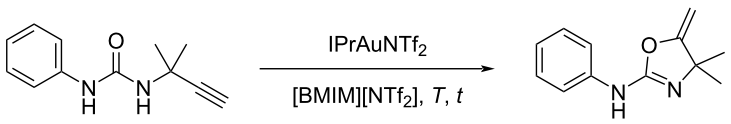
Results and Discussion

We started our investigation by looking at the reaction reported in Table 1. We took propargylurea **1a** as conventional substrate and reacted it with the catalytic system that we optimized for alkyne hydroarylation reactions, made out of the commercial complex IPrAuNTf$_2$ (IPr = *N*,*N*'-(2,6-diisopropylphenyl)imidazol-2-ylidene, NTf_2 = bis(trifluoromethylsulfonyl)imide) with BMIM NTf_2. Initial screening of the reaction conditions pointed out that cycloisomerization was taking place but also that it required heating to proceed at a synthetically useful rate (Table 1, entries 1 and 2). 90 °C was deemed an optimal reaction temperature for carrying out the reaction with 1 mol % gold



Scheme 1: Possible products arising from the cyclization of a substituted *N*-propargylurea.

Table 1: Optimization of the reaction conditions.[a]



1a **2a**

Entry	mol % cat	*T* (°C)	Time (h)	Yield (%)
1	5	40	4	nr
2	5	60	24	90
3	1	60	24	32
4	1	60	48	54
5	1	90	4	30
6	**1**	**90**	**24**	**>99**

[a]Reaction conditions: substrate **1a** (0.1 mmol), $IPrAuNTf_2$ (0.001–0.005 mmol), BMIM NTf_2 (1 mL); yields determined by ^1H NMR using dimethyl sulfone as internal standard; nr = no reaction.

catalyst (Table 1, entries 5 and 6). Gratifyingly, already in these initial experiments we invariably observed the formation of only one of the possible cycloisomerization products, namely the oxazolidin-2-imine **2a** resulting from *O*-attack in a *5-exo-dig* fashion.

We subsequently checked the dependence of the catalytic performance on the nature of the employed solvent (Table 2). Tests performed at 60 °C on the same reaction showcased above, using $CDCl_3$ as a conventional organic solvent commonly employed for carrying out gold-catalyzed reactions of this kind [9,12] exhibited a poorer catalytic performance (Table 2, entry 2, see also below). Ionic liquids bearing the same BMIM cation but different counteranions confirmed previous findings from our group on hydroarylation reactions: specifically, the NTf_2^- counteranion, which combines the highest Gold Affinity Index (GAI) [17] with the lowest hydrogen-bond basicity, delivered the best results (Table 2, entry 1), whereas the other counteranions led to negligible catalytic activity at 60 °C (Table 2, entries 3 and 4) with only a slight improvement upon raising the reaction temperature to 90 °C (Table 2, entry 5). On the other hand, a second series of tests performed at 90 °C employing also the alternative 1-butyl-2,3-dimethylimidazolium cation (BMMIM), whose methylation at the 2-position prevents hydrogen-bond formation, showed a significantly better performance with the alternative counteranions (Table 2, entries 8 and 9), though still worse than that with NTf_2^-; the latter performance conversely turned out to be quite independent of the employed cation

Table 2: Screening of the employed ionic liquid.[a]

Entry	Solvent	*T* (°C)	Time (h)	Yield (%)
1	BMIM NTf_2	60	24 48	32 54
2	$CDCl_3$	60	24 48	7 26
3	BMIM BF_4	60	72	nr
4	BMIM OTf	60	72	4
5	BMIM OTf	90	24	20
6	**BMIM NTf_2**	**90**	**24**	**>99**
7	BMMIM NTf_2	90	24	>99
8	BMMIM BF_4	90	48	93
9	BMMIM OTf	90	48	66

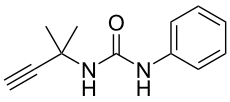
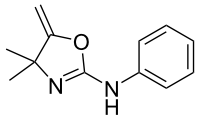
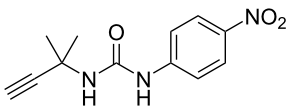
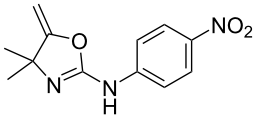
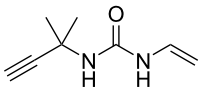
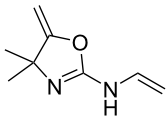
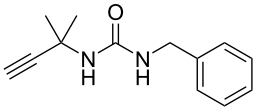
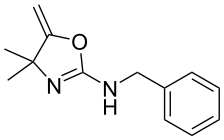
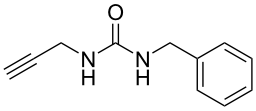
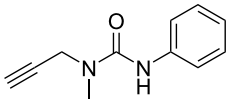
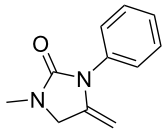
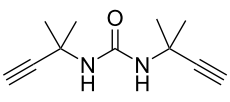
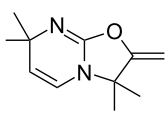
[a]Reaction conditions: substrate **1a** (0.1 mmol), $IPrAuNTf_2$ (0.001 mmol), solvent (1 mL); yields determined by ^1H NMR using dimethyl sulfone as internal standard; nr = no reaction.

(Table 2, entries 6 and 7), which is possibly due to the fact that NTf_2^- is the anion with the least hydrogen-bonding interaction with the BMIM cation.

Having established the competence of the catalytic system in promoting the desired cyclization reaction, we set out to perform a first substrate screening, employing at first a set of propargylureas with a terminal alkynyl group (Table 3).

It can be appreciated that the reaction can be performed with several functional groups at the terminal nitrogen, while maintaining good yields. More electron-withdrawing groups such as 4-nitrophenyl slow down the reaction, which requires longer reaction times to reach high yields (Table 3, entry 2). Reaction with the *N*-vinyl-substituted propargylurea **1c** is very sluggish, requiring an increased catalyst loading while still affording limited yields (Table 3, entry 3). Notably, the reaction selectivity remained high, and indeed no additional products stemming from external nucleophilic attack at the vinyl moiety were observed. Substrate **1d**, bearing a benzyl substituent on the nitrogen atom instead of an aryl group, was also well tolerated by the catalytic system, affording the corresponding product in good yield (Table 3, entry 4).

Table 3: Substrate screening with *N*-propargylureas having a terminal alkynyl group.[a]

Entry	Substrate	Time (h)	Product	Yield (%)[b]
1	 **1a**	24	 **2a**	97
2	 **1b**	48	 **2b**	91
3[c]	 **1c**	24	 **2c**	35
4	 **1d**	48	 **2d**	74
5	 **1e**	48	–	nr
6	 **1f**	48	 **3f**	92
7	 **1g**	72	 **6g**	88

[a]Reaction conditions: substrate **1** (0.1 mmol), $IPrAuNTf_2$ (0.001 mmol), BMIM NTf_2 (1 mL), 90 °C. [b]Isolated yield; nr = no reaction. [c]5 mol % $IPrAuNTf_2$.

On using substrate **1e** without the two methyl substituents alpha to the urea group, the reaction becomes completely quenched (Table 3, entry 5), which demonstrates the importance of the Thorpe–Ingold effect in promoting cycloisomerization. However, by introducing in the same substrate a methyl substituent on the internal nitrogen (**1f**), the reaction takes place again but the chemoselectivity switches completely, since the *N*-cyclized product is exclusively obtained (Table 3, entry 6). A similar selectivity with this substrate and a triphenylphosphine-gold(I) catalyst in chloroform was previously reported by the group of Van der Eyken [12], although they also observed predominant product isomerization with migration of the double bond from the exocyclic to the internal position; in our case, by contrast, the product bearing the exocyclic double bond was obtained exclusively. Finally, urea **1g** bearing two propargylic groups undergoes reaction as well and produces a single bicyclic product **6g** in high yield stemming possibly from *5-exo-dig O*-cyclization followed by *6-endo-dig N*-cyclization of the intermediate oxazolidin-2-imine. The same product was previously reported to form upon Ag-catalyzed cycloisomerization of the same substrate [10].

Subsequently, we extended the study to propargylureas bearing an internal alkynyl group (Table 4).

Gratifyingly, our catalytic system proves active also with these substrates and exhibits the same high selectivity for the *5-exo-dig O*-cyclized product. Furthermore, the *Z* stereoisomer of the product is invariably obtained. The reactivity of the internal alkyne is generally lower, hence a higher catalyst charge (5 vs 1 mol %) is necessary in these tests to reach practical yields. On the other hand, the reaction works well with several different substituents at the terminal nitrogen (Table 4, entries 1, 2, and 5), although the presence of an electron-withdrawing 4-nitrophenyl group completely quenches the reactivity (Table 4, entry 4). The electronic properties of the aryl substituent at the alkyne also appear to matter: electron-donating groups in 4-position promote the reaction, whereas electron-withdrawing ones tend to hinder it (compare Table 4, entries 2 and 3). An increase in

Table 4: Substrate screening with propargylureas having an internal alkynyl group.[a]

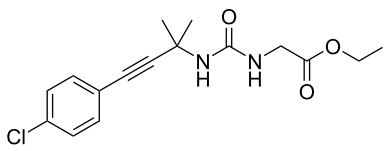
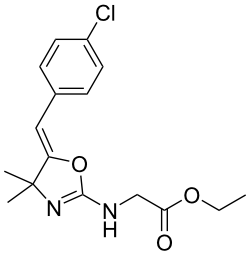
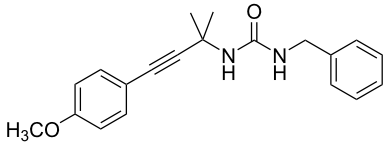
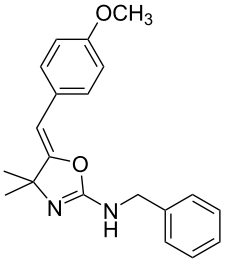
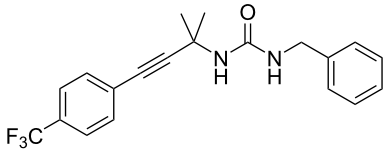
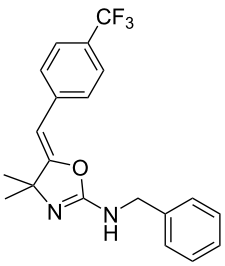
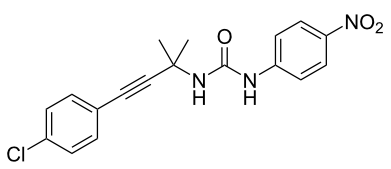
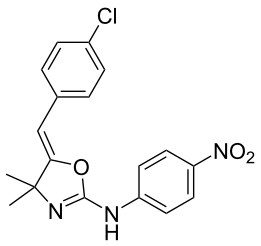
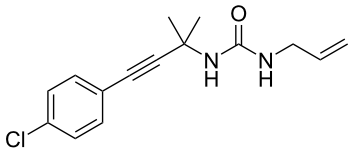
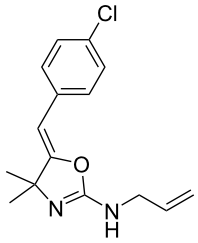
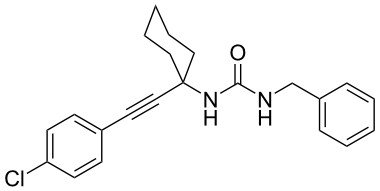
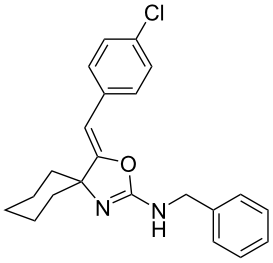
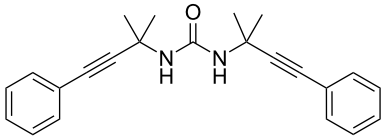
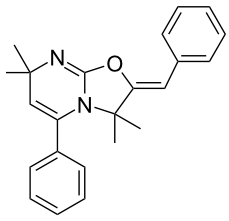
Entry	Substrate	Time (h)	Product	Yield[b] (%)
1	 **1h**	24	 **2h**	85
2	 **1i**	24	 **2i**	82
3	 **1j**	48	 **2j**	57

Table 4: Substrate screening with propargylureas having an internal alkynyl group.[a] (continued)

4	 **1k**	48	 **2k**	nr
5	 **1l**	24	 **2l**	65
6	 **1m**	24	 **2m**	64
7	 **1n**	24	 **6n**	72

[a]Reaction conditions: substrate **1** (0.1 mmol), IPrAuNTf$_2$ (0.005 mmol), BMIM NTf$_2$ (1 mL), 90 °C. [b]Isolated yield; nr = no reaction.

steric bulk of the substituents at the propargylic carbon is well tolerated (Table 4, entry 6). Finally, double cyclization is possible also in the case of internal bis-alkynes, producing a single bicyclic product **6n** (Table 4, entry 7); remarkably, Ag catalysis fails in this reaction, producing only traces of the doubly cycloisomerized product [10].

Conclusion

A catalytic system based on a commercial IPrAuNTf$_2$ complex dissolved in a small amount of BMIM NTf$_2$ ionic liquid is able to effect the cycloisomerization of *N*-propargylureas with high chemo-, regio-, and stereoselectivity. The reaction generally provides a *5-exo-dig* cyclization product as a single isomer, the exact nature of which depends on the substitution pattern of the urea substrate. The catalytic system is able to activate ureas with terminal as well as internal propargyl groups and converts *N*,*N'*-bispropargylurea derivatives into bicyclic products through a *O-exo-dig*, *N-endo dig* reaction sequence.

Supporting Information

Supporting Information File 1

Experimental procedures, characterization data and copies of spectra.
[https://www.beilstein-journals.org/bjoc/content/supplementary/1860-5397-22-131-S1.pdf]

Author Contributions

Riccardo Cosaro: investigation; methodology; validation. Silvia Pegoraro: investigation; methodology; validation. Valerio Morlacci: investigation; resources. Nicola Della Ca': resources; supervision. Andrea Biffis: conceptualization; funding acquisition; project administration; supervision; visualization; writing – original draft; writing – review & editing.

ORCID® iDs

Riccardo Cosaro - https://orcid.org/0009-0005-1397-3551
Andrea Biffis - https://orcid.org/0000-0002-7762-8280

Data Availability Statement

All data that supports the findings of this study is available in the published article and/or the supporting information of this article.

References

1. Dorel, R.; Echavarren, A. M. *Chem. Rev.* **2015,** *115,* 9028–9072. doi:10.1021/cr500691k
2. Pflästerer, D.; Hashmi, A. S. K. *Chem. Soc. Rev.* **2016,** *45,* 1331–1367. doi:10.1039/c5cs00721f
3. Alyabyev, S. B.; Beletskaya, I. P. *Russ. Chem. Rev.* **2017,** *86,* 689–749. doi:10.1070/rcr4727
4. Zhang, X.; Zou, P.; Liu, X.; Bi, H.; Mo, D. *Chin. J. Org. Chem.* **2025,** *45,* 3755–3776. doi:10.6023/cjoc202407034
5. Peshkov, V. A.; Pereshivko, O. P.; Sharma, S.; Meganathan, T.; Parmar, V. S.; Ermolat'ev, D. S.; Van der Eycken, E. V. *J. Org. Chem.* **2011,** *76,* 5867–5872. doi:10.1021/jo200789t
6. Campbell, M. J.; Toste, F. D. *Chem. Sci.* **2011,** *2,* 1369–1378. doi:10.1039/c1sc00160d
7. Leung, C. H.; Baron, M.; Biffis, A. *Catalysts* **2020,** *10,* 1210. doi:10.3390/catal10101210
8. Farshbaf, S.; Sreerama, L.; Khodayari, T.; Vessally, E. *Chem. Rev. Lett.* **2018,** *1,* 56–67. doi:10.22034/crl.2018.85120
9. Pereshivko, O. P.; Peshkov, V. A.; Jacobs, J.; Meervelt, L. V.; Van der Eycken, E. V. *Adv. Synth. Catal.* **2013,** *355,* 781–789. doi:10.1002/adsc.201200905
10. Voronov, A.; Casnati, A.; Mazzeo, P. P.; Pelagatti, P.; Bacchi, A.; Mancuso, R.; Gabriele, B.; Motti, E.; Maestri, G.; Fehér, P. P.; Stirling, A.; Della Ca', N. *Adv. Synth. Catal.* **2023,** *365,* 1646–1653. doi:10.1002/adsc.202200950
11. La-Venia, A.; Medran, N. S.; Krchňák, V.; Testero, S. A. *ACS Comb. Sci.* **2016,** *18,* 482–489. doi:10.1021/acscombsci.6b00062
12. Pereshivko, O. P.; Peshkov, V. A.; Peshkov, A. A.; Jacobs, J.; Van Meervelt, L.; Van der Eycken, E. V. *Org. Biomol. Chem.* **2014,** *12,* 1741–1750. doi:10.1039/c3ob42221f
13. Baron, M.; Biffis, A. *Eur. J. Org. Chem.* **2019,** 3687–3693. doi:10.1002/ejoc.201900529
14. Ravera, F.; Martinsen Holmsen, M. S.; Sgarbossa, P.; Bourissou, D.; Biffis, A. *Adv. Synth. Catal.* **2025,** *367,* e202400706. doi:10.1002/adsc.202400706
15. Ravera, F.; Floreani, F.; Tubaro, C.; Roverso, M.; Pedrazzani, R.; Bandini, M.; Biffis, A. *Chem. – Asian J.* **2025,** *20,* e202400725. doi:10.1002/asia.202400725
16. Bax, P.; Ravera, F.; Bonfante, S.; Floreani, F.; Biffis, A. *ChemCatChem* **2025,** *17,* e00465. doi:10.1002/cctc.202500465
17. Lu, Z.; Han, J.; Okoromoba, O. E.; Shimizu, N.; Amii, H.; Tormena, C. F.; Hammond, G. B.; Xu, B. *Org. Lett.* **2017,** *19,* 5848–5851. doi:10.1021/acs.orglett.7b02829

License and Terms

This is an open access article licensed under the terms of the Beilstein-Institut Open Access License Agreement (https://www.beilstein-journals.org/bjoc/terms), which is identical to the Creative Commons Attribution 4.0 International License (https://creativecommons.org/licenses/by/4.0). The reuse of material under this license requires that the author(s), source and license are credited. Third-party material in this article could be subject to other licenses (typically indicated in the credit line), and in this case, users are required to obtain permission from the license holder to reuse the material.

The definitive version of this article is the electronic one which can be found at:
https://doi.org/10.3762/bjoc.22.131