



## A facile and regioselective synthesis of 2,5-disubstituted pyrroles via gold-catalyzed cycloisomerization of acetylenylaziridines

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### ABSTRACT

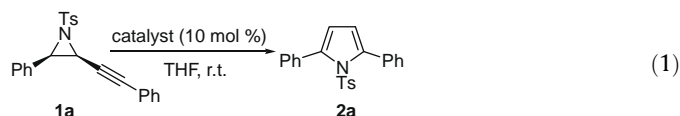
Gold-catalyzed cycloisomerization reaction of acetylenylaziridines provides 2,5-disubstituted pyrroles in high yields. The presence of protic species accelerates the reaction rate and improves the yields of pyrrole products.

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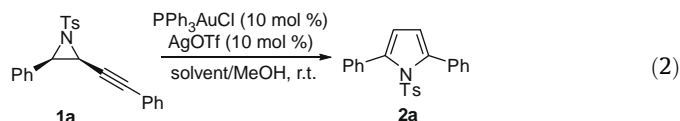
Transition-metal-catalyzed cyclizations and cycloisomerization reactions of enynes have so far been a convenient protocol to render a variety of functionalized ring structures.<sup>1</sup> Among them the gold catalysts have demonstrated their unique catalytic activities through the activation of alkynes, emerging as the powerful catalyst for this rapidly developing research area in past few years.<sup>2</sup> The transformations of epoxides<sup>3</sup> and cyclopropanes<sup>4</sup> containing carbon–carbon triple bond to furans, polycyclic ring systems and other functionalized compounds in the presence of gold compounds as catalyst have been reported. However, few reports were given on the gold-catalyzed transformation of aziridines in spite of the fact that the metal-catalyzed conversions of aziridines have well been documented.<sup>5</sup> We have developed several simple procedures for the synthesis of functionalized aziridines including acetylenylaziridines.<sup>6</sup> We envisage that such triple bond in acetylenylaziridines could be activated by gold compounds and the pyrrole formation<sup>7</sup> seems to be feasible via intramolecular attack of nitrogen of the aziridine towards gold(I)-activated triple bond. Herein, we present a new synthetic approach to 2,5-disubstituted pyrroles utilizing the acetylenylaziridines in the presence of Au catalyst.<sup>8</sup>

The choice of catalyst to activate the nitrogen of aziridine with low nucleophilicity is vital,<sup>7a,9</sup> although it was easy with which the alkyloxiranes were isomerized to furan with gold(III) chloride as a catalyst via the attack of oxygen of epoxide as a nucleophile to the activated triple bond.<sup>10</sup> Thus, different metal salts and complexes were screened by using aziridine **1a** for our initial investigation (Eq. 1, Table 1). In the presence of 10 mol % of transition-metal complexes IPrCuCl and Ru(PPh<sub>3</sub>)<sub>2</sub>Cl<sub>2</sub> or metal salts Y(OTf)<sub>3</sub>, In(OTf)<sub>3</sub>, PtCl<sub>2</sub><sup>11</sup> and AgOTf, the formation of pyrrole **2a** was not observed (entries 1–6). However, a few percentage of pyrrole **2a** was detected when Au compounds were used (entries 7, 8 and 10). The yield of **2a** increased dramatically when 10 mol % of AgOTf

was added (entries 11, 12, 14 and 15).<sup>12</sup> The presence of protic species plays an important role. Good yield of **2a** was provided if 0.1 mL of MeOH was added to the reaction system (entries 14 and 15) while lower yield of **2a** was furnished without the use of MeOH (entry 11).<sup>13</sup> It is noticeable that removing trace amount of water from the system with 4 Å MS prohibited this reaction (entry 13). The reaction still proceeded smoothly if the catalyst loading decreased to 5 mol %, providing 60% yield of **2a** in 17 h (entry 15).



Then we investigated the influence of solvents on these isomerizations (Eq. 2, Table 2). We found that the pyrrole **2a** was afforded efficiently if the reaction ran in toluene, DCM and THF (entries 1–3), among them THF was a better choice, while poor results were provided if CH<sub>3</sub>CN and CH<sub>3</sub>OH were used as solvents (entries 4 and 5).



With the optimized conditions in hand, we have probed the scope of this isomerization reaction (Eq. 3, Table 3). Varying the aryl and alkyl substituents at either aziridines ring or the terminal carbon of triple bond had a little influence on the yield of the reaction, all reactions proceeded smoothly at room temperature and were completed within 10 h to afford 2,5-disubstituted pyrroles in high yields, except that of aziridine **1j** with Phenyl and acetylenyl group in 19 h (entry 10). High yields (87–99%) of pyrroles **2** were furnished when one substituent or two substituents on the aziridines ring and the terminal carbon of triple bond were alkyl (entries 4–8 and 13–14) while the yields were a little bit lower

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**Table 1**  
Screening of metal catalysts in the cycloisomerization of aziridine **1a**<sup>a</sup>

Entry	Catalyst	Time (h)	Yield <sup>b</sup> (%)
1	IPrCuCl	48	N.R.
2	Y(OTf) <sub>3</sub>	48	N.R.
3	In(OTf) <sub>3</sub>	48	N.R.
4	PtCl <sub>2</sub>	16	N.R.
5	Ru(PPh <sub>3</sub> ) <sub>2</sub> Cl <sub>2</sub>	24	N.R.
6	AgOTf	16	N.R.
7	NaAuCl <sub>2</sub> ·H <sub>2</sub> O	96	8
8	AuCl <sub>3</sub>	72	<5
9	PicAuCl <sub>2</sub> <sup>c</sup>	48	N.R.
10	PPh <sub>3</sub> AuCl	48	<5
11	PPh <sub>3</sub> AuCl/AgOTf	36	58
12	AuCl <sub>3</sub> /AgOTf	4	50
13	PPh <sub>3</sub> AuCl/AgOTf <sup>d</sup>	20	N.R.
14	PPh <sub>3</sub> AuCl/AgOTf <sup>e</sup>	9	69
15	PPh <sub>3</sub> AuCl/AgOTf <sup>f</sup>	17	60

<sup>a</sup> Reactions were conducted with a solution of **1a** (74.7 mg, 0.2 mmol) and 10 mol % catalyst (0.5 mL 0.04 M AgOTf–THF solution was used if necessary) in THF (0.2 M) protected from light at rt.

<sup>b</sup> Isolated yield.

<sup>c</sup> Pic = pyridine-2-carboxylato.

<sup>d</sup> 4 Å MS was added.

<sup>e</sup> MeOH (0.1 mL) was added.

<sup>f</sup> 5 mol % catalyst was used with MeOH (0.1 mL).

**Table 2**  
Influence of different solvents on the cycloisomerization of aziridine **1a**<sup>a</sup>

Entry	Solvent	Time (h)	Yield <sup>b</sup> (%)
1	THF	9	69
2	Toluene	4	63
3	DCM	4	67
4	CH <sub>3</sub> CN	6	N.R.
5	CH <sub>3</sub> OH	6	Complex

<sup>a</sup> Reactions were carried out as follows: **1a** (74.7 mg, 0.2 mmol) and PPh<sub>3</sub>AuCl (10 mg, 0.02 mmol) with AgOTf–THF solution (0.5 mL, 0.04 M, 0.02 mmol) in solvent (0.5 mL) and MeOH (0.1 mL) protected from light at rt.

<sup>b</sup> Isolated yield.

**Table 3**  
Scope of gold(I)-catalyzed cycloisomerization of aziridines **1a**<sup>a</sup>

Entry	Substrate <b>1</b>	R <sup>1</sup>			R <sup>3</sup>	Time (h)	Yield <sup>b</sup> (%)
		R <sup>1</sup>	R <sup>2</sup>	R <sup>3</sup>			
1	<b>a</b>	Ph	Ph	Ts	9	69 ( <b>2a</b> )	
2	<b>b</b>	<i>o</i> -ClC <sub>6</sub> H <sub>5</sub>	Ph	Ts	6	86 ( <b>2b</b> )	
3	<b>c</b>	1-Nap	Ph	Ts	2	74 ( <b>2c</b> )	
4	<b>d</b>	<i>i</i> -Pr	Ph	Ts	5	95 ( <b>2d</b> )	
5	<b>e</b>	Cy	Ph	Ts	6	94 ( <b>2e</b> )	
6	<b>f</b>	<i>n</i> -Pr	Ph	Ts	3	99 ( <b>2f</b> )	
7	<b>g</b>	Ph	Ph	Ms	10	76 ( <b>2g</b> )	
8	<b>h</b>	Cy	TMS	Ts	3	95 ( <b>2h</b> ) <sup>c</sup>	
9	<b>i</b>	Ph	TMS	Ts	12	70 ( <b>2i</b> ) <sup>c</sup>	
10	<b>j</b>	Ph	H	Ts	19	59 ( <b>2j</b> )	
11	<b>k</b>	Ph	<i>c</i> -Pr <sup>d</sup>	Ts	3	94 ( <b>2k</b> )	
12	<b>l</b>	1-Nap	<i>n</i> -Bu	Ts	2	71 ( <b>2l</b> )	
13	<b>m</b>	Cy	<i>n</i> -Bu	Ts	4	94 ( <b>2m</b> )	
14	<b>n</b>	Cy	CH <sub>2</sub> OCH <sub>3</sub>	Ts	3	87 ( <b>2n</b> )	

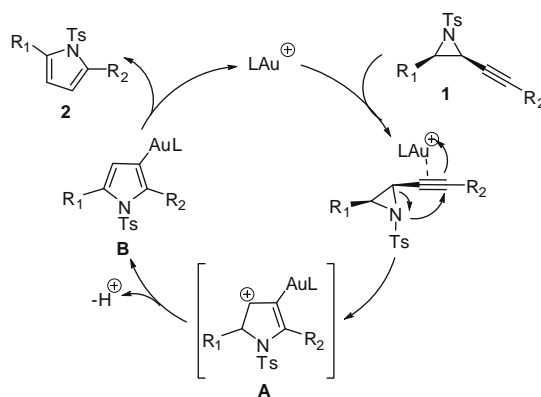
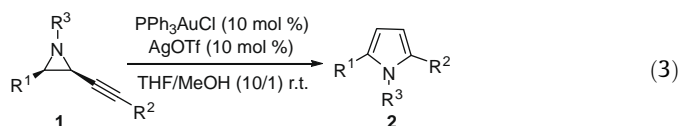
<sup>a</sup> Reactions were carried out as follows: **1** (0.2 mmol) and PPh<sub>3</sub>AuCl (10 mg, 0.02 mmol) with AgOTf–THF solution (0.5 mL, 0.04 M, 0.02 mmol) in mixed solvents of THF/MeOH = 5/1 (0.6 mL) protected from light at rt.

<sup>b</sup> Isolated yield.

<sup>c</sup> R<sub>2</sub> = H in the product.

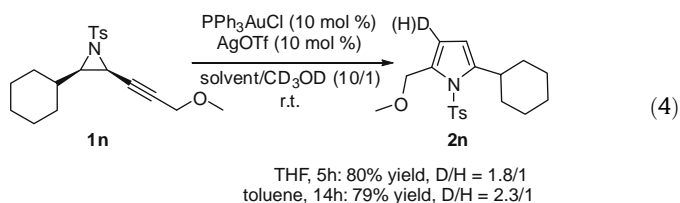
<sup>d</sup> *c*-Pr = cyclopropyl.

(59–74%) if both substituents are aryl (entries 1, 3 and 7) or aryl and TMS or H (entries 9 and 10) with the exception of the reaction of **1b** and **1l** (entries 2 and 12).

**Scheme 1.** Mechanistic hypothesis for the cycloisomerization of aziridines.

The reaction seems to be like that reported in the literature by Hashmi and Sinha<sup>10</sup> to proceed via the gold(I)-activation of alkyne followed by cycloisomerization to produce intermediate **A**, deprotonation of it affords intermediate **B**, which is converted to pyrrole immediately via the deprotonation and regenerates Au catalyst (Scheme 1).

To study the reaction mechanism, the deuterium exchange experiments were carried out (Eq. 4). Moderate proportion of deuterated product **2n** observed with deuterium-labelled methanol suggests that the proton sources are supplied not only from methanol but also from the proton released from the intermediate **A** (Scheme 1). A similar deuteration was also observed when the reaction proceeded in either polar or apolar solvent (Eq. 4). The fast intramolecular protonation process is supported further by the fact that we failed to trap the intermediate **B** with different electrophiles. These results suggest that gold(I)-activation of alkyne cycloisomerization might be the rate-determining step.



In summary, we have developed a new and simple pathway to form 2, 5-disubstituted pyrroles in high yields with gold(I)-catalyzed efficient cycloisomerization of acetylenylaziridines. The presence of protic species accelerates the reaction rate and improves the yields of pyrrole products. Further studies on the acetylenylaziridines transformations using Au catalyst and the applications in organic synthesis are underway.

## Acknowledgements

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## Supplementary data

Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tetlet.2009.05.091.

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11. The reaction of **1j** afforded 40% yield of **2j** by using 10 mol % of PtCl<sub>2</sub> as catalyst at 40 °C. But **1a** failed to react under PtCl<sub>2</sub>.
12. When AgBF<sub>4</sub> was used, the reaction was complicated; **2a** was provided in 55% yield if AgSbF<sub>6</sub> was added.
13. The reaction afforded 63% yield of **2a** in 29 h with AcOH (0.1 mL) as additive while it gave 26% yield of **2a** in 53 h and recover 51% **1a** with H<sub>2</sub>O (0.1 mL) as additive.