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Counterion Effects in a Gold-Catalyzed Synthesis of Pyrroles from Alkynyl Aziridines

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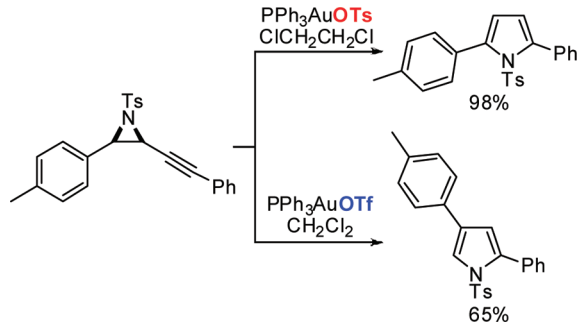
ABSTRACT



Aryl-substituted *N*-tosyl alkynyl aziridines undergo a gold-catalyzed ring expansion to afford 2,5-substituted pyrrole products. Under certain conditions, a ring-expansion and rearrangement leads to 2,4-substituted pyrroles. The reaction pathway is determined by the counterion to the gold catalyst.

Over the past few years, the activation of an alkyne by a π-acidic transition-metal catalyst, such as gold or platinum, has been employed as the basis of a wide range of powerful new transformations.[1,2] Excellent chemoselectivity is displayed in processes which require experimentally simple and mild conditions. The cationic gold systems prepared by a metathesis reaction between a simple gold complex LAuCl and a silver salt AgX (X = "noncoordinating" counterion) are widely applied and are particularly effective catalysts which show superb reactivity profiles.[3] The properties of this catalyst system are tunable through modification of the spectator ligand L or the counterion X, which provides a vacant coordination site for the alkyne substrate to bind to the gold fragment. Significant alterations have been made to the spectator ligand (where L is a phosphine, phosphite, or *N*-heterocyclic carbene ligand), while the effect of modifying counterion X on the reactivity of cationic gold catalysts is well accepted.[4] However, the influence of the counterion on determining the reaction pathway in cycloisomerizations is much less well established.[5] Counterion effects on the reaction pathway have recently been observed in processes including diyne isomerization,[6] cycloisomerization of allenynes,[7] the reaction of alkenyl allyl units,[8] the selective synthesis of fluorenes or styrenes,[9] and in bromoallenyl ketone cycloisomerization.[10] The counterion has been

(1) For a discussion and review of π-acid alkyne activation by platinum and gold see: Fürstner, A.; Davies, P. W. *Angew. Chem., Int. Ed.* **2007**, *46*, 3410.

(2) For selected recent reviews of gold catalysis: (a) Hashmi, A. S. K. *Chem. Rev.* **2007**, *107*, 3180. (b) Li, J.; Brouwer, C.; He, C. *Chem. Rev.* **2008**, *108*, 3239. (c) Gorin, D. J.; Toste, F. D. *Nature* **2007**, *446*, 395C. (d) Núñez, E. J.; Echavarren, A. M. *Chem. Rev.* **2008**, *109*, 3326. (e) Arcadi, A. *Chem. Rev.* **2008**, *109*, 3266.

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(4) For a comprehensive review concerning ligand effects in homogeneous gold catalysis, see: Gorin, D. J.; Sherry, B. D.; Toste, F. D. *Chem. Rev.* **2008**, *108*, 3351.

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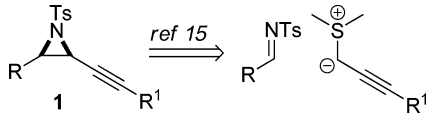
shown to be particularly important in the intramolecular hydroalkoxylation of allenols,[11] with a striking example employing chiral counterions to effect enantiocontrol.[12]

In this Letter, we report a new gold-catalyzed synthesis of *N*-tosyl-2,5-substituted pyrroles and demonstrate a counterion effect which alters the course of the reaction to yield *N*-tosyl-2,4-substituted pyrroles.

As key structural constituents in biologically active compounds and functional materials, and useful synthetic intermediates for complex molecule preparation, pyrroles are attractive targets for methodology development. Gold-catalyzed cycloisomerization approaches to pyrroles are potentially attractive due to the intrinsic atom-economy and the mild and practical reaction conditions employed alongside excellent functional group tolerance.[13,14]

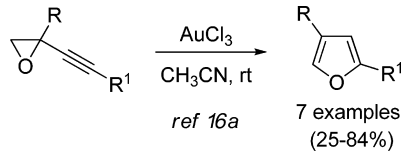
With this in mind, we became interested in a gold-catalyzed ring expansion of alkynyl aziridines **1** as a means to access pyrroles. As a prospective cyclization precursor, **1** can be prepared by a modular coupling of a readily accessible imine and a propargylic sulfonium ylide according to the method of Dai which leads to the *cis*-aziridine in high diastereoselectivity (Scheme 1).[15]

Scheme 1. Alkynyl Aziridine Preparation



The $AuCl_3$-catalyzed ring expansion of 2,2-disubstituted alkynyl epoxides to 2,4-substituted furans (Scheme 2)

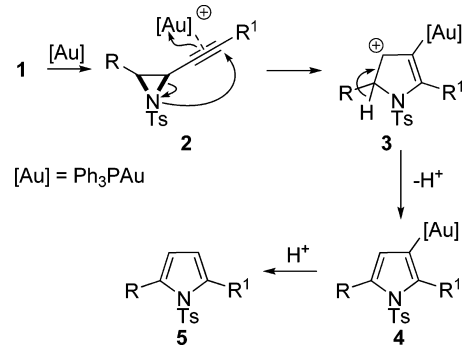
Scheme 2. Furan Synthesis by Ring Expansion



provided good precedent for triggering a ring expansion through activation of the alkyne in **1** by a π-acidic template (Scheme 3).[16] While our 2,3-disubstituted aziridines have a reduced electronic bias toward ring opening with the desired regioselectivity, we thought that the π-bond selective and strongly electrophilic cationic gold systems LAuX would be sufficient to activate the system toward our desired reactivity. After coordination of gold, ring-opening and attack of the nitrogen to the distal position of the alkyne would afford the metal-substituted cation **3**. Aromatization by proton elimination followed by protodemetalation should be facile to afford the desired pyrrole and release the catalyst.

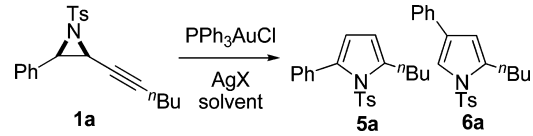
Our studies commenced with phenyl-substituted alkynyl aziridine **1a**, which was subjected to a standard combination

Scheme 3. Proposed Mechanism of Pyrrole Formation



of PPh_3AuCl and AgOTf in toluene at room temperature (entry 1, Table 1).[17] Pleasingly, the desired pyrrole **5a** was

Table 1. Survey of Reaction Conditions for the Cycloisomerization of Alkynyl Aziridines[a]



entry	X =	solvent	time/h	% yield[b]	**5**:**6**
1	OTf	toluene	4	75	24:1
2	OTf	CH_2Cl_2	0.75	60	1:7.6
3	OTf	$ClCH_2CH_2Cl$	1	50	1:24
4	OTf	CH_3NO_2	20	29	0:1
5	OTf	$CHCl_3$	20	72	1.1:1
6	OTf	EtOH	2	56	>50:1
7	OTf	Et_2O	20	79	>50:1
8	OTf	*o*-xylene	20	79	15:1
9	NTf_2	CH_2Cl_2	20	42	1:5
10	NTf_2	toluene	20	45	2.8:1
11	PF_6	CH_2Cl_2	36	60	2:1
12	PF_6	toluene	48	63	20:1
13	OTs	$ClCH_2CH_2Cl$	24	<10	1:0
14	OTs	toluene	24	<10	1:0
15	OTs	$ClCH_2CH_2Cl$[c]	3	98	1:0

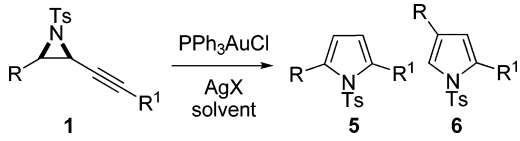
[a] AgX (5 mol %), PPh_3AuCl (5 mol %), **1** (0.1 mmol), solvent (0.5 mL) with all reactions run at rt unless otherwise specified. [b] Yields calculated by NMR against a known quantity of internal standard. [c] Reaction performed at 70 °C.

formed in good yield. However, a small amount of isomeric byproduct was observed. When the reaction was performed in dichloromethane, this unexpected isomer was isolated as the major product and identified as the 2,4-substituted regioisomer **6a** (entry 2).[18] **6a** was a major component of the product when the reaction was performed in 1,2-dichloroethane, nitromethane, and chloroform. Alternatively, when ethanol, ether, or xylene were employed as solvent, isomer **5a** was favored. A similar trend was observed when the triflimidate and hexafluorophosphate counterions were employed with either toluene or dichloromethane (entries 9−12).

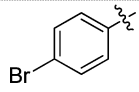
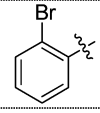
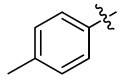
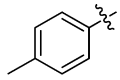
Switching counterion to tosylate led to isomer **5a** as the sole product, regardless of solvent (entries 13 and 14). The reaction was considerably slower than previously observed; however, mild heating allowed a quantitative yield of pure pyrrole **5a** to be obtained in 3 h (entry 15). The lower activity of the $Ph_3PAuOTs$ system is assigned to the tighter ion pair present in comparison to $Ph_3PAuOTf$.

A range of aryl-substituted aziridines were then prepared to further study these effects. The substrates were subjected to three sets of conditions based on the use of PPh_3AuCl as precatalyst (Table 2): System A employs AgOTf in dichloromethane; System B employs AgOTf in toluene; System C employs AgOTs in 1,2-dichloroethane at 70 °C.

Table 2. Gold-Catalyzed Synthesis of Pyrroles[a]



1 **5** **6**

entry	R	R^1	time/h	system[b]	**5**:**6**	yield[c]
1		*n*Bu **1a**	2	**A**	1:7.6	60
2			5	**B**	24:1	75
3			3.5	**C**	1:0	98
4		*n*Bu **1b**	2.5	**A**	1:1.1	74
5			12	**B**	1:0	85
6			4	**C**	1:0	98
7		*n*Bu **1c**	3	**A**	3:1	90
8			12	**B**	50:1	75
9			4	**C**	1:0	98
10		*n*Bu **1d**	1.5	**A**	1:50	32
11			1	**B**	1.5:1	30
12			5	**C**	1:0	98
13		Ph **1e**	0.5	**A**	1:6	98
14			5	**B**	1.4:1	79
15			3	**C**	1:0	98
16		Ph **1f**	0.5	**A**	0:1	65
17			1	**B**	0:1	60
18			3.5	**C**	1:0	98

[a] All reactions are run using 0.2 mmol of substrate with 5 mol % of gold and silver species at 0.2 M concentration. [b] System A employs AgOTf in CH_2Cl_2 at rt. System B employs AgOTf in toluene at rt. System C employs AgOTs in $ClCH_2CH_2Cl$ at 70 °C. [c] Isolated percentage yields of pyrrole products with ratio of isomers determined from ^1H NMR.

Across all substrates, the use of System C led exclusively to the single isomers **5a**−**5f** in quantitative yield (Table 2). Reaction workup and purification consisted solely of filtering the reaction mixture through a plug of silica gel. System B generally gave a mixture of isomers **5** and **6** with the ratio dependent on the nature of the substituents. System A generally led to the formation of isomer **6** as the major (or sole) product.

Aziridines substituted with electron-deficient aryl units (**1b** and **1c**) give lower proportions of the 2,4-isomer **6** with systems A and B. Increased amounts of 2,5-isomer **5** were seen when the bromine was in the *ortho*-position (entries 7 and 8 vs entries 4 and 5). The presence of a more electron-rich aromatic substituent (**1d** and **1f**) led to the 2,4-isomer **6** as the major product (entries 10 and 16).[19] The substitution pattern of the benzene unit remains unchanged over the process. Interestingly, the presence of an additional aryl unit at the alkyne terminus appears to aid the formation of **6** under certain conditions (entries 17 vs 11).

The results can be explained by considering the basicity of the counterion. In the presence of a sufficiently basic counterion such as tosylate (System C), proton elimination and transfer from **3** is facilitated (Scheme 4, Path I), regardless of reaction solvent. In the absence of such a counterion, an aromatic or otherwise weakly Lewis basic solvent can also mediate the proton transfer pathway, at a sufficient rate to see formation of **5** (System B). The intermediacy of the vinyl gold unit is established by the predominant incorporation of a deuterium label in that position when the reaction was run in D_2O-washed 1,2-

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(12) Hamilton, G. L.; Kang, E. J.; Mba, M.; Toste, F. D. *Science* **2007**, *317*, 496.

(13) For selected reviews of heterocycle synthesis by gold, see: (a) Patil, N.; Yamamoto, Y. *Chem. Rev.* **2008**, *108*, 3395. (b) Kirsch, S. F. *Synthesis* **2008**, 3183. (c) Patil, N. T.; Yamamoto, Y. *Arkivoc* **2007**, 121. (d) Shen, H. C. *Tetrahedron* **2008**, *64*, 7847. (e) Shen, H. C. *Tetrahedron* **2008**, *64*, 3885.

(14) For examples of gold-catalyzed pyrrole synthesis, see: (a) Witham, C. A.; Mauleon, P.; Shapiro, N. D.; Sherry, B. D.; Toste, F. D. *J. Am. Chem. Soc.* **2007**, *129*, 5838. (b) Istrate, F. M.; Gagosz, F. *Org. Lett.* **2007**, *9*, 3181. (c) Seregin, I. V.; Gevorgyan, V. *J. Am. Chem. Soc.* **2006**, *128*, 12050. (d) Harrison, T. J.; Kozak, J. A.; Corbella-Pané, M.; Dake, G. R. *J. Org. Chem.* **2006**, *71*, 4525. (e) Gorin, D. J.; Davis, N. R; Toste, F. D. *J. Am. Chem. Soc.* **2005**, *127*, 11260. (f) Arcadi, A.; Di Guiseppe, S.; Marinelli, F.; Rossi, E. *Tetrahedron: Asymmetry* **2001**, *12*, 2715. (g) Arcadi, A.; Di Guiseppe, S.; Marinelli, F.; Rossi, E. *Adv. Synth. Catal.* **2001**, *343*, 443.

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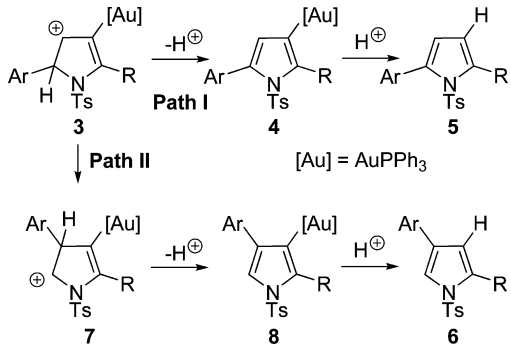
(17) Throughout this study, the aziridines were used as mixtures of the *cis*- and *trans*-diastereomers, with the *cis*-diastereomer predominant. See Supporting Information for ratios.

(18) Isomers **5a** and **6a** were distinguished spectroscopically by a comparison of the chemical shifts for the protons attached to the pyrrole rings [(^1H NMR; $CDCl_3$) **5a**: 6.07 ppm and 6.04 ppm (J = 3.3 Hz); **6a**: 7.58 ppm and 6.33 ppm (J = 1.9 Hz)]. **6a** shows the relative deshielding which is characteristic for a proton in the 5-position of a pyrrole. 1D GOESY (NOE) experiments confirm the regiochemistry within **6a** (see Supporting Information).

(19) The use of the 4-methoxyphenyl substituent led to degradation of the starting material.

Scheme 4. Possible Regiodivergence Pathway



dichloroethane (see Supporting Information). When both counterion and solvent are insufficiently basic (System A), path I is disfavored, and an alternative pathway takes precedence.[20] Although the mechanism is not yet established, a 1,2-aryl shift would place the aryl unit in the 4-position and afford intermediate **7**.[21] Electron-deficient aromatic units will be less prone to undergo the shift, matching the results seen. The proton to be eliminated is now adjacent to the gold fragment. Subjecting **5f** to reaction System A led to no interconversion to **6f**.

A recent thorough theoretical and experimental investigation into the gold-catalyzed reactions of bromoallenyl ketones shows a gold-associated chloride participating in H-migration. In the same work, the tetrafluoroborate and hexafluoroantimonate counterions are shown to be highly effective at bypassing H-migration in favor of alternate pathways, while the triflate counterion is sufficiently basic to mediate H-migration.[9,22]

In contrast, the triflate counterion is shown to be relatively ineffective at mediating the H-migration path from **3** to **5** in our process. However, when substrates bearing electron-deficient aryl units were employed, a significant amount of product resulting from direct deprotonation of **3** was observed. Substrate **1c** was therefore subjected to catalyst systems derived from $AgBF_4$ and $AgSbF_6$ to see if a similar trend was observed. While use of $AgSbF_6$ was ineffective, using $AgBF_4$ did give a slight improvement in the ratio of **6b** to **5b**. However, the reaction rate and overall recovery of pyrrole were severely reduced (see Supporting Information).

In summary, the effect of the counterion on reaction path is demonstrated in a new gold-catalyzed pyrrole synthesis from alkynyl aziridines. The atom-economic formation of 2,5-substituted pyrroles proceeds with quantitative yields and avoids extractive workup or lengthy purification with PPh_3AuOTs as catalyst. A novel reaction pathway is accessed on changing the catalyst system to PPh_3AuOTf, affording 2,4-substituted pyrroles. This study highlights the importance of selecting the correct counterion for gold-catalyzed processes as it can play an important role in determining reaction pathway.

Further studies to explore the impact of counterions on pathway determination in gold catalysis are ongoing, as are explorations of the scope and mechanism of this process.

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Supporting Information Available: Experimental details and ^1H and ^{13}C NMR spectra for compounds **1**, **5**, and **6**. 1D GOESY spectra for **6a**. Reaction scheme, experimental details, and ^1H NMR spectra for the reaction of **1d** in the presence of D_2O. Reaction schemes for the cyclization of **1c** employing $AgBF_4$ and $AgSbF_6$. This material is available free of charge via the Internet at http://pubs.acs.org.

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(20) An alternative analysis is that close association of a Lewis basic counterion or solvent to the cation may disfavor or block the orbital alignment required for the 1,2-aryl shift to take place.

(21) For examples of 1,2-alkyl and aryl shifts in gold-catalyzed reactions see, ref 13d and (a) Kirsch, S. F.; Binder, J. T.; Liébert, C.; Menz, H. *Angew. Chem., Int. Ed.* **2006**, *45*, 5878. (b) Lee, J. H.; Toste, F. D. *Angew. Chem., Int. Ed.* **2007**, *46*, 912. (c) Dudnik, A. S.; Gevorgyan, V. *Angew. Chem., Int. Ed.* **2007**, *46*, 5195. (d) Dudnik, A. S.; Schwier, T.; Gevorgyan, V. *Org. Lett.* **2007**, *9*, 3181. For a review, see: (e) Crone, B.; Kirsch, S. F. *Chem.—Eur. J.* **2008**, *14*, 3514.

(22) For a theoretical investigation into the role of a triflate counterion in the proton-transfer step of gold-catalyzed hydroamination of alkenes, see: Kovács, G.; Ujaque, G.; Lledós, A. *J. Am. Chem. Soc.* **2008**, *130*, 853.