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Gold Sulfinyl Mesoionic Carbenes: Synthesis, Structure, and Catalytic Activity

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Supporting Information

ABSTRACT: Gold mesoionic carbenes having a chiral sulfoxide group attached to the C4 position of the five membered ring have been prepared and tested as catalysts in the cycloisomerization of enynes. These new catalysts are very efficient, with the sulfoxide moiety playing a key role in their activity and the *N*1-substituent in control of the regioselectivity of these processes.

In 2008, 1,2,3-triazole carbene complexes were unveiled by Albrecht,[1] initiating a lightning race in the preparation of new structural types and their use as catalysts.[2] The synthesis of this type of heterocycle is performed through the highly efficient and regioselective Cu(I)-catalyzed Huisgen cycloaddition between a terminal alkyne and an azide (CuAAC).[3] A large number of functional groups with different electronic and steric properties are compatible providing a high tunability of the electronic properties of the carbenes. These new features could be transferred to the coordinating metal center with the aim of seeking novel applications.[4] New groups can be introduced in the core of the heterocycle through the terminal alkyne, the azide, or both, which could also be accompanied by chirality, should the functional group of the alkyne be chiral or the azide contain a chiral center.

Sulfoxides have emerged as a paramount alternative among the scarce chiral functional groups based on elements different from chiral-carbon groups.[5] In fact, enantiopure ethynyl sulfoxides are, in general, easy to make through the Andersen method, which involves the reaction between acetylenic Grignard reagents and enantiopure menthyl sulfinate.[6] The incorporation of an enantiomerically pure sulfoxide moiety in a 1,2,3-triazolylidene carbene could present some uncertainties. First, the chirality of the sulfoxide center introduced through the alkyne must be preserved along the synthetic pathway. The second challenge would arise in the alkylation of the triazole to yield the corresponding triazolium salts since the compatibility of the sulfoxide group with strong alkylating agents is not obvious.[7] Deprotonation of the salt using Ag_2O followed by transmetalation with a metal source could yield the enantiopure (*S*)-sulfoxide carbene complexes. The coordinating nature of the sulfoxide would compete with the emerging carbene in another conceivable problem in the achievement of the metal complexes.

Sulfur based ligands can be present in hybrid *N*-heterocyclic carbenes (NHC).[8] Nevertheless, there are few examples of sulfoxide containing Arduengo type carbenes in the literature and, to the best of our knowledge, none in which the sulfoxide group is directly attached to one of the carbons of the heterocycle. Tato and Cárdenas[9] reported the synthesis of an imidazolylidene by alkylating a racemic sulfinyl bromide with different 1-substituted imidazoles to prepare mono- and binuclear Pd-complexes.[10] Previously, Huynh et al. had reported a bridged Pd-bis(imidazolylidene) complex containing a racemic sulfoxide ligand building the sulfoxide moiety by oxidation of a bis(imidazolesulfide).[11] These Pd-derivatives were active as catalysts in the C−H activation of arenes and in the Heck reaction, respectively.

Herein we describe the first examples of the synthesis of a new class of mesoionic triazolylidene ligands containing enantiopure (*S*)-sulfoxides, the preparation of the corresponding gold complexes, the determination of their structures, and their catalytic activity in the cycloisomerization reaction of enynes.

Alkynyl sulfoxides **1a**−**c** were reacted with azides **2a**−**e** under the usual conditions (1.20 equiv of organic azide, 1.00 equiv of alkyne, 0.50 equiv of sodium L-ascorbate and 0.25 equiv of $CuSO_4 \cdot 5H_2O$ in DMF) yielding enantiomerically pure triazoles **3** in good to excellent yields. Moreover, to confirm that the CuAAC reaction proceeds without racemization of the sulfoxide, a secondary chiral group was introduced through

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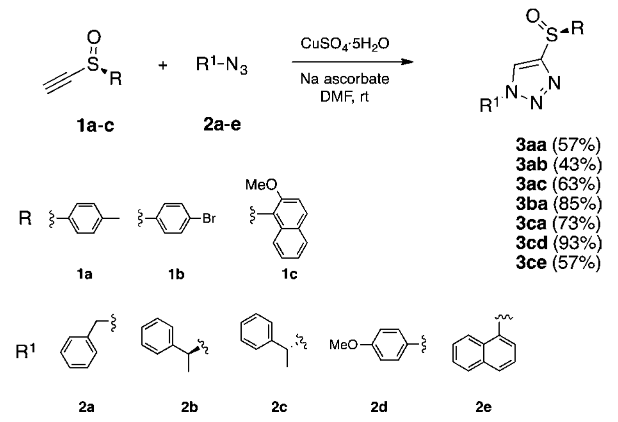
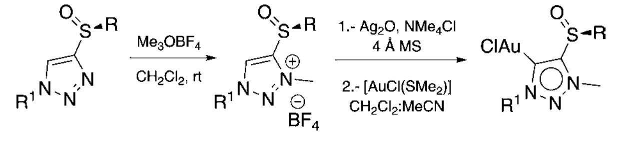
the enantiopure *α*-phenylethyl azides **2b** and **2c**. The formation of only one diastereoisomer (**3ab** and **3ac**) proved the selectivity of the cycloaddition (Scheme 1). (*R*)-1-Bromo-4-(ethynylsulfinyl)benzene **1b** was reacted with benzyl azide **2a** to form triazole **3ba** in excellent yield. The bulkier (*R*)-1-(ethynylsulfinyl)-8-methoxynaphthalene derivative **1c** reacted with benzyl azide **2a**, 4-methoxyphenyl azide **2d**, and 1-naphthyl azide **2e** uneventfully rendering triazoles **3ca**, **3cd**, and **3ce** in good yields. Therefore, the synthesis of triazoles **3** is compatible with alkyl and aryl azides as well as with differently substituted sulfoxides.

Scheme 1. Synthesis of 1,2,3-Triazoles 3



To our delight, triazoles **3** were methylated (Me_3OBF_4) yielding the *N*-3-methyltriazolium salts **4** in essentially quantitative yields.[12] Finally, the triazolium salts (1.00 equiv) were reacted with 0.75 equiv of Ag_2O in the presence of 1.50 equiv of NMe_4Cl. The complete formation of the intermediate silver carbene complexes was ensured by ^1H NMR analysis. Transmetalation with [AuCl(SMe_2)] gave the corresponding (*S*)-sulfinyl gold carbenes **5** that were isolated and fully characterized (Scheme 2).

Scheme 2. Synthesis of Gold Carbenes 5



3aa	**4aa** (98%)	**5aa** (98%)
3ab	**4ab** (91%)	**5ab** (87%)
3ac	**4ac** (85%)	**5ac** (79%)
3ba	**4ba** (89%)	**5ba** (69%)
3ca	**4ca** (quantitative)	**5ca** (87%)
3cd	**4cd** (96%)	**5cd** (91%)
3ce	**4ce** (quantitative)	**5ce** (87%)

The structures proposed above were confirmed by NMR analysis. A remarkable deshielding of the triazole proton signal ($\Delta\delta$ = 0.66 and 0.86 ppm) upon formation of the triazolium salts is observed.[13] This signal disappears as a consequence of formation of the silver and the subsequent gold carbenes. For ^{13}C NMR spectra, signals corresponding to the CH of triazolium salts appear at lower field (δc 130.2−132.3 ppm) compared with those of the corresponding triazoles (δc 122.7−127.3 ppm). The new C−Au bonds formed appear between δc 157.5−162.3 ppm, which is in agreement with other gold carbenes previously reported.[2c,d,14]

The HRMS spectra show a peak at *m*/*z* $[M - Cl^-]^+$, which is consistent with the gold carbene structures proposed. The structures of some gold complexes (**5aa**, **5ab**, **5ac**, and **5ca**) were unambiguously confirmed by X-ray diffraction analysis (Figure 1).

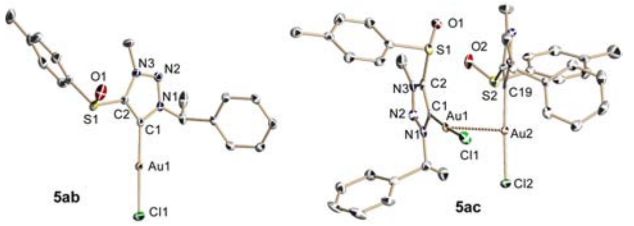
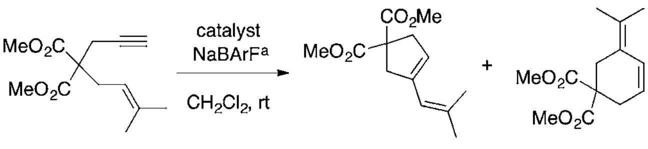


Figure 1. Molecular structures of **5ab** and **5ac** in the solid state depicted at a 50% thermal ellipsoid level.

The gold-cations in **5ab** and **5ac** show typical nearly perfect linear geometries for gold(I) with C−Au−Cl angles between 175° and 177°. All Au−C distances (1.980 to 1.991 Å) and Au−Cl distances (2.272 to 2.282 Å) lie in normal ranges for NHC−Au−Cl complexes. A gold(I)−gold(I) distance of 3.223 Å in the case of **5ac** reflects unsupported strong aurophilic interactions in the solid state. The two involved C−Au−Cl units show a crossed arrangement with a C−Au−Au−C torsion angle of 66.5°.

With the synthesis of structurally diverse enantiopure mesoionic gold carbene complexes **5** confirmed, their catalytic activity was next tested. Mesoionic gold carbenes have been applied as effective catalysts in a limited number of processes and that prompted us to explore the cycloisomerization of enynes.[15] Complex **5aa** was chosen, as well as the more sterically hindered at *N*1 **5ab** and its diastereoisomer **5ac**. Thus, enyne **6** was reacted with complexes **5aa**, **5ab**, and **5ac** using 3 mol % complex in the presence of 3 mol % NaBArF (Table 1, entries 1−3). The reaction carried out using complex **5aa** afforded a mixture of **7** and **8** (1:1.4) along with unreacted material after 24 h (22% conversion) (Table 1, entry 1). Interestingly, complex **5ab** reacted with **6** in only 5 min producing exclusively cyclopentene **7** (Table 1, entry 2). An

Table 1. Optimization of Catalytic Conditions for the Reaction of Enyne 6



6 **7** **8**

entry	complex	complex load (mol %)	product	time	conversion (%)
1	**5aa**	3	**7**/**8** (1:1.4)	24 h	22
2	**5ab**	3	**7**	5 min	100
3	**5ac**	3	**7**	1 min	100
4	**5ab**	1	**7**	60 min	100
5	**5ac**	1	**7**/**8** (1:1)	24 h	91
6	**9b**	3		24 h	[c]
7	**9c**	3		24 h	[c]
8				24 h	[c]

[a] NaBArF load was used in a 1:1 proportion to complex. [b] Conversion was calculated measuring ^1H NMR spectra of the crude. [c] No reaction.

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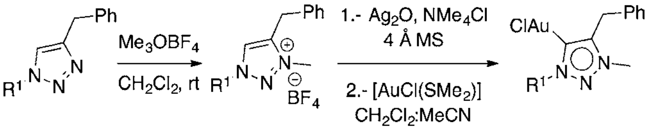
analogous result was obtained with complex **5ac** (Table 1, entry 3).

Apparently, complex **5aa** having a sulfoxide and a benzyl group attached to *N*1 is not as efficient as complexes **5ab** or **5ac** in either conversion or controlling the reaction regioselectivity. To determine the origin of this effect, complexes **9b** and **9c** lacking the sulfoxide group were prepared from benzylacetylene and enantiomerically pure azides **2b** and **2c**, as described above (Scheme 3).

Scheme 3. Synthesis of Gold Carbenes 9a and 9b



11b (88%)
11c (80%)

12b (83%)
12c (90%)

9b (76%)
9c (62%)

Complexes **9b** and **9c** were then used as complexes in the cycloisomerization of **6** (Table 1, entries 6–7). No reaction was observed after 24 h under identical conditions to those used for **5ab** and **5ac**. Clearly, the sulfoxide moiety is required for the reaction, while the presence of both the sulfoxide and the α-phenylethyl groups in the gold carbene complex is required to achieve good conversions and complete regioselectivities.

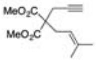
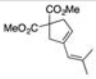
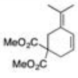
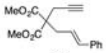
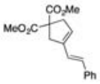
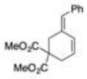
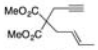
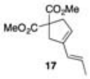
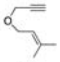
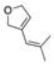
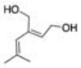
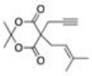
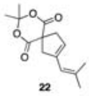
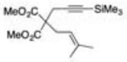
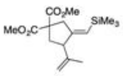
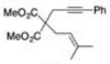
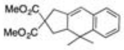
Lower catalyst loads were tested for **5ab** and **5ac** (Table 1, entries 4–5). The use of 1 mol % of **5ab** promotes the complete conversion of **6** to form **7** in 1 h, while 1 mol % of **5ac** produces a partial transformation of the starting material to a mixture of **7** and **8**.

Since the ability of silver catalysts to promote cycloisomerization reactions is known,[16] enyne **6** was reacted using the silver carbene obtained from triazolium salt **4ac** under conditions already described.[17] No reaction was observed after 24 h, recovering unaltered enyne **6** (Table 1, entry 8).

After determining the optimum catalyst, the effect of the structure of the enyne in the outcome of the reaction was next addresed. Enynes **6**, **13**, and **16** having a terminal alkyne and a monosubstituted or disubstituted alkene nicely cyclized to the five-membered derivatives in high yields (Table 2, entries 1–3). It is worth noting that compound **18** lacking the Thorpe–Ingold effect imposed by the methoxycarbonyl groups in **6**, **13**, and **16** formed the five membered derivative **19** together with diol **20** arising from the opening of the dihydrofuran ring in a quantitative combined yield (3:1 mixture, Table 2, entry 4). Meldrum's acid derivative **21** formed spirane **22** in a respectable 50% yield (Table 2, entry 5). In contrast, substitution of the terminal acetylenic hydrogen (compounds **23** and **25**) inhibits the reaction.

Despite of the efforts devoted to this cycloisomerization, issues such as the 5-exo/6-endo selectivity still deserve attention.[15c] Remarkably, our results point to a crucial effect of the sulfoxide moiety in determining the activity of the complex, while the bulkiness of the N-substituent (contributed by the azide) is involved in the 5-exo vs 6-endo selectivity. The lack of reactivity of substituted alkyne derivatives **23** and **25** proves that at least in the first reaction step, formation of gold carbene complexes **I** (5-exo cyclization) and **II** (6-endo cyclization) should occur through the standard triple-bond coordination by the gold complex followed by cyclization (Scheme 4). The role of the sulfoxide at this point seems to be a mere spectator. However, the inability of complexes **9b** and **9c** to promote the cyclization questions this assertion.

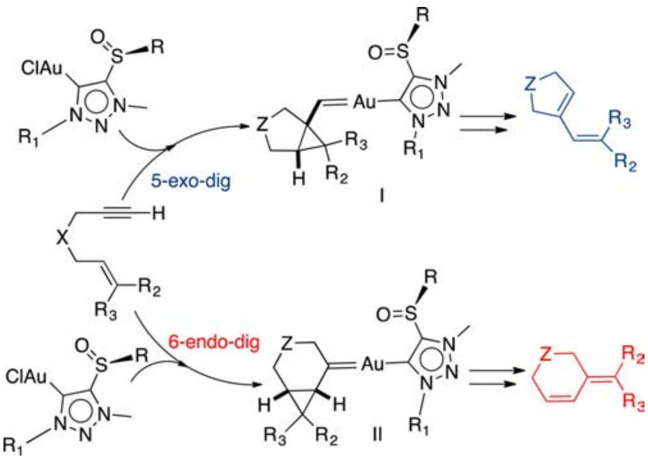
Table 2. Gold Carbene 5ab Catalyzed Cycloisomerization of Enyne 6

entry	substrate	products	time	yield (%)[a]
1	 **6**	 **7**  **8**	10 min	100 (**8** traces)
2	 **13**	 **14**  **15**	60 min	89 (5:1)
3	 **16**	 **17**	60 min	86[b]
4	 **18**	 **19**  **20**	1 min	100 (3:1)
5	 **21**	 **22**	180 min	50
6	 **23**	 **24**	24 h	no reaction
7	 **25**	 **26**	24 h	no reaction

[a] Isolated products. [b] *E*/*Z*, 5:1.

Results above pointed to the involvement of the sulfoxide oxygen to stabilize gold carbene intermediates **I** and **II** probably by interaction either of the oxygen or the sulfur lone pair with the carbene carbon or the gold center.[18] This stabilization should allow the reaction to proceed, thence the inertia of complexes lacking the sulfoxide moiety. Intermediates **I** and **II**

Scheme 4. Mechanistic Hypothesis



will evolve to the cyclized products through the well-established pathways (Scheme 4).[19] Formation of intermediate **I** over **II** is related to the bulkiness of the carbon linked to *N*1 position (compare **5aa** with **5ab** or **5ac** in Table 1). Although much experimental and computational work remains to be done, this working hypothesis is congruent with the results obtained and confers to the apparently ancillary moiety (the sulfoxide group) a key role unprecedented in the literature.

To conclude, the synthesis of new homochiral *C*-4-sulfinyl triazole derivatives using the CuAAC is reported. These functionalized triazoles are transformed uneventfully into gold mesoionic carbenes, fully characterized spectroscopically and by X-ray analysis, by standard methods. Their ability as cycloisomerization catalysts has been studied finding that their catalytic activity is due to the presence of the sulfoxide group acting in a previously unreported fashion. Moreover, the high degree of 5-exo-dig selectivity in these processes is attributed to the bulkiness of the substituent at the *N*-1-triazole ring.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b01555.

Experimental procedures and ^{1}H and ^{13}C spectra for all the compounds and experimental data for the catalytic tests (PDF)
Crystallographic information for compound **5aa** (CIF)
Crystallographic information for compound **5ab** (CIF)
Crystallographic information for compound **5ac** (CIF)
Crystallographic information for compound **5ca** (CIF)

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Notes

The authors declare no competing financial interest.

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