Organic LETTERS
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Formal [4 + 1] Cycloadditions of *β*,*β*-Diaryl-Substituted *ortho*-(Alkynyl)styrenes through Gold(I)-Catalyzed Cycloisomerization Reactions

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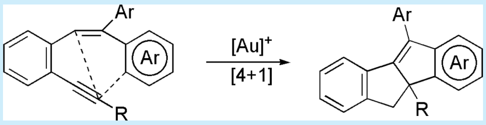
S *Supporting Information*

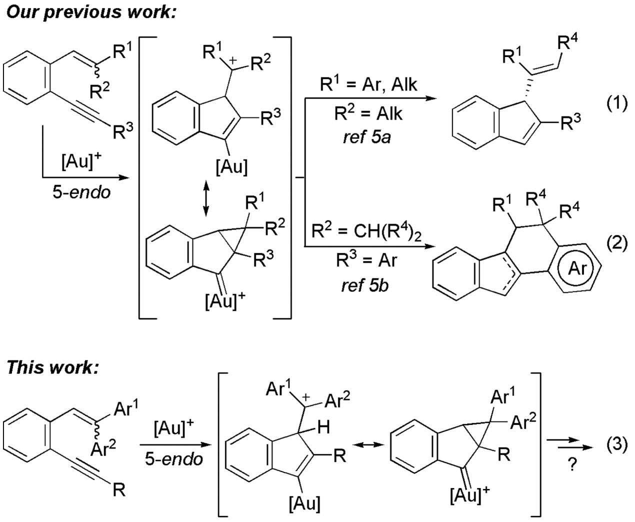
ABSTRACT: Gold(I)-catalyzed cycloisomerization of *β*,*β*-diaryl-*o*-(alkynyl)-styrenes at 80 °C selectively yields dihydroindeno[2,1-*a*]indenes in a transformation that encompasses a formal [4 + 1] cycloaddition and takes place through a cascade 5-*endo*-cyclization–diene activation–*iso*-Nazarov cyclization. In addition, by performing the reaction at 0 °C, the same substrates exclusively give rise to benzofulvene derivatives, which have also been shown to be intermediates in the formation of the tetracyclics.



Gold(I) catalysis is currently well established as a powerful tool for the straightforward construction of complex molecules from readily available starting materials.[1] Intense research on this topic during the past decade has demonstrated the unique ability of gold(I) complexes to selectively activate triple bonds toward the attack of a wide range of different nucleophiles.[2] In particular, the cycloisomerization of enynes has attracted great interest, and its usefulness has been demonstrated in the construction of intricate carbocyclic skeletons not easily accessible by other methodologies, through the development of diverse cascade processes.[3]

In this context, we became interested in gold(I)-catalyzed cycloisomerizations of conjugated dienynes,[4] with particular attention to *o*-(alkynyl)styrenes.[5] Thus, we described an enantioselective synthesis of indenes by gold(I)-catalyzed cycloisomerization of *o*-(alkynyl)styrenes (Scheme 1, eq 1).[5a] Moreover, we found that when an *o*-(alkynyl)styrene having a secondary alkyl group at the *β*-position of the styrene moiety is used as starting material, a formal [3 + 3] cycloaddition occurs, involving the aromatic group initially bonded to the triple bond and finally giving rise to dihydrobenzo[*a*]fluorenes (Scheme 1, eq 2).[5b] In both cases, the reaction is proposed to proceed through a common carbocationic intermediate, which can be also described as a cyclopropyl gold carbene-like intermediate,[6] generated by a 5-*endo* nucleophilic attack of the olefin to the gold-activated alkyne. This gold intermediate evolves through a proton elimination in the first case and through a more complex cascade process in the second one. Taking these results into account, we wondered about the outcome of the reaction under gold(I) catalysis of *β*,*β*-diaryl-*o*-(alkynyl)-styrenes, for which none of the previously described pathways is available (Scheme 1, eq 3).

Scheme 1. Previous Work and Proposed Study



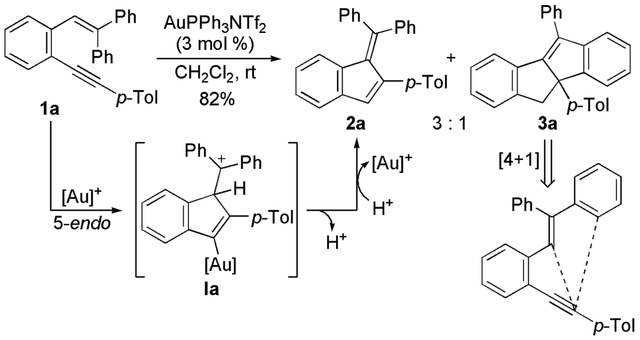
Herein we report the gold(I)-catalyzed cycloisomerization of *β*,*β*-diaryl-*o*-(alkynyl)styrenes through a cascade process leading to dihydroindeno[2,1-*a*]indenes by a formal [4 + 1] cycloaddition process.

To start our investigations, we selected *β*,*β*-diphenyl-*o*-(*p*-tolylethynyl)styrene **1a** as model substrate and performed its reaction with $AuPPh_3NTf_2$ as catalyst in DCM as the solvent at room temperature (Scheme 2). Under these conditions and not surprisingly, benzofulvene **2a** was obtained as a major product, presumably coming from the elimination of the only proton available in intermediate **Ia**. More interestingly, a minor product **3a** was also formed which presented a tetracyclic skeleton coming from a formal [4 + 1] cycloaddition involving

Received: January 20, 2016

DOI: 10.1021/acs.orglett.6b00191

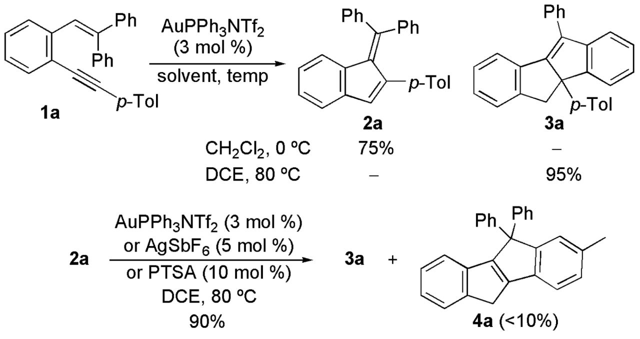
Scheme 2. Preliminary Result



the double bond, one of the phenyl rings, and the external carbon of the alkyne.[7] The structure of **3a** was confirmed by X-ray diffraction analysis.[8]

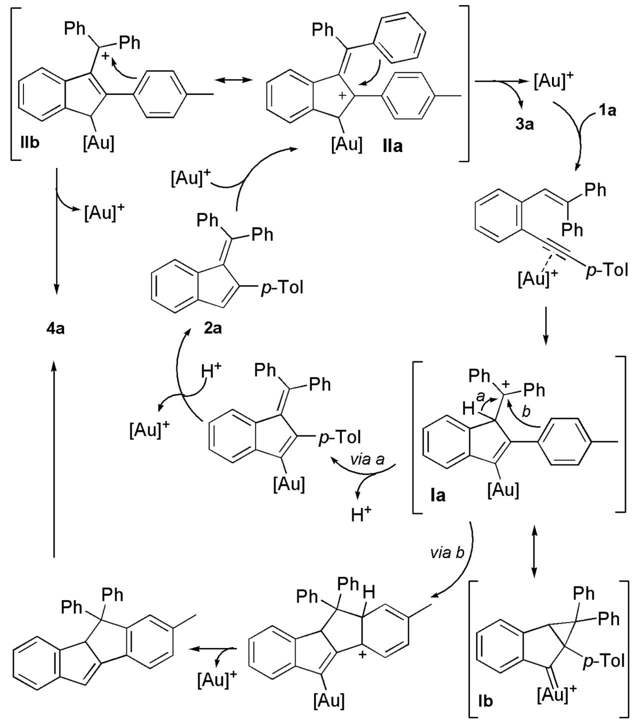
With the aim of increasing the selectivity of the process, we screened several parameters. Different gold catalysts with ligands of diverse nature lead in all cases to mixtures of products (**2a**, **3a**, and others) in variable amounts.[9] Gratifyingly, selective reactions could be achieved by controlling the reaction temperature (Scheme 3). Thus, performing the reaction at 0 °C allowed for the selective synthesis of benzofulvene **2a**, which could be isolated in 75% yield. Moreover, we were pleased to find that by merely increasing the reaction temperature to 80 °C dihydroindeno[2,1-*a*]indene **3a** was exclusively formed in excellent yield. These results, apart from setting useful synthetic conditions, suggest that **2a** could be an intermediate in the formation of **3a**. In fact, isolated **2a** could be transformed in **3a** by heating it in the presence of the gold catalyst, a silver salt, or a Brønsted acid, thus confirming our hypothesis. Trace amounts of isomeric tetracyclic compound **4a** were also formed in these essays.

Scheme 3. Effect of the Temperature in the Selectivity



With these results in hand, we propose the following mechanism that accounts for all the previously discussed observations (Scheme 4). The reaction would start with the coordination of the gold catalyst to the triple bond followed by intramolecular formal 5-*endo* attack of the olefin generating carbocationic intermediate **Ia** (that could also be represented by resonance structure **Ib**), analogously to what was previously proposed for other *o*-(alkynyl)styrenes.[5] Then, proton elimination followed by protodemetalation would lead to benzofulvene **2a** and regenerate the gold catalyst (*via a*). Under appropriate reaction conditions, the diene moiety in **2a** could be activated by coordination of the gold catalyst,[10] leading to an allylic carbocation species **II**. This is trapped by one of the aromatic rings bonded to the olefin yielding **3a** in a process that could be understood as an *iso*-Nazarov cyclization or an intramolecular Friedel–Crafts reaction. Moreover, formation of minor amounts of **4a** could be explained by nucleophilic attack of the aromatic ring initially bonded to the triple bond either in intermediate **Ia** followed by alkene isomerization (*via b*) or, alternatively, from intermediate **IIb**. The transformation of **2a** into **3a** and **4a** could also be catalyzed by another Lewis or Brønsted acid, as shown in Scheme 3, presumably through an analogous mechanism.[11]

Scheme 4. Proposed Mechanism



Besides the mechanistic interest for the developed procedures, the relevance of the molecules obtained should be noted. Thus, benzofulvene derivatives are present in biologically and pharmaceutically active molecules as well as in molecular materials.[12] On the other hand, little is known about the possible applications of dihydroindeno[2,1-*a*]-indenes, which is not surprising considering the lack of efficient methodologies for their synthesis to date.[13] In contrast, structurally related dibenzopentalenes have been extensively studied and shown as promising substrates for material science.[14]

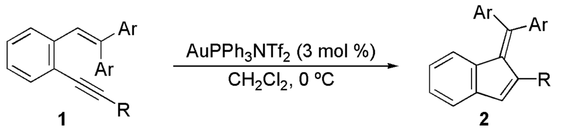
With these considerations in mind, the scope of these new transformations was examined. First, we checked the generality of the encountered methodology for the synthesis of benzofulvenes by performing the gold(I)-catalyzed reaction of a series of *o*-(alkynyl)styrenes at 0 °C (Table 1). Pleasantly, this transformation provided benzofulvenes **2** in high yields for most of the *o*-(alkynyl)styrenes tested, including those with electron-rich and -poor aromatic, heteroaromatic, and aliphatic groups initially bonded to the triple bond.

Once we had demonstrated the generality of the synthesis of benzofulvenes **2**, we focused on analyzing the scope of the gold(I)-catalyzed formal [4 + 1] cycloaddition of *o*-(alkynyl)-styrenes to produce dihydro[2,1-*a*]indenes having a quaternaty center at the ring junction.

First, we selected *o*-(alkynyl)styrenes **1a–j** having two identical aryl groups as substituents of the olefin, and we

DOI: 10.1021/acs.orglett.6b00191
Org. Lett. XXXX, XXX, XXX−XXX

Table 1. Synthesis of Benzofulvenes 2[a]

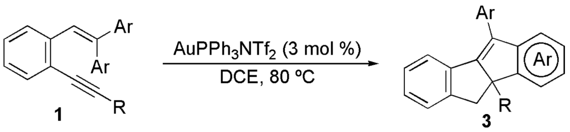


entry	1	Ar	R	2	yield[b] (%)
1	**1a**	Ph	4-MeC_6H_4	**2a**	79
2	**1b**	Ph	Ph	**2b**	91
3	**1c**	Ph	4-MeOC_6H_4	**2c**	76
4	**1d**	Ph	3-FC_6H_4	**2d**	95
5	**1e**	Ph	3-Th	**2e**	69
6	**1f**	Ph	*c*-C_3H_5	**2f**	82
7	**1g**	4-MeC_6H_4	4-MeC_6H_4	**2g**	91
8	**1h**	4-MeC_6H_4	*n*-Bu	**2h**	76

[a]Reaction conditions: **1** (0.2 mmol), $AuPPh_3NTf_2$ (3 mol %), CH_2Cl_2 (0.8 mL), 0 °C, 3−4 h. [b]Yield of isolated product referred to starting product **1**.

were pleased to find that all of them provided the corresponding [4 + 1] cycloaducts **3a−j** in high to excellent yields (Table 2). Dihydroindeno[2,1-*a*]indenes having as a substituent of the quaternary center electron-rich (entries 1, 3, and 7) and electron-poor aromatic (entry 4), heteroaromatic (entry 5), and aliphatic groups (entries 6 and 8−10), including cyclic (entry 6) and functionalized ones (entry 10), could be efficiently synthesized using this methodology.[15]

Table 2. Synthesis of Dihydroindenes 3[a]

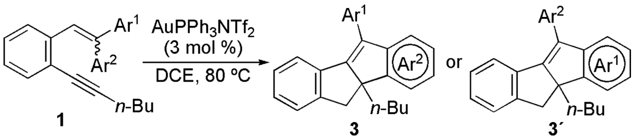


entry	1	Ar	R	3	yield[b] (%)
1	**1a**	Ph	4-MeC_6H_4	**3a**	96
2	**1b**	Ph	Ph	**3b**	75
3	**1c**	Ph	4-MeOC_6H_4	**3c**	76
4	**1d**	Ph	3-FC_6H_4	**3d**	80
5	**1e**	Ph	3-Th	**3e**	74
6[c]	**1f**	Ph	*c*-C_3H_5	**3f**	84
7	**1g**	4-MeC_6H_4	4-MeC_6H_4	**3g**	86
8	**1h**	4-MeC_6H_4	*n*-Bu	**3h**	81
9	**1i**	Ph	*n*-Bu	**3i**	78
10[d]	**1j**	Ph	$(CH_2)_3CN$	**3j**	80

[a]Reaction conditions: **1** (0.2 mmol), $AuPPh_3NTf_2$ (3 mol %), DCE (0.8 mL), 80 °C, 2−3 h. [b]Yield of isolated product referred to starting product **1**. [c]Reaction time: 15 h. [d]Carried out in the presence of additional DNBSA (10 mol %).

Next, we decided to check the reactivity of *o*-(alkynyl)-styrenes **1k−n**, having two different aryl groups in the olefin, in order to explore the selectivity of the formal [4 + 1] cycloaddition.[16] Gratifyingly, we found that all reactions were highly selective, yielding as the major product the one coming from the nucleophilic attack of the more electron-rich aryl group, as expected (Table 3). Noteworthy, complete selectivity was achieved when *o*-(alkynyl)styrene **1n**, having a highly electron-rich group, was used as starting material. Nevertheless, even substrates with less prominent electronic differences (Ph vs 4-ClC_6H_4 or Ph vs 4-MeOC_6H_4) lead to notable high selectivities (∼10:1).

Table 3. Synthesis of Dihydroindenes 3k−n from *o*-(Alkynyl)styrenes 1k−n Bearing Different Aryl Substituents

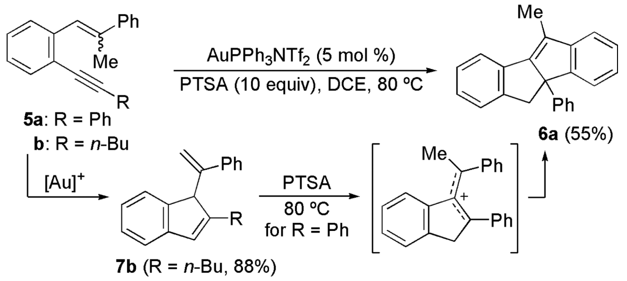


entry	1	Ar[1]	Ar[2]	product	ratio[a]	yield[b] (%)
1	**1k**	4-ClC_6H_4	Ph	**3k** + **3k′**	10:1	73
2	**1l**	4-FC_6H_4	4-MeOC_6H_4	**3l** + **3l′**	12:1	86
3	**1m**	Ph	4-MeOC_6H_4	**3m** + **3m′**	10:1	74
4	**1n**	Ph	3,4,5-$(MeO)_3C_6H_2$	**3n**	–	82

[a]Determined by ^1H NMR analysis of the crude reaction mixture. [b]Yield of isolated mixture of products **3** and **3′** referred to starting *o*-(alkynyl)styrene **1**.

Finally, we wondered if *o*-(alkynyl)styrenes **5** having an alkyl and an aryl group as *β*-substituents of the olefin would allow the preparation of dihydroindeno[2,1-*a*]indenes **6** with an alkyl substituent at position 10. Although first assays provided only indenes **7** even when the reaction was heated to 80 °C,[5a] we determined that the formal [4 + 1] cycloadduct **6a** could be prepared with moderate yield in one step using a Brønsted acid as an additive (Scheme 5). However, if the alkyne substituent is not aromatic, such as in **5b**, the second cyclization is disfavored and only the corresponding indene **7b** is obtained.

Scheme 5. [4 + 1] Formal Cycloaddition of *β*-Alkyl, *β*-Aryl-Substituted *o*-(Alkynyl)styrene 5a



In summary, we have shown that *β*,*β*-diaryl-*o*-(alkynyl)-styrenes cycloisomerize under gold(I) catalysis giving rise selectively to benzofulvenes at 0 °C and to dihydroindeno[2,1-*a*]indenes at 80 °C. The formation of these tetracycles implies a formal [4 + 1] cycloaddition and proceeds through a cascade 5-*endo*-cyclization−diene activation−*iso*-Nazarov (Friedel−Crafts) cyclization. These compounds were obtained with high yields and with a variety of substituents, including a quaternary center at the ring junction and aryl or alkyl groups at the C-10 position. These results further demonstrate the usefulness of gold(I)-catalyzed cycloisomerizations of *o*-(alkynyl)styrene derivatives in the selective synthesis of polycyclic compounds.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b00191.

Full experimental procedures, characterization data, and copies of NMR spectra (PDF)

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We are grateful to the Junta de Castilla y León (BU237U13) and Ministerio de Economía y Competitividad (MINECO) and FEDER (CTQ2013-48937-C2-1-P) for financial support. A.M.S. and C.V. thank Junta de Castilla y León (Consejería de Educación) and Fondo Social Europeo and Universidad de Burgos, respectively, for predoctoral contracts. P. G.-G. thanks MINECO for a "Ramón y Cajal" contract.

■ REFERENCES

(1) For representative recent reviews, see: (a) Xie, J.; Pan, C.; Abdukader, A.; Zhu, C. *Chem. Soc. Rev.* **2014**, *43*, 5245−5256. (b) Fensterbank, L.; Malacria, M. *Acc. Chem. Res.* **2014**, *47*, 953−965. (c) Hashmi, A. S. K. *Acc. Chem. Res.* **2014**, *47*, 864−876. (d) Fürstner, A. *Acc. Chem. Res.* **2014**, *47*, 925−938. (e) Hashmi, A. S. K.; Toste, F. D. *Modern Gold Catalyzed Synthesis*; Wiley-VCH: Weinheim, 2012.

(2) For a comprehensive review on activation of alkynes by gold(I) catalysts, see: Dorel, R.; Echavarren, A. M. *Chem. Rev.* **2015**, *115*, 9028−9072.

(3) For selected revisions, see: (a) Obradors, C.; Echavarren, A. M. *Acc. Chem. Res.* **2014**, *47*, 902−912. (b) Aubert, C.; Fensterbank, L.; García, P.; Malacria, M.; Simonneau, A. *Chem. Rev.* **2011**, *111*, 1954−1993. (c) Hashmi, A. S. K. *Pure Appl. Chem.* **2010**, *82*, 1517−1528. (d) Michelet, V.; Toullec, P. Y.; Genêt, J.-P. *Angew. Chem., Int. Ed.* **2008**, *47*, 4268−4315. (e) Jiménez-Núñez, E.; Echavarren, A. M. *Chem. Rev.* **2008**, *108*, 3326−3350. For leading references on the cycloisomerization of 1,5-enynes, see: (f) Gagosz, F. *Org. Lett.* **2005**, *7*, 4129−4132. (g) Zhang, L.; Kozmin, S. A. *J. Am. Chem. Soc.* **2004**, *126*, 11806−11807. (h) Luzung, M. R.; Markham, J. P.; Toste, F. D. *J. Am. Chem. Soc.* **2004**, *126*, 10858−10859. (i) Mamane, V.; Gress, T.; Krause, H.; Fürstner, A. *J. Am. Chem. Soc.* **2004**, *126*, 8654−8655.

(4) (a) Barluenga, J.; Fernández-Rodríguez, M. A.; García-García, P.; Aguilar, E. *J. Am. Chem. Soc.* **2008**, *130*, 2764−2765. (b) García-García, P.; Fernández-Rodríguez, M. A.; Aguilar, E. *Angew. Chem., Int. Ed.* **2009**, *48*, 5534−5537. (c) García-García, P.; Martínez, A.; Sanjuán, A. M.; Fernández-Rodríguez, M. A.; Sanz, R. *Org. Lett.* **2011**, *13*, 4970−4973. (d) Sanjuán, A. M.; García-García, P.; Fernández-Rodríguez, M. A.; Sanz, R. *Adv. Synth. Catal.* **2013**, *355*, 1955−1962.

(5) (a) Martínez, A.; García-García, P.; Fernández-Rodríguez, M. A.; Rodríguez, F.; Sanz, R. *Angew. Chem., Int. Ed.* **2010**, *49*, 4633−4637. (b) García-García, P.; Rashid, M. A.; Sanjuán, A. M.; Fernández-Rodríguez, M. A.; Sanz, R. *Org. Lett.* **2012**, *14*, 4778−4781. (c) Sanjuán, A. M.; Rashid, M. A.; García-García, P.; Martínez-Cuezva, A.; Fernández-Rodríguez, M. A.; Rodríguez, F.; Sanz, R. *Chem. - Eur. J.* **2015**, *21*, 3042−3052.

(6) (a) López-Carrillo, V.; Huguet, N.; Mosquera, A.; Echavarren, A. M. *Chem. - Eur. J.* **2011**, *17*, 10972−10978. (b) Dorel, R.; Echavarren, A. M. *J. Org. Chem.* **2015**, *80*, 7321−7332. For reviews about the nature of proposed intermediates in gold catalysis, see: (c) Hashmi, A. S. K. *Angew. Chem., Int. Ed.* **2010**, *49*, 5232−5241. (d) Obradors, C.; Echavarren, A. M. *Chem. Commun.* **2014**, *50*, 16−28.

(7) For a recent revision on gold-catalyzed cycloaddition reactions: Muratore, M. E.; Homs, A.; Obradors, C.; Echavarren, A. M. *Chem. - Asian J.* **2014**, *9*, 3066−3082.

(8) CCDC-1429680 contains the supplementary crystallographic data for **3a**. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

(9) See Supporting Information for complete details.

(10) For a previous example of activation of conjugated dienes by gold(I) catalysts, see: Kanno, O.; Kuriyama, W.; Wang, Z. J.; Toste, F. D. *Angew. Chem., Int. Ed.* **2011**, *50*, 9919−9922.

(11) (a) Zhang, X.; Teo, W. T.; Rao, W.; Ma, D.-L.; Leung, C.-H.; Chan, P. W. H. *Tetrahedron Lett.* **2014**, *55*, 3881−3884. (b) Strom, K. R.; Impastato, A. C.; Moy, K. J.; Landreth, A. J.; Snyder, J. K. *Org. Lett.* **2015**, *17*, 2126−2129.

(12) For selected examples of synthesis of benzofulvenes, see: (a) Dyker, G.; Borowski, S.; Henkel, G.; Kellner, A.; Dix, I.; Jones, P. G. *Tetrahedron Lett.* **2000**, *41*, 8259−8262. (b) Chen, W.; Cao, J.; Huang, X. *Org. Lett.* **2008**, *10*, 5537−5540. (c) Ye, S.; Yang, X.; Wu, J. *Chem. Commun.* **2010**, *46*, 2950−2952. (d) Li, D.-Y.; Wei, Y.; Shi, M. *Chem. - Eur. J.* **2013**, *19*, 15682−15688. (e) Martinelli, C.; Cardone, A.; Pinto, V.; Talamo, M. M.; D'arienzo, M. L.; Mesto, E.; Schingaro, E.; Scordari, F.; Naso, F.; Musio, R.; Farinola, G. M. *Org. Lett.* **2014**, *16*, 3424−3427. (f) Xiao, Q.; Zhu, H.; Li, G.; Chen, Z. *Adv. Synth. Catal.* **2014**, *356*, 3809−3815. (g) Álvarez, E.; Nieto Faza, O.; Silva López, C.; Fernández-Rodríguez, M. A.; Sanz, R. *Chem. - Eur. J.* **2015**, *21*, 12889−12893.

(13) Only a few particular examples of dihydroindeno[2,1-*a*]indenes having a quaternary center at the ring junction have been described in the literature, and they were generally obtained by low yielding procedures: (a) Ten Hoeve, W.; Wynberg, H. *J. Org. Chem.* **1980**, *45*, 2930−2937. (b) Shim, S. C.; Chae, J. S.; Choi, J. H. *J. Org. Chem.* **1983**, *48*, 417−421. (c) Kuck, D.; Eckrich, R.; Tellenbröker, J. *J. Org. Chem.* **1994**, *59*, 2511−2515.

(14) Hopf, H. *Angew. Chem., Int. Ed.* **2013**, *52*, 12224−12226.

(15) In the cycloisomerization of **1j**, addition of catalytic amounts of DNBSA to the reaction media proved necessary to promote the second cyclization step. The corresponding benzofulvene **2j** was obtained otherwise even at 80 °C.

(16) *o*-(Alkynyl)styrenes **1k,l** reacted at 0 °C to yield the corresponding benzofulvenes **2k,l** in good yields and as ca. 1:1 mixtures of geometrical isomers. On the other hand, **1m,n** gave rise to **3m,n** even at 0 °C.