Gold Catalysis

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Gold(I)-Catalyzed Synthesis of Benzoxocines by an 8-*endo*-dig Cyclization**

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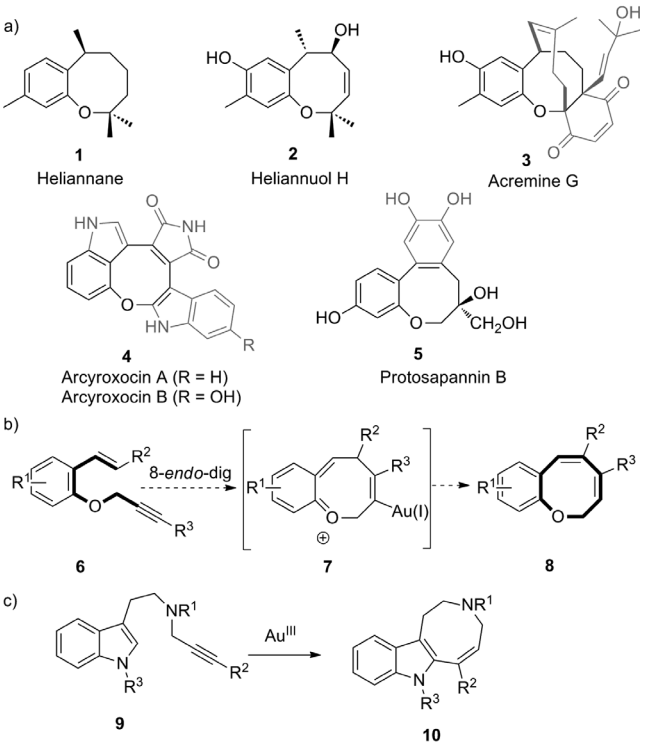
The activation of alkynes by organogold catalysts has emerged as a powerful method for the efficient synthesis of carbo- and heterocycles, including scarcely accessible ring systems.[1–9] Unsaturated benzoxocine ring systems occur in numerous bioactive natural products, in particular the heliannane family of cyclic ethers,[10–15] (Scheme 1a) and have been synthesized by different methods.[16–18] Given the strong interest in this natural product class,[19,20] we envisioned that an efficient and flexible synthetic route to 2*H*-1-benzoxocines **8** could be developed based on a gold-catalyzed 8-*endo*-dig cyclization of readily accessible *o*-propargyloxy styrenes **6** (Scheme 1b).

We anticipated that for 1,7-enynes **6** the regiospecific addition of the olefin to the alkyne, that is, an 8-*endo*-dig cyclization, might be favored because of the formation of a stable carbocationic intermediate **7**. Alternatively, a seven-membered benzoxepine ring could form through a 7-*exo*-dig cyclization.[21]

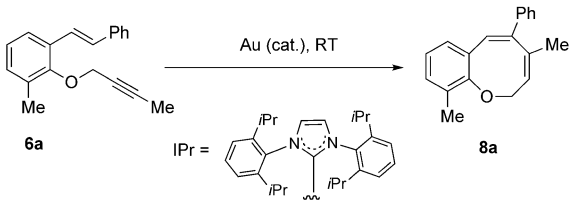
Gold-catalyzed 8-*endo*-dig cyclizations have rarely been observed. Echavarren and Ferrer reported a gold(III)-catalyzed *endo*-dig hydroarylation of indole substrates **9** (Scheme 1c).[22] However, mechanistically these products most likely arise from a 7-*endo* cyclization[23,24] with a subsequent 1,2-shift and isomerization.[25] The same group also reported that 1,7-enynes, which can be considered analogous to propargyl ethers **6**, undergo cyclization by an *exo* pathway followed by rearrangement of the cyclopropyl intermediate to a diene.[26] Herein, we report the gold-catalyzed 8-*endo*-dig cyclization of *o*-propargyloxy styrenes to yield functionalized 2*H*-1-benzo[*b*]oxocines, and the mechanism of this novel catalytic cyclization.

In light of the successful 8-*endo*-dig hydroarylation catalyzed by gold(III) (Scheme 1c),[22] we explored whether such catalysts would also induce the formation of 2*H*-benzo[*b*]oxocine **8a** from propargyl ether **6a** (Table 1).



Scheme 1. a) Natural products containing benzoxocine rings. b) Gold-catalyzed synthesis of benzoxocines by an 8-*endo*-dig cyclization; c) Gold(III)-catalyzed synthesis of indoles with annulated eight-membered rings.

Table 1:



Entry	Catalyst (mol%)	Solvent	*t*	Yield [%] **8a**[a]
1	$[Au(SMe_2)Cl]/AgSbF_6$ (10)	DCE	18 h	–
2	$[Au(PPh_3)Cl]/AgSbF_6$ (10)	THF or MeCN	18 h	–
3	$[Au(PPh_3)Cl]/AgSbF_6$ (10)	DCE	5 min	61
4	$[Au(PPh_3)Cl]/AgSbF_6$ (5)	DCE	25 min	58
5	$[Au(PMe_3)Cl]/AgSbF_6$ (10)	DCE	30 min	52
6	[AuIPrCl]/$AgSbF_6$ (5)	DCE	50 min	75
7	[AuIPrCl]/$AgSbF_6$ (10)	DCE	25 min	76

[a] Yields determined by GC analysis using *n*-octadecane as internal standard. DCE = 1,2-dichloroethane, THF = tetrahydrofuran.

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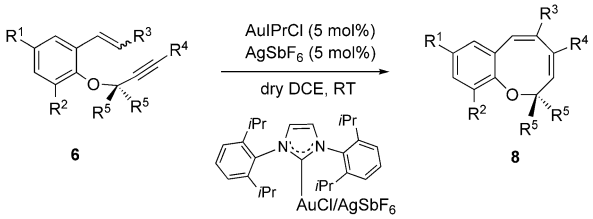
However, neither in the presence of $AuBr_3$, $AuBr_3/AgBF_4$, nor $AuCl_3/AgSbF_6$ in dichloromethane or dichloroethane was any product formation observed.

Accordingly, we turned to gold(I) salts. While $[Au(SMe)_2Cl]/AgSbF_6$ did not induce product formation (Table 1, entry 1), the cationic complexes generated in situ from $[Au(PR_3)Cl]$ and $AgSbF_4$ in dichloroethane (but not in acetonitrile) led to the smooth formation of the desired ether with an eight-membered ring, at room temperature (Table 1, entries 2–5). The use of the more nucleophilic PMe_3 instead of PPh_3 did not increase the yield (Table 1, entries 3 and 5). $AgSbF_6$ alone and Lewis acids $BF_3{\cdot}OEt_2$ and $TiCl_4$, in up to equimolar amounts, did not catalyze the cyclization, thus indicating a gold-specific catalysis. Finally, the use of a cationic gold complex **11** ([AuIPrCl]/$AgSbF_6$) with an N-heterocyclic carbene ligand with relatively low electrophilicity gave the best results and gave the benzoxocines in yields up to 76% (Table 1, entries 6 and 7).[27,28]

With these reaction conditions established the scope of the gold-catalyzed synthesis of functionalized benzoxocines, eight-membered-ring ethers, was explored and the substituents on the alkyne, the olefin, and the aromatic ring were varied (Table 2). Different substituents on the terminal carbon atom of the alkyne were well tolerated and the benzoxocines were obtained in moderate to high yield (Table 2, entries 1–4). Similarly substituents R^1 and R^2 on the aromatic ring could be changed considerably (Table 2, entries 3–7).

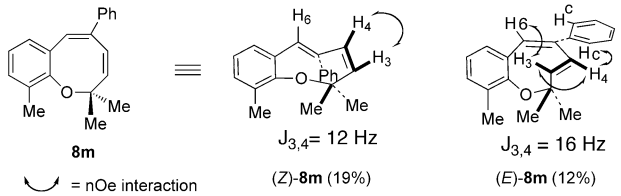
Table 2:



Entry	R^1	R^2	R^3	R^4	R^5	*t*	**8**	Yield [%][a]
1	H	Me	Ph	Me	H	30 min	**8a**	60
2	H	Me	Ph	H	H	30 min	**8b**	72[b]
3	H	Me	Ph	Ph	H	1 h	**8c**	47[b]
4	H	Br	Ph	Et	H	50 min	**8d**	55
5	H	OMe	Ph	H	H	2 h	**8e**	56
6	Cl	Me	Ph	Et	H	1 h	**8f**	62
7	H	Br	Ph	H	H	1.5 h	**8g**	55
8	H	Me	4-$NO_2C_6H_4$	H	H	50 min	**8h**	69
9	H	Me	4-$CO_2MeC_6H_4$	H	H	50 min	**8i**	53
10	H	Me	Me	Me	H	2 h	**8j**	47[b]
11	H	Me	H	Et	H	50 min	**8k**	41[c]
12	H	Me	CO_2Et	H	H	28 h	**8l**	29
13	H	Me	Ph	H	Me	1 h	**8m**	31[b]

[a] Yields of the isolated products. [b] *Z* and *E* diastereomers were formed in the ratio 2:3 to 3:4; for details of the isolation and characterization of these isomers see the Supporting Information. [c] Yield determined by GC analysis using *n*-octadecane as internal standard.[29]

In several cases the newly formed *E*- and *Z*-configured olefins could be isolated and separated. In the reactions employing terminal acetylene, the two diastereomeric forms could be easily identified by their corresponding olefinic *cis* and *trans* coupling constants, as depicted for benzoxocine **8m** in Scheme 2.[30,31] The nOe interactions observed in the two



Scheme 2. Structural assignment of (*Z*)- and (*E*)-benzoxocine **8m**.

isomers further supported the structural assignments (Scheme 2, for detailed analysis see the Supporting Information). Palladium-catalyzed hydrogenation of the different diastereomers resulted in identical tetrahydro-2*H*-benzo[*b*]-oxocines (see Scheme 5 and the Supporting Information).

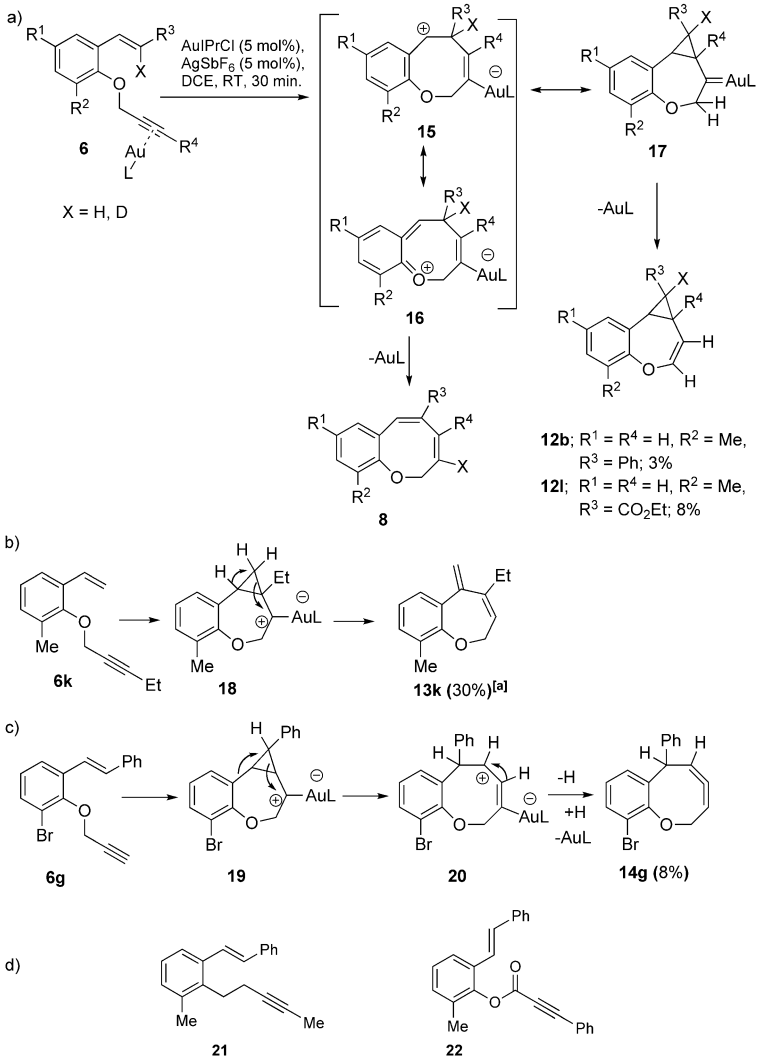
With the assumption that the decisive step of the cyclization might include nucleophilic attack of the olefin on the alkyne activated by the gold catalyst, the substituent on the alkene was varied (Table 2, entries 7–12). Introduction of aryl groups with electron-withdrawing substituents led to product formation in respectable yields (Table 2, entries 8 and 9), whereas introduction of electron-donating methoxy groups induced the formation of a different product (see Scheme 4).

Introduction of a terminal methyl group or, even more pronounced, an electron-withdrawing ester on the olefin led to a reduced reaction rate (Table 2, entries 10 and 12). In the absence of any substituent on the olefin (**6k**), an additional product was formed (Scheme 3b).

To mimic the substitution pattern of naturally occurring heliannanes, dimethyl-substituted *o*-propargyloxy-β-phenylstyrene **6m** was employed in the gold-catalyzed cyclization to yield the benzoxocine **8m** in 31% yield (Table 2, entry 13).

The formation of several minor products and unexpected cyclization products, as well as the investigation of additional custom-made potential cyclization precursors allowed us to gain insight into the mechanism of the gold-catalyzed cyclization reaction. Cyclopropane-fused benzoxocines **12** (Scheme 3a) were isolated from the reaction mixtures, and, in addition, the formation of cyclopropanes was routinely detected in the crude reaction mixtures by means of NMR spectroscopy. Attempts to convert cyclopropane **12b** into the corresponding benzoxocine (**8b**) did not result in product formation even after prolonged treatment with gold(I) complexes.

Cyclization substrate **6k** having a terminal olefin yielded benzoxepine **13k** in addition to the desired benzoxocine (Scheme 3b), and bromo-substituted cyclization precursor **6g** delivered the side product benzoxocine **14g** with an allene incorporated in the eight-membered ring (Scheme 3c). The



Scheme 3. a) Mechanistic proposal for the formation of benzoxocines **8** and cyclopropyl oxepenes **12** and b,c) other side products. d) Substrates that do not yield any benzoxocine or other rings under gold catalysis. [a] Yield determined by GC analysis.

cyclic allene structure was corroborated by the characteristic allenic carbon signals in the ^{13}C NMR spectrum ($\delta = 208.7$, 90.4, 90.0 ppm) and a highly characteristic IR signal at 1954 cm^{-1} for allene stretching.[32,33] To obtain **14g** an apparent 1,2-shift of the aryl group has occurred.

The formation of compounds **12** suggests a cationic intermediate may have been formed and that this intermediate can either lead to the formation of the desired 8-membered cyclic ethers, or undergo ring closure to give a cyclopropane ring, and then undergo protodeauration (Scheme 3a). In this case, gold(I) could coordinate to the alkyne, thus promoting cyclization and inducing the formation of benzylic cation **15**. The cation is stabilized by the electron-donating influence of the ether oxygen atom which also promotes the cyclization. Cation **16** can then either collapse to benzoxocine **8** or alternatively cyclopropane-substituted gold intermediate **17** may be generated and upon protodeauration this intermediate can yield benzoxepines **12**.

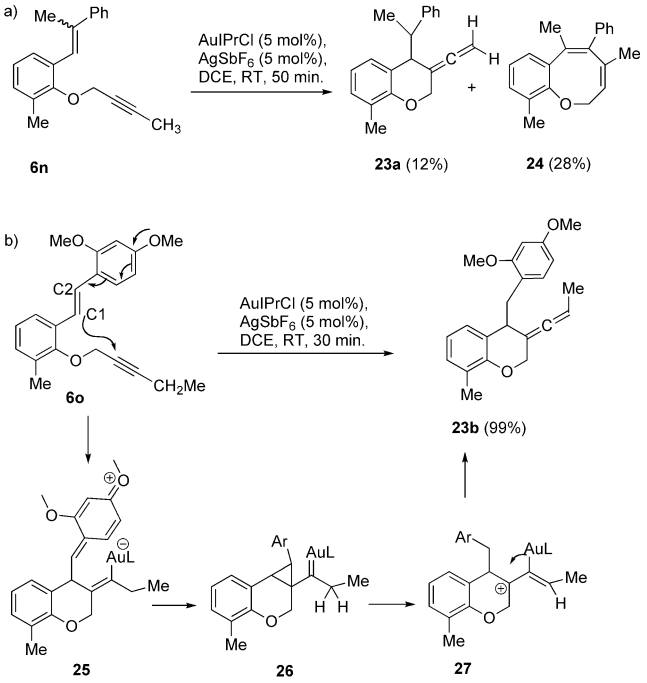
In this scenario, the electron-donating influence of the ether oxygen plays an important role, and in agreement with this hypothesis, CH_2-substituted analogue **21** and ester analogue **22** (Scheme 3d) did not cyclize, even in the presence of up to four-fold excess of gold(I) complex.

These mechanistic observations are in agreement with the results obtained by Toste and coworkers, who had shown that propargylvinyl ethers cyclize in the presence of gold catalysts and external nucleophiles by a 6-*endo*-dig process to yield tetrahydropyrans.[34–36] This mechanistic rationale is also supported by the observation that the overall process follows a different pathway if, instead of formation of the benzylic cation at the C1-position, formation of a carbocation at the C2-position of the olefin of the cyclization precursors predominates (Scheme 4).[34] Thus, whereas aryl rings with electron-withdrawing substituents at C2 lead to formation of the eight-membered ethers (Table 2, entries 8 and 9), introduction of electron-donating substituents onto the aryl ring, or double substitution of the olefin, which stabilizes the carbocation formation at C2, induces the formation of six-membered ethers with an exocyclic allene (Scheme 4).

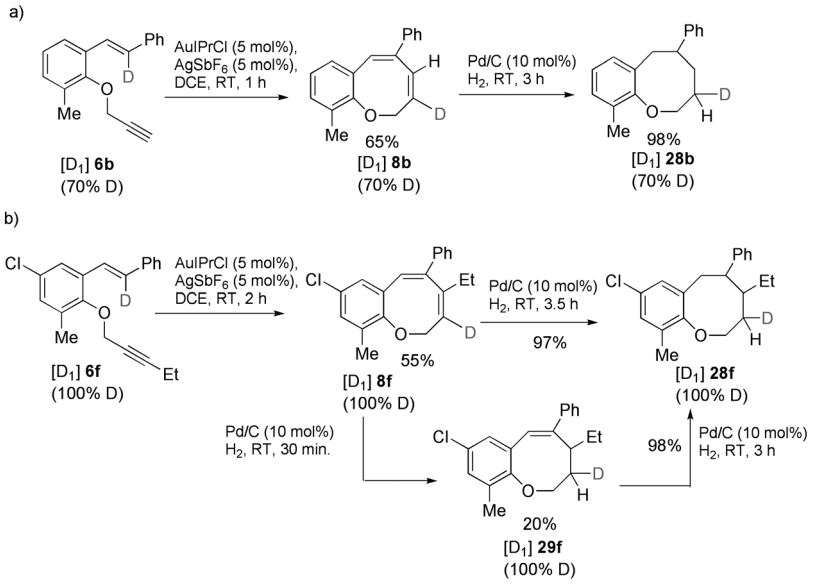
As shown in Scheme 4, compound **6n**, which has a methyl and a phenyl substituent on the olefin terminal carbon atom, led to the formation of exocyclic allene **23a** and benzoxocine **24**, the latter presumably arising from a migration of the methyl group in the intermediate benzylic cation, which is analogous to **16** (Scheme 3a). By analogy, the highly electron-rich dimethoxyphenyl-substituted cyclization precursor **6o** gives rise to allene **23b** in quantitative yield. Formation of this allene may involve the nucleophilic attack of the olefin on the alkyne to form benzopyran intermediate **25** and then possibly **26** (Scheme 4).

Finally, support for the proposed mechanism was obtained by the selective deuteration of cyclization precursor [D_1]-**6b** (Scheme 5a). Thus, as expected, exposure of [D_1]-**6b** to the reaction conditions detailed above yielded medium-sized cyclic ether [D_1]-**8b**. The analogous C-ethyl-substituted propargyl ether [D_1]-**6f** reacted similarly. Hydrogenation of the deuterated 2*H*-1-benzoxocines yielded the analogous saturated cyclic ethers, which were fully characterized by NMR spectroscopy (see Scheme 5 and the Supporting information).

We have discovered a novel 8-*endo*-dig cyclization of *o*-propargyloxy styrenes catalyzed by cationic gold(I) complexes. The transformation is broad in scope and provides rapid and efficient access to cyclic eight-membered-ring ethers, characteristic of a large group of biologically relevant natural products. Functionalized benzoxocines have been made available with limited success so far. The cyclization



Scheme 4. Synthesis of exocyclic allenic pyrans and a proposed mechanism.



Scheme 5. a) Gold(I)-catalyzed 8-*endo*-dig cyclization of deuterated substrate **6b** and hydrogenation of deuterated benzoxocine **8b** to confirm the location of the deuterium label. b) Gold(I)-catalyzed synthesis of deuterated benzoxocine **8f** and further partial and complete hydrogenation.

reaction reported here promises to yield efficient access to the corresponding natural products and various analogues for biological studies.

Experimental Section

(1,3-Bis(2,6-diisopropylphenyl)imidazol-2-ylidene)gold chloride (12.5 mg, 0.02 mmol, 0.05 equiv) and silver hexafluoroantimonate (7 mg, 0.02 mmol, 0.05 equiv) were dried in a 25 mL two-neck round-bottom flask for 1.5 h under high vacuum. **6b** (99 mg, 0.4 mmol) and n-octadecane (29.7 mg, 0.12 mmol, 30 weight %), as internal standard, were dissolved in dry DCE (4 mL) under argon. This solution was added to the catalyst and the resulting mixture was stirred at room temperature. After 30 min the starting material had been consumed and the mixture was filtered through a short pad of silica gel with CH_2Cl_2 and Et_2O as eluents. The solvents were evaporated under reduced pressure and purification of the crude residue by preparative TLC (silica gel) with 0.5% Et_2O/petroleum ether (5 runs) provided **8b** in 72% yield (*Z* isomer: 61%, 60.5 mg, 0.24 mmol; *E* isomer: 11%, 10.9 mg, 0.04 mmol) as a colorless oil.

Z isomer; $R_f = 0.4$ (1% Et_2O/petroleum ether); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 7.36$–7.27 (m, 3H), 7.26–7.23 (m, 2H), 6.97 (d, $J = 7.6$ Hz, 1H), 6.87 (dd, $J = 7.5$, 1.4 Hz, 1H), 6.79 (dd, $J = 7.5$ Hz, 1H), 6.61 (d, $J = 12.0$ Hz, 1H), 6.52 (s, 1H), 6.27 (d, $J = 12.1$ Hz, 1H), 4.47 (s, 1H), 2.14 ppm (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta =$ 151.75, 138.36, 131.06, 130.63, 130.58, 128.65, 128.34, 128.11, 127.37, 126.02, 124.84, 124.45, 122.73, 120.89, 66.96, 15.46 ppm.

E isomer; $R_f = 0.38$ (1% Et_2O/petroleum ether); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 7.45$ (d, $J = 7.2$ Hz, 2H), 7.34 (dd, $J =$ 7.6 Hz, 2H), 7.27–7.23 (m, 1H), 6.98 (d, $J = 7.5$ Hz, 1H), 6.89 (dd, $J = 7.2$, 1.4 Hz, 1H), 6.87 (d, $J = 16.5$ Hz, 1H), 6.79 (dd, $J = 7.4$ Hz, 1H), 6.51 (s, 1H), 6.45 (d, $J = 16.4$ Hz, 1H), 5.11 (s, 2H), 2.22 ppm (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 151.70$, 137.02, 130.73, 130.39, 128.72, 127.76, 127.69, 126.69, 126.38, 124.84, 124.67, 124.36, 122.19, 120.88, 65.58, 15.52 ppm; HRMS (EI): *m/z*: calcd for $C_{18}H_{16}O$: 248.11957 $[M]^+$, found: 248.11991.

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[29] The very nonpolar nature of benzoxocines **8** (highly conjugated and with aromatic character) render their purification by silica gel column chromatography very difficult. These compounds could be purified only by preparative TLC (silica gel) using 0.5% Et_2O in petroleum ether as eluent. Benzoxocine **8k** could be purified only by preparative HPLC with n-heptane as eluent. Therefore, yields of the isolated benzoxocines **8** do not reveal the real efficiency of this novel gold-catalyzed cyclization reaction. The yields determined by GC analysis of all the benzoxocines are given in a separate table in the Supporting Information.
[30] For a comparison of the NMR data of (*E*)-**8** with (*E*)-cyclooctene, see: D. Bourgeois, A. Pancrazi, L. Ricard, J. Prunet, *Angew. Chem.* **2000**, *112*, 741 – 744; *Angew. Chem. Int. Ed.* **2000**, *39*, 725 – 728.
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