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Regio- and Stereoselective Construction of Highly Functionalized 3-Benzazepine Skeletons through Ring-Opening Cycloamination Reactions Catalyzed by Gold

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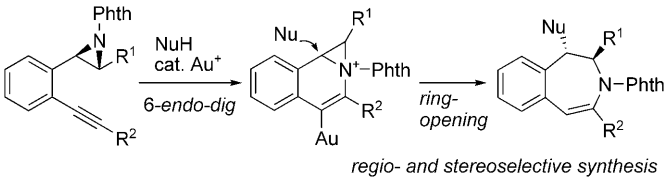
The intramolecular cyclizations of alkynes containing proximate C, O, N nucleophiles catalyzed by transition metals is a powerful strategy to provide a rapid and highly efficient access to carbo- and heterocyclic structural motifs.[1] Recent studies demonstrated that gold complexes and their salts are emerging as unique catalysts for cyclization reactions owing to their superior chemoselectivities and reactivities.[2] Aziridines are versatile synthetic building blocks for the preparation of functional materials and nitrogen-containing biologically active molecules, as they can undergo facile ring opening and expansion reactions because of their extremely strained ring structures.[3] Despite the growing interests in gold-catalyzed nucleophilic-addition reactions of structurally similar epoxides to alkynes,[4] few applications have been reported for the synthetic transformation of aziridine/alkynes.[5] For instance, Sarpong and coworkers have reported a platinum(II)-catalyzed cycloisomerization of aziridinyl propargylic esters to 1,2-dihydropyridines via a metallocarbenoid intermediate.[5a] Zhao et al. have developed a gold-catalyzed rearrangement reaction of propargylic aziridine ethers involving an tandem cyclization/ring-opening/Wagner–Meerwein process.[5b] Recently, our research group[5c] and others[4l,5d,e] have also succeeded in the incorporation of aziridines as nucleophiles in annulations reactions with alkynes through gold-catalyzed cycloisomerization of alkynylaziridines—an efficient synthesis of functionalized pyrroles. These reactions likely proceed through the formation of aziridinium ions that result from the nucleophilic attack of the aziridinyl nitrogen on the gold-complexed alkyne. We envisioned that the resulted intermediate might be further attacked by a nucleophile, thus leading to 1,2-difunctional ring-opened products. To test this hypothesis, we then designed and synthesized (*o*-alkynyl)phenyl aziridines. Herein, we describe a gold-catalyzed ring-opening cyclization of (*o*-alkynyl)phenyl aziridines assisted by external nitrogen and oxygen nucleophiles (Scheme 1). The reaction provides a highly regio- and stereoselective route to 3-benzazepine and its derivatives. It is noted that the attack of the aziridine to the alkyne moiety results in a highly regioselective 6-*endo-dig* cyclization, and a selective benzylic C3–N bond cleavage of the aziridine ring by nucleophiles is also highlighted. Recently, a gold-catalyzed conversion of 2-alkynylaryl epoxides into 3-acylindenes has been reported by Hashmi et al.[4g] The reaction proceeds through a different pathway that involves an intramolecular oxygen transfer and the cyclization of a pentadienyl cation as key steps.



Scheme 1. Proposed formation of 3-benzazepine derivatives. Nu = Nucleophile.

There has been considerable interest in the synthesis of functionalized 3-benzazepines as they present as key structural subunits in alkaloids such as Cephalotaxus[6a] and Benzindenoazepine alkaloids (Figure 1).[6b] Derivatives with a 3-benzazepine framework have also displayed important biological activities for pharmaceutical use.[7] For example, they are well known to act as dopamine receptor agonists and antagonists (e.g., SCH-23390)[8] They are also active in animal models of various neurological disorders, like Parkinson's disease[9] and Alzheimer's disease.[10]

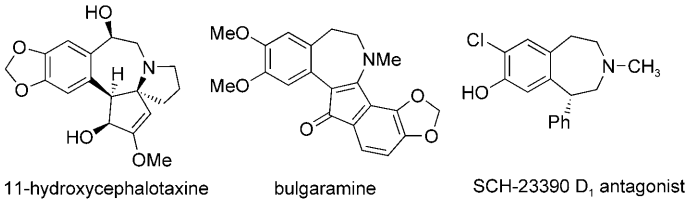


Figure 1. Representative alkaloids and pharmacologically interesting substances containing 3-benzazepine derivatives.

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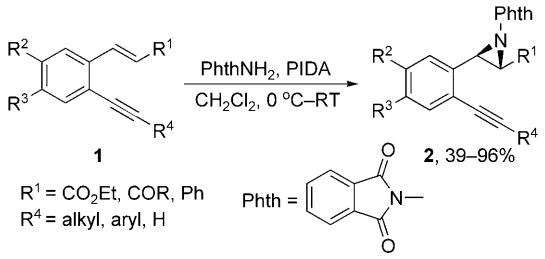
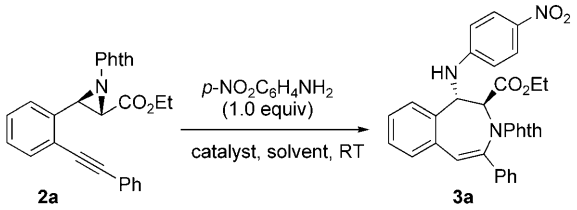
The required (*o*-alkynyl)phenyl aziridines **2** were synthesized easily through aziridination of the readily available enynes **1** using the *N*-aminophthalimide/phenyliodine(III) diacetate (PIDA) system.[5c,11] This method was reported to be versatile with regard to the electronic nature of the olefin unit, and also to lead to high diastereoselectivities. A series of *trans*-aziridine **2** with -CO_2R, -COR, and -Ph functionalities was conveniently prepared in good yields and with high stereoselectivities from *trans*-enynes using this method (Scheme 2). The isomer *trans*-**2a**, in which the phthalimido residue and the ester group have the *cis* configuration, was also characterized by X-ray crystallographic analysis[12]. In the case of **2m**, the aziridine exists as a mixture of invertomers as determined by ^{1}H NMR analysis.



Scheme 2. Aziridination of the enynes.

The reaction of 3-[2-(phenylethynyl)phenyl]aziridine-2-carboxylate **2a** with 4-nitroaniline was selected as the prototypical case to screen the experimental conditions (Table 1). Satisfyingly, the reaction proceeded smoothly, and the desired 3-benzazepines **3a** was obtained in 84% yield at room temperature in THF with the use of [(PPh_3)AuCl] (5 mol%) and AgOTf (5 mol%) as catalysts (Table 1, entry 1). The results indicated that a 6-*endo-dig* heterocyclization took place preferentially rather than the expected 5-*exo-dig* mode. It is also clear that the amine-mediated ring opening occurs selectively at C3 of the aziridine moiety, and only *trans*-diastereomer of **3a** was detected, as revealed by the value of the coupling constant of the methine protons (5.6 Hz determined by ^{1}H NMR spectroscopy). The configuration was further confirmed by X-ray crystallographic analysis of **3a**.[12] Cationic gold complexes [(PPh_3)AuSbF_6] or [(PPh_3)AuNTf_2] also showed significant reactivity (Table 1, entries 2 and 3). The reaction could also be carried out in toluene, CH_2Cl_2, DCE or 1,4-dioxane (Table 1, entries 4–7). Acetonitrile afforded a moderate yield of **3a** at 50°C (Table 1, entry 8). The use of AgOTf alone afforded low yield (Table 1, entry 9). $PtCl_2$ was not effective for this reaction (Table 1, entry 10).

Table 1. Optimization studies for the formation of 3-benzazepine derivatives.



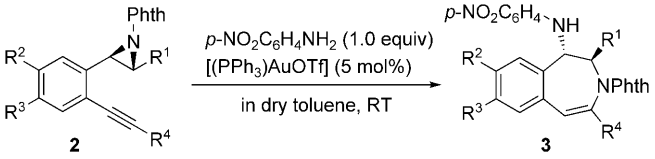
	Catalyst [5 mol%]	Solvent	*t* [h]	Yield [%][a]
1	[(PPh_3)AuOTf]	THF	5	84
2	[(PPh_3)AuSbF_6]	THF	3	86
3	[(PPh_3)AuNTf_2]	THF	3	76
4	[(PPh_3)AuOTf]	toluene	3	88
5	[(PPh_3)AuOTf]	CH_2Cl_2	3	72
6	[(PPh_3)AuOTf]	DCE	4	75
7	[(PPh_3)AuOTf]	1,4-dioxane	4	89
8	[(PPh_3)AuOTf]	CH_3CN	4.5	56[b]
9	AgOTf	toluene	11.5	16[c]
10	$PtCl_2$[d]	toluene	21	little

[a] Yield of isolated product. [b] The reaction was carried out at 50°C. [c] Yield determined upon NMR analysis. [d] 10 mol%.

We chose the reaction conditions shown in Table 1, entry 4 to examine the scope of this reaction. As illustrated in Table 2, this gold-catalyzed ring-opening cycloamination accommodates a wide range of substrates. The functional groups Me, MeO, and Cl on the alkynyl aromatic ring (R^4) were well-tolerated during the reaction, and led to the corresponding 3-benzazepines **3b**–**3e** in 43–83% yields (Table 2, entries 2–5). However, the use of the stronger electron-withdrawing group CF_3 resulted in a low yield (32%) of **3f**, along with several undefined by-products (Table 2, entry 6). The electronic nature of the aryl substituents influences the reaction rates, usually electron-rich alkynes made the reaction faster than the electron-poor ones (Table 2, compare entry 3 and 5). The thienyl-substituted alkyne **2g** was well-suited in this cyclization, and a high yield of **3g** could be achieved (Table 2, entry 7). Alkyl-substituted alkyne **2h** was also compatible, and led to **3h** in 50% yield (Table 2, entry 8). However, the use of a terminal alkyne only resulted in a complicated mixture (Table 2, entry 9). With a ketone present in the aziridine **2j**, the regioselective ring-opening product **3j** was also generated smoothly in 90% yield (Table 2, entry 10). The substituents F or Me on the parent aromatic ring were well-tolerated (Table 2, entries 11 and 12). When aziridine **2m** with a phenyl substituent as R^1 group was employed, the reaction resulted complicated and the desired benzazepines could not be isolated (Table 2, entry 13). This result indicates that the electron-withdrawing group on the aziridine ring plays an important role for controlling the regioselectivity and the reaction pathway. Other nitrogen nucleophiles such as *p*-methoxyaniline, *p*-chloroaniline, and benzamide are not compatible for this reaction.

Next, we proceeded to examine the reactions with oxygen nucleophile of water instead of amine. After much effort, we found that the cationic gold complex [(PPh_3)AuOTf] showed high catalytic activity in THF in the presence of H_2O (5 equiv; Scheme 5). However, the desired hydroxy product **4** was hard to be purified by column chromatography. Therefore, **4** was oxidized by IBX (2-iodoxybenzoic acid) to allow for product purification. To our surprise, the oxidation followed by the treatment with base resulted in the clean formation of 1-oxo-1*H*-benzo[*d*]azepin-1-one **5**[12]

Table 2. Gold-catalyzed regio- and stereoselective synthesis of 3-benzazepine derivatives.

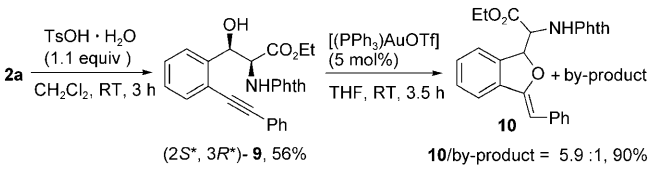


	Aziridine	R^1	R^2	R^3	R^4	t [h]	Product	Yield [%][a]
1	**2a**	CO_2Et	H	H	Ph	3	**3a**	88
2	**2b**	CO_2Et	H	H	*p*-MeC_6H_4	1	**3b**	79
3	**2c**	CO_2Et	H	H	*p*-$MeOC_6H_4$	1	**3c**	83
4	**2d**	CO_2Et	H	H	3,4,5-tri-$MeOC_6H_2$	1	**3d**	43
5	**2e**	CO_2Et	H	H	*p*-ClC_6H_4	6	**3e**	73[b]
6	**2f**	CO_2Et	H	H	*p*-$CF_3C_6H_4$	4.5	**3f**	32[c]
7	**2g**	CO_2Et	H	H	2-thienyl	1	**3g**	96
8	**2h**	CO_2Et	H	H	*n*Bu	2	**3h**	50
9	**2i**	CO_2Et	H	H	H	2	–[d]	–
10	**2j**	COPh	H	H	Ph	2	**3j**	90
11	**2k**	CO_2Et	F	H	Ph	4	**3k**	91
12	**2l**	CO_2Et	H	Me	Ph	4	**3l**	74
13	**2m**	Ph	H	H	Ph	24	–[b,c,d]	–

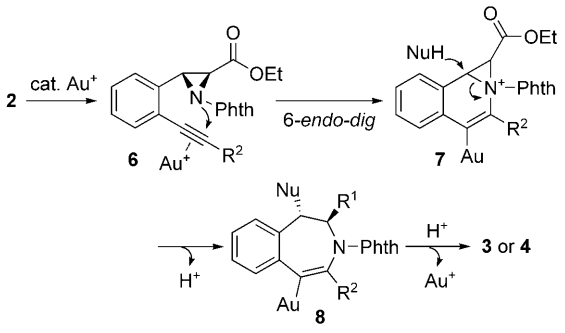
[a] Yield of isolated product. [b] The reaction was carried out in THF. [c] The reaction was carried out at 80 °C. [d] Product not determined.

with the elimination of the phthalimido (Phth) group. This further transformation by facile removal of the phthalimido protection group also makes this method attractive for assembling multisubstituted 1-oxo-benzo[*d*]azepines. As shown in Scheme 5, the substrates containing aryl, heteroaryl, and 1-naphthyl groups afforded moderate to good yields of the desired **5a**–**5j** with multiple functionalities, which should be very useful for further elaborations. The hydroxylated products **4c** and **4i** could be obtained in a pure form in 90% and 44% yield, respectively. In both cases, only the *trans*-diastereomers were observed. The structural assignment of the *trans*-isomers was verified by X-ray crystallographic analysis of **4a** purified by recrystallization.[12]

These cycloamination reactions can be rationalized by the regioselective 6-*endo-dig* cyclization of the aziridine nitrogen with gold(I)-alkyne complex, which leads to the aziridinium ion intermediate **7** (Scheme 3).[13] Instead of deprotonation, **7** undergoes rapid nucleophilic ring opening by amine or H_2O at the benzylic carbon through an S_N2 reaction followed by proton transfer/protondeauration to give the *trans*-products.[14] According to our results, the presence of the electron-withdrawing R^1 group is crucial for regioselective ring opening. The results can be explained by considering the electronic effect.[15] In the intermediate **7**, the newly formed positive charge on the nitrogen is dispersed through the aziridine ring, while weakening the C–N bonds. The bond between N1 and benzylic carbon C3 accommodates the positive charge better than the N1–C2 bond which has an ester substituent, thus it get easier to be broken toward the attack of the nucleophile. On the other hand, the addition of water to the aziridine **2a** promoted by *p*-TsOH·H_2O occurred also regioselectively at the benzylic position to give acyclic (2*S**,3*R**)-β-hydroxy-α-amino acid derivative **9** in 56% yield as a single diastereomer (Scheme 4).



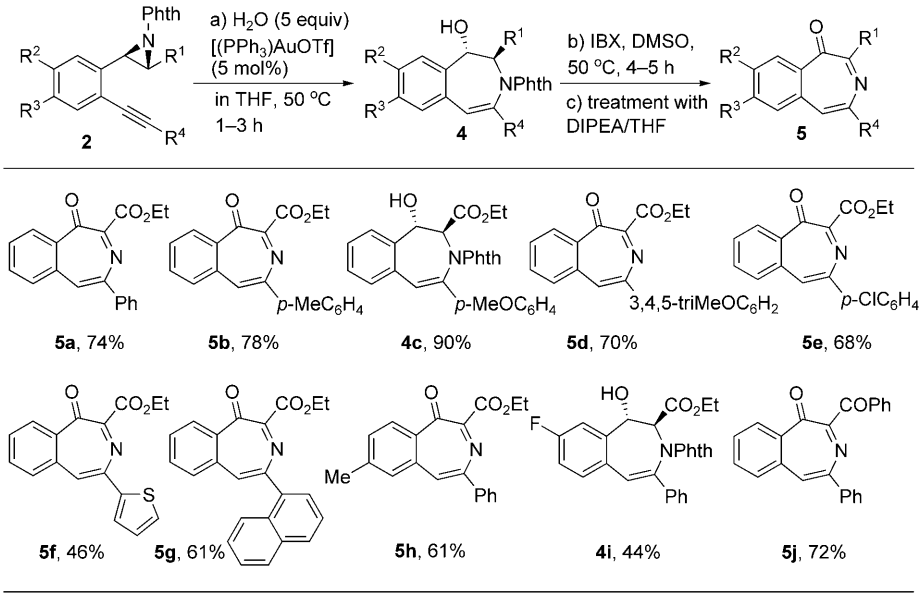
Scheme 4. Ring-opening reaction mediated by TsOH·H_2O. Tf = trifluoromethanesulfonyl.



Scheme 3. Proposed mechanism for the gold-catalyzed heterocyclization.

The *syn*-stereochemistry of **9** was confirmed by X-ray crystallographic analysis.[12] To our surprise, the results indicated that the configuration of C3 is retained by unusual *syn*-attack during the reaction, which is quite rare in ring-opening reactions of aziridines.[16] Compound **9** did not lead to the benzazepine derivative under the catalysis of [(PPh_3)AuOTf]; instead, a mixture of **10** and one unknown by-product[17] were obtained in a combined yield of 90% (Scheme 4). The structural assignment of **10** was deduced from a series of 2D NMR spectra of a pure sample. We also prepared a mixture of *syn*- and *anti*-isomers of **9** through a BF_3·Et_2O mediated reaction.[18] The gold-catalyzed reaction of these isomers also did not afford the benzazepine derivative.[19] Based on these results, we suggest that the gold-catalyzed cyclization of **2** with nucleophiles to form 3-benzazepine derivatives probably does not involve the ring-opening intermediate **9** or its diastereomer, that means, the starting aziridine **2** might not be first opened by nucleophile.

In conclusion, we have developed a gold-catalyzed cyclization of (*o*-alkynyl)phenyl aziridines[20] with heteronucleophiles to highly functionalized 1-amino or -hydroxy-1*H*-benzo[*d*]azepines with *trans*-stereoselectivity. The latter could be further transformed to 1*H*-benzo[*d*]azepin-1-ones by oxidation/elimination sequence using IBX and base. The cyclization reaction likely proceeds through the formation of an aziridinium ion intermediate through a regioselective 6-*endo-dig* cycloaddition. The existence of the electron-withdrawing group on the aziridine ring is also important to induce the regioselective ring opening at the benzylic position. Further studies to expand the scope of these reactions are in progress.



Scheme 5. Gold-catalyzed synthesis of 1-oxo-4-phenyl-1*H*-benzo[*d*]azepines. Overall yield of the isolated products **5** for the three reaction steps. DMSO = dimethyl sulfoxide.

Experimental Section

Typical procedure for gold(I)-catalyzed cyclization reactions of (*o*-alkynyl)phenyl aziridines 2 with 4-nitroaniline to 1-amino-1*H*-3-benzo[*d*]azepines: All the reactions were carried out on 0.2 or 0.4 mmol scale. 4-nitroaniline (27.6 mg, 0.2 mmol) was added to a solution of aziridine **2a** (87.3 mg, 0.2 mmol) in toluene (2 mL). Once the 4-nitroaniline was mostly dissolved, [(PPh_3)AuCl] (5.0 mg, 0.01 mmol) was added followed by AgOTf (0.01 mmol, 0.2 mL, used as a 0.05 M solution in THF). The resulting solution was stirred at room temperature until the reaction was complete as monitored by thin-layer chromatography. The solvent was removed under reduced pressure and the residue was purified by flash chromatography on silica gel (petroleum ether/ethyl acetate/dichloromethane = 4:1:1) to afford (1*S**, 2*S**)-ethyl 3-(1,3-dioxo-isoindolin-2-yl)-1-(4-nitrophenyl-amino)-4-phenyl-2,3-dihydro-1*H*-benzo[*d*]-azepine-2-carboxylate (**3a**) in 88% yield as a yellow solid. m.p. 118 °C. ^{1}H NMR ($CDCl_3$, Me_4Si, 400 MHz): δ = 0.98 (t, J = 7.6 Hz, 3H), 3.98–4.12 (m, 2H), 4.97 (d, J = 5.6 Hz, 1H), 5.64 (dd, J = 10.0, 6.0 Hz, 1H), 5.79 (s, 1H), 6.36 (d, J = 10.0 Hz, 1H), 6.76 (d, J = 9.2 Hz, 2H), 7.14–7.25 (m, 6H), 7.42 (d, J = 7.6 Hz, 1H), 7.57–7.68 (m, 5H), 7.68–7.70 (m, 1H), 7.94 ppm (d, J = 9.2 Hz, 2H); ^{13}C NMR ($CDCl_3$, Me_4Si, 100.6 MHz): δ = 13.74, 58.28, 61.57, 68.10, 108.70, 111.79, 123.50, 123.59, 125.35, 126.10, 127.91, 127.98, 128.20, 128.35, 128.57, 130.72, 132.11, 133.63, 134.20, 134.75, 134.84, 137.90, 138.11, 142.55, 151.28, 165.32, 166.33, 166.35 ppm; IR (neat): $\tilde{\nu}$ = 3335, 1753, 1596, 1311, 1112, 713 cm^{-1}; HRMS (ESI): calcd for $C_{33}H_{26}N_4NaO_6$ $[M+Na]^+$: 597.1745; found: 597.1769.

Typical procedure for gold(I)-catalyzed cyclization reactions of (*o*-alkynyl)phenyl aziridines 2 with water followed by oxidation: H_2O (18 uL, 1 mmol), [(PPh_3)AuCl] (5.0 mg, 0.01 mmol), and AgOTf (0.2 mL, 0.01 mmol, used as a 0.05 M solution in THF) were added to a solution of aziridine **2a** (87.3 mg, 0.2 mmol) in THF (2 mL). The flask was then immersed in an oil bath at 50 °C and stirred at this temperature until the reaction was complete as monitored by thin-layer chromatography. The gold catalyst was removed by filtration and the filtrate was concentrated under reduced pressure. IBX (1.2 equiv, 67.2 mg, 0.24 mmol) was added to a solution of the above crude product **4a** in DMSO (1.5 mL). The resulting solution was stirred at 50 °C until the reaction was complete as monitored by thin-layer chromatography. Then H_2O was added and the mixture was extracted with ether. The aqueous phase was extracted with ether for three times. The combined organic layers were dried over anhydrous $MgSO_4$, filtrated, and concentrated under reduced pressure. *N,N*-diisopropylethylamine (DIPEA; 0.5 mL) was added to a solution of the above crude product in THF (3.0 mL). The resulting solution was stirred at room temperature until the reaction was complete as monitored by thin-layer chromatography. Then a 5% NaOH solution was added and the mixture was extracted with ether. The aqueous phase was extracted twice with ether. The combined organic layers were dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The crude product was purified by flash chromatography on silica gel (petroleum ether/ethyl acetate = 7:1) to give (2*E*,4*Z*)-ethyl 1-oxo-4-phenyl-1*H*-benzo[*d*]azepine-2-carboxylate (**5a**) in 74% yield as a pale yellow solid. m.p. 103 °C. ^{1}H NMR ($CDCl_3$, Me_4Si, 400 MHz): δ = 1.40 (t, J = 7.6 Hz, 3H), 4.43 (q, J = 7.2 Hz, 2H), 7.37–7.48 (m, 4H), 7.67–7.71 (m, 1H), 7.74–7.76 (m, 2H), 7.93–7.96 (m, 2H), 8.07 ppm (d, J = 8.0 Hz, 1H); ^{13}C NMR ($CDCl_3$, Me_4Si, 100.6 MHz): δ = 14.07, 62.39, 122.02, 127.03, 128.02, 128.75, 129.17, 130.52, 131.65, 133.23, 135.20, 136.71, 138.50, 146.43, 149.98, 163.99, 183.51 ppm; IR (neat): $\tilde{\nu}$ = 1734, 1510, 1373, 1246, 886, 707 cm^{-1}; HRMS (EI): calcd for $C_{19}H_{15}NO_3$: 305.1052; found: 305.1054.

Acknowledgements

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Keywords: benzazepines · aziridine · cyclization · gold catalysis · heterocycles

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[18] For details, see the Supporting Information.

[19] In this reaction, a mixture of four isomers was obtained, and two of which are the same as that obtained from the *syn*-**9** isomer.

[20] During the preparation of this manuscript, a gold-catalyzed reaction of aziridinyl alkynes with arenes was reported, in which six-membered tetrahydroisoquinolines were obtained through a Friedel–Crafts reaction/cyclization sequence. Z. Zhang, M. Shi, *Chem. Eur. J.* **2010**, *16*, 7725.

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