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Pyrrole Synthesis Catalyzed by AgOTf or Cationic Au(I) Complexes

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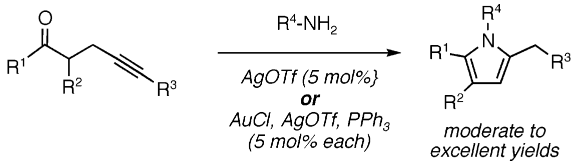
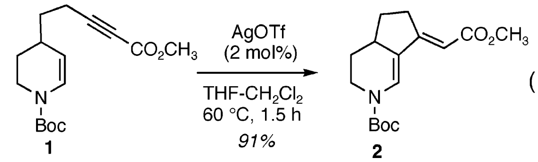


Either silver trifluoromethanesulfonate or a mixture of gold(I) chloride, silver trifluoromethanesulfonate, and triphenylphosphine catalyze the formation of pyrroles from substituted β-alkynyl ketones and amines. The reactions proceed by using 5 mol % of catalyst with yields of isolated pyrroles ranging from 13% to 92%. Sixteen examples are used to compare the effectiveness of each catalyst.

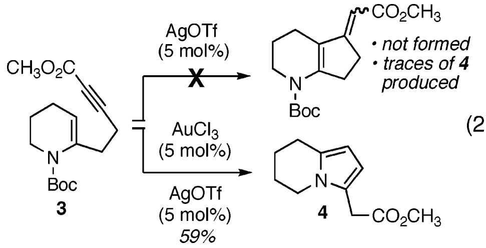
Introduction

Reactions catalyzed by silver and gold salts have recently experienced a renaissance in the chemical literature.[1] Classical transformations that were previously impractical for the laboratory setting due to the severe conditions required are now made synthetically useful with silver and gold catalysts.[2] We recently demonstrated that silver(I) trifluoromethanesulfonate (AgOTf) smoothly catalyzes the addition of an enesulfonamide or an enecarbamate onto a tethered alkyne to form five-membered rings in high yield, as exemplified in the conversion of **1** to **2** (eq 1).[3]



(1)

In our attempts to define the scope of this process, enecarbamate **3** was subjected to the conditions used for the cyclization of **1** (eq 2). Unfortunately, none of the desired product was obtained, but small traces of bicyclic pyrrole **4** could be observed in the crude product mixture. The addition of a catalytic amount of gold(III) chloride enhanced the reaction to produce **4** in 59% yield. Importantly, simple heating of **3** gave no reaction and treatment of **3** with TFA led to decomposition. Interestingly, the conversion of **3** to **4** does not proceed to a significant extent (<10%) with gold(III) chloride in the absence of AgOTf.



(2)

The formation of pyrroles under these conditions is perhaps not too surprising considering the work of Marshall forming oxygen heterocycles using silver catalysis.[4] Silver salts have also been used to promote the intramolecular addition of nitrogen nucleophiles to alkynes and allenes previously.[5] The pyrrole

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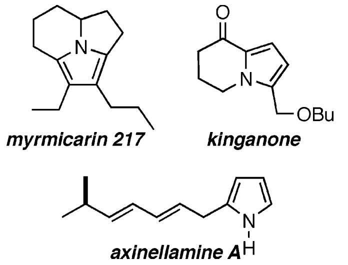
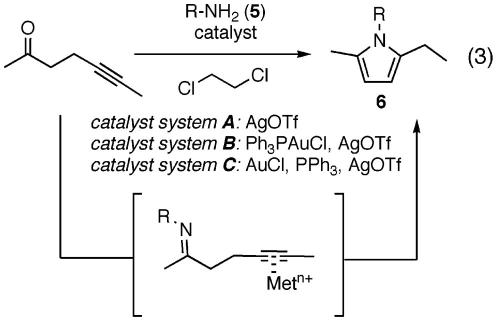


FIGURE 1. Examples of pyrrole containing natural products.

ring is of particular interest to the synthetic organic chemist as it is present in a large number of alkaloid natural products[6] that can exhibit biological activity[7] and structural complexity, as exemplified by the compounds in Figure 1.[8] Many solutions are available for the synthesis of pyrroles.[9] The cyclization of alkynylimines with 30 mol % of CuI in a triethylamine–dimethylacetamide mixture at 130 °C generates pyrroles in 50–93% yields.[10] Cyclizations with 5 mol % of a gold(III) species, NaAuCl$_4$, in ethanol at 40 °C proceed in high yields.[11] Platinum(II) chloride (20 mol % loading) at 60 °C for 100 h enabled the cycloisomerization of an alkynyl imine in 77% yield.[12] A recent silver(I) promoted pyrrole synthesis suggested that metal-promoted hydroamination of an alkyne followed by an intramolecular alkylation reaction took place.[13] Stoichiometric silver salts have been used for pyrrole synthesis, as well.[14] Inspired by the serendipitous result outlined in eq 2, we decided to examine the effectiveness of pyrrole formation using recently popular metal catalysts such as AgOTf or "cationic" gold(I) complexes.[15]

Results and Discussion

Our initial results are presented in eq 3 and Table 1. The test reaction involved the condensation of 5-heptyn-2-one with a monosubstituted amine derivative under either silver(I) (method A) or gold(I) catalysis. Importantly, two sets of conditions for



(3)

a) R=benzyl; **b**) R=allyl; **c**) R=*n*-pentyl; **d**) R=phenyl; **e**) R=cyclohexyl; **f**) R=*p*-toluenesulfonyl; **g**) R=*p*-methoxybenzyl; **h**) R=*p*-methoxyphenyl

TABLE 1. Test of Amine Scope[a]

entry	amine	method	*T* (°C)	*t* (h)	yield (%)[b]
1	**5a**	A	50	3	76
2	**5a**	B	50	2	79
3	**5a**	C	50	12	87
4	**5b**	A	50	12	66
5	**5b**	C	50	18	80
6	**5c**	A	50	12	77
7	**5c**	C	50	18	70
8	**5d**	A	80	24	13
9	**5d**	B	80	23	38
10	**5d**	C	80	24	59
11	**5e**	A	80	24	1
12	**5e**	C	80	24	27
13	**5f**	A	80	24	37
14	**5f**	C	80	24	35
15	**5g**	A	50	16	74
16	**5g**	C	50	12	68
17	**5h**	A	80	24	41
18	**5h**	C	80	24	60

[a] Reactions were carried out with 1 equiv of **5**, 1 equiv of ketone, and 5 mol % of catalyst system. [b] Isolated yields.

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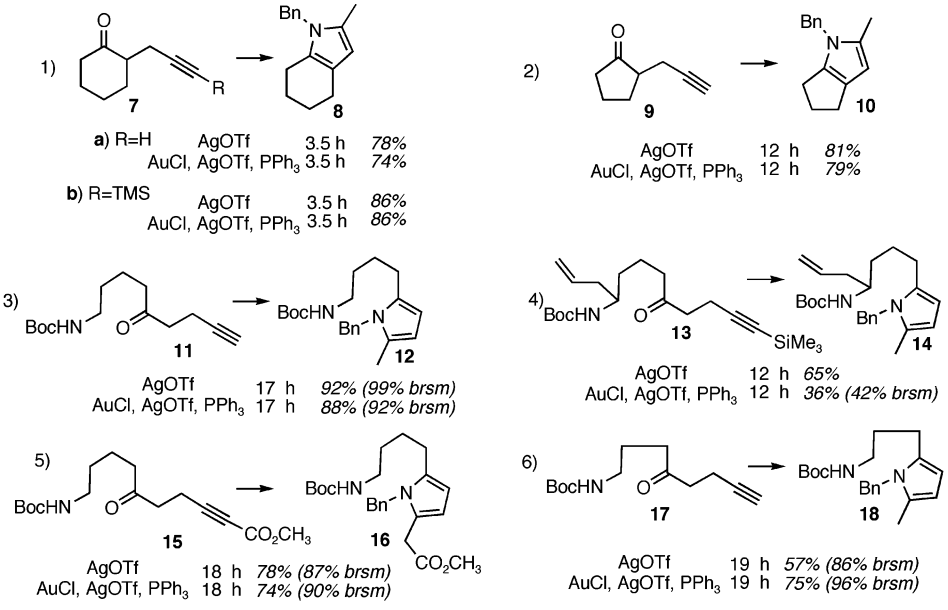

All reactions were carried out in 1,2-dichloroethane (0.2M) at 50 °C using 5 mol% of catalyst
brsm=based on recovered starting material

FIGURE 2. Examples of AgOTf or Au(I)-catalyzed pyrrole formation with benzylamine.

gold catalysis were attempted—the first with prepared (PPh$_3$)AuCl[16] and AgOTf (denoted as method B in Table 1) and a second set in which AuCl, AgOTf, and PPh$_3$ were mixed in situ prior to the addition of substrates (denoted as method C). Somewhat surprisingly, higher yielding results were obtained with method C compared to method B (entries 2 and 3; 9 and 10). Consequently, method C was adopted as the "standard conditions" for gold catalysis. The yields for these reactions are generally good (entries 1−7, 15, and 16) except when sterically demanding amines such as aniline, cyclohexylamine, or *tert*-butylamine are used (entries 8−12). No product is formed when *tert*-butylamine is used. Reactions between *p*-toluenesulfonamide (**5f**) and 5-heptyn-2-one proceed, but are not high yielding (entries 13 and 14).

No pyrrole products were observed between **5a** and 5-heptyn-2-one when the reactions were run at 80 °C for 24 h in the absence of a metal catalyst, or in the presence of 30 mol % of camphorsulfonic acid or 30 mol % of BF$_3$·OEt$_2$. The yields were not affected when reactions between 5-heptyn-2-one and **5a** with AgOTf catalysis were run in the presence of 1.5 equiv of bases such as magnesium oxide or calcium hydride. These experiments suggest that adventitious acid catalysis is not responsible for the observed reactivity. Yields suffer largely due to the lack of conversion to product, a phenomenon that appears to be largely dependent on the amine component. There was no change in yield in the reaction between 5-heptyn-2-one and **5a** with AgOTf catalysis when run in the presence of 2 equiv of water or in the presence of added **6a** (1 equiv) at the start of the reaction, implying that catalyst inhibition by the reaction products was not a significant factor.[17] The AuCl/AgOTf/ligand combination appears to be more thermally stable compared to AgOTf and consequently reactions that require higher temperatures progress to a greater extent. On the other hand, the use of AgOTf results in a qualitatively faster reaction rate and thus, for reactive amines, these two counteracting features tend to result in comparable yields with either catalyst.

The reaction also proceeds well in toluene, isopropyl alcohol, and dichloromethane, but works poorly in methanol, acetonitrile, and ethyl acetate, and fails in tetrahydrofuran. Comparable yields can be obtained with other silver sources (silver(I) trifluoroacetate and silver(I) tetrafluoroborate), but only traces of pyrrole products were observed with other metal salts such as platinum(II) chloride or iron(III) chloride. The addition of 5 mol % of PPh$_3$ to the AgOTf precatalyst system (ligand:metal ratio 1:1) resulted in a significantly less reactive catalyst (35% yield of **6a** after 24 h at 50 °C).

With these results in hand, a number of functionalized 4-pentynones were reacted with benzylamine in the presence of either AgOTf or AuCl/AgOTf/PPh$_3$ (Figure 2). As can be seen in Figure 2, this reaction smoothly forms pyrroles within bicycles (entries 1 and 2).[18] In addition, the reaction is reasonably tolerant of functional groups. Substrates **11**, **13**, **15**, and **17** were designed to examine the relative facility of intramolecular pyrrole formation (cf. eq 2) compared to intermolecular reactions with benzylamine. As can be seen, the intermolecular reaction involving benzylamine typically is the dominant process (entries 3−6). The reactions are usually completed prior to the reaction times indicated in Figure 2. The efficiency of the reaction did not significantly depend on the catalyst.

Deprotection of the *tert*-butyl carbamate in **11** and **17** (TFA, CH$_2$Cl$_2$) produced, as expected, imines **19** and **20**. Acid-promoted pyrrole formation was not observed. Treatment of these imines with either AgOTf or AuCl/AgOTf/PPh$_3$ generated bicyclic pyrroles **21** and **22** in moderate yields (Scheme 1).

Our preliminary investigations of the gold species formed upon mixing gold(I) chloride, AgOTf, and triphenylphosphine

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[16] Bruce, M. I.; Nicholson, B. K.; Shawkataly, O. B. *Inorg. Synth.* **1989**, *26*, 324−325.

[17] There was also no change in yield in the reaction between 5-heptyn-2-one and **5a** with AgOTf catalysis when run open to air or in a foil-wrapped flask.

[18] These compounds are known: see ref 9h.

SCHEME 1. Cyclization of Imines

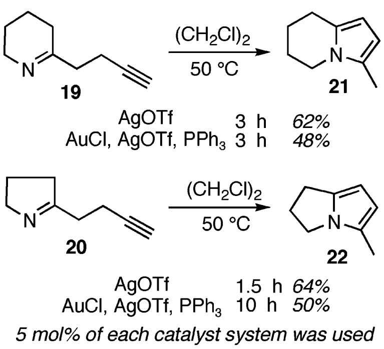
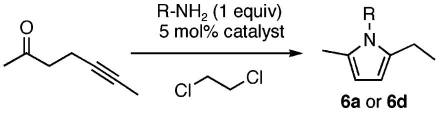


TABLE 2. ^{31}P NMR Data of Precatalyst Mixtures in $CDCl_3$

entry	mixture	δ[a]	δ (lit.)[b]
1	PPh_3AuCl	33.8	32.9
2	$(PPh_3)_2AuCl$	29.7	29.7
3	$AuCl + PPh_3$	33.8	
4	$PPh_3AuCl + AgOTf$	28.8	28.1
5	$(PPh_3)_2AuCl + AgOTf$	45.6	
6	$AuCl + PPh_3 + AgOTf$	45.6	

[a] Referenced to an external standard of 85% H_3PO_4. [b] Consult ref 19.

generated intriguing, but not definitive, results. ^{31}P NMR analysis of the mixture suggested that a single phosphorus-containing species was generated (Table 2). The chemical shift of this phosphorus-containing compound (δ 45.6) is consistent with that found when $(PPh_3)_2AuCl$[19] was treated with AgOTf (δ 45.6). If all added phosphine was consumed to form the bis(phosphine)gold(I) cation, reaction stoichiometry would dictate that three nonphosphine-containing byproducts, AuCl, AgOTf, and AgCl, could also be present in the reaction mixture and consequently be responsible for the observed catalytic activity. We therefore performed the following catalyst screening experiments (eq 4 and Table 3).



(4)

TABLE 3. Evaluation of Plausible Gold Species for Catalysis[a]

entry	amine	catalyst	T (°C)	t (h)	yield (%)[b]
1	**5a**	AuCl, AgOTf, PPh_3	50	12	87
2	**5a**	PPh_3AuCl, AgOTf	50	2	79
3	**5a**	$(PPh_3)_2AuCl$, AgOTf	50	19	80
4	**5a**	AuCl, AgOTf	0−25	10	39
5	**5a**	$AuCl_3$, AgOTf	50	21	21
6	**5a**	$[(PPh_3)_2AuCl + AgOTf)]$, $[AuCl + AgOTf]$[c]	50	12	40
7	**5a**	$[(PPh_3)_2AuCl + AgOTf]$, $[AuCl_3 + AgOTf]$[c]	50	22	69
8	**5d**	AuCl, AgOTf, PPh_3	80	24	59
9	**5d**	PPh_3AuCl, AgOTf	80	23	38
10	**5d**	$(PPh_3)_2AuCl$, AgOTf	80	24	48

[a] Reactions were carried out with 1 equiv of **5**, 1 equiv of ketone, and the designated catalyst system. [b] Isolated yields. [c] Only 2.5 mol % of each precatalyst was used.

For comparison, the reaction between **5a** and 5-heptyne-2-one forming **6a** with PPh_3, AuCl, AgOTf (87%), PPh_3AuCl and AgOTf (79%) are given in entries 1 and 2. Somewhat satisfyingly, the use of $(PPh_3)_2AuCl$ and AgOTf (5 mol % each) gave a 80% yield, lending credence to the suggestion that the bis(phosphine) gold cation was the active catalytic species (entry 3). This result was paralleled somewhat by using aniline (**5d**) as the nucleophile rather than benzylamine (**5a**) (entries 8−10). However, the efficiency of this process at 5 mol % loading still did not compare favorably to that in entry 1, where the reaction stoichiometry dictated that only 2.5 mol % of the bis(phosphine) gold cation would be formed under a "best-case" scenario. We then questioned whether a phosphine-containing species was in fact serving as the active catalyst.

Attempts to form a highly reactive "Au(I)OTf" species necessitated low temperatures (0 °C). Although the species was proficient at promoting the desired process, the reaction progress stalled relatively quickly (39%), possibly because "Au(I)OTf" is not thermally stable (entry 4). It does not appear that this compound is the active catalytic species at 50 °C. We were curious if an oxidation−reduction process takes place under the reaction conditions, generating a Au(III) species and Ag(0). In the event, the reaction with $AuCl_3$ and AgOTf gave a poor result (21% yield, entry 5). We then speculated that a mixed system of $(PPh_3)_2AuOTf$ in the presence of other "cationic" Au(I) or Au(III) species might be catalytically viable. At 2.5 mol % loading (mimicking the stoichiometry of the generation of the catalytic species under the conditions in entry 1) of $(PPh_3)_2AuOTf$ mixed with either "AuOTf" or "$AuCl_2OTf$" the overall yields of **6a** were 40% and 69%, respectively. A single catalytic species generated under these conditions is still elusive. Although it appears that a (bis)phosphine gold(I) cationic species is generated under the reaction conditions, its presence is not responsible for all of the observed reactivity of this catalyst system. Multiple entities capable of catalysis may be generated under these reaction conditions, complicating the reaction analysis. Even so, the pyrrole-forming process remains a useful and effective transformation.

In summary, either silver or gold catalysts efficiently facilitate the reactions between imines (formed in situ) and alkynes to form functionalized pyrroles in good yields. These methods may prove useful in the synthesis of pyrrole containing natural products. An interesting observation in our studies was the confirmation of increased thermal stability of the gold(I) precatalyst relative to the silver salt. However, it appeared qualitatively that reactions catalyzed by the silver salt proceed faster. The lower cost of silver salts relative to gold salts obviously may dictate the selection of catalyst for this transformation. Efforts in applying this reaction to natural product synthesis are ongoing in our laboratory.

Experimental Section

Sample Procedures for Pyrrole Synthesis: AgOTf Catalysis. To a solution of 3.7 mg of silver(I) trifluoromethanesulfonate (0.014 mmol) in 1.5 mL of 1,2-dichloroethane was added 31.3 mg of 5-heptyn-2-one (0.29 mmol) followed by 46 μL of benzylamine (0.42 mmol) and the reaction was stirred at 50 °C for 3 h. The reaction mixture was filtered through Celite and concentrated by rotary evaporation in vacuo to afford a crude brown oil. Purification by gradient column chromatography on triethylamine washed silica

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[19] For the preparation of $(PPh_3)_2AuCl$, see: (a) McAuliffe, C. A.; Parish, R. V.; Randall, P. D. *J. Chem. Soc., Dalton Trans.* **1979**, 1730−1735. For the ^{31}P NMR data for PPh_3AuCl and $(PPh_3)_2AuCl$, see: (b) Woehrle, G. H.; Brown, L. O.; Hutchinson, J. E. *J. Am. Chem. Soc.* **2005**, *127*, 2172−2183. For the ^{31}P NMR data of PPh_3AuOTf, see: (c) Preisenberger, M.; Schier, A.; Schmidbaur, H. *J. Chem. Soc., Dalton Trans.* **1999**, 1645−1650.

gel (petroleum ether → 20:1 petroleum ether:diethyl ether) afforded 43 mg (76%) of **6a** as a colorless oil.

AuCl, AgOTf, and PPh_3 Catalysis. To a flask charged with 4.7 mg of triphenylphosphine (0.018 mmol), 4.2 mg of gold(I) chloride (0.018 mmol), and 4.8 mg of silver(I) trifluoromethanesulfonate (0.019 mmol) was added 2 mL of 1,2-dichloroethane and the mixture was stirred at room temperature for 5 min. To the resulting opaque solution was added 42 mg of 5-heptyn-2-one (0.38 mmol) followed by 40 μL of benzylamine (0.37 mmol) and the reaction mixture was stirred at 50 °C for 12 h. The reaction mixture was filtered through Celite and concentrated by rotary evaporation in vacuo to afford a crude brown oil. Purification by gradient column chromatography on triethylamine washed silica gel (petroleum ether → 20:1 petroleum ether:diethyl ether) afforded 63 mg (87%) of **6a** as a colorless oil.

IR (film): 2070, 1419, 1300 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 7.28−7.41 (m, 3H), 6.97 (d, $J = 7.3$ Hz, 2H), 5.98−6.04 (m, 2H), 5.11 (s, 2H), 2.57 (quartet, $J = 7.6$ Hz, 2H), 2.24 (s, 3H), 1.29 (t, $J = 7.6$ Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 138.6, 134.3, 128.6, 127.9, 126.9, 125.5, 105.4, 103.4, 46.4, 19.7, 12.8, 12.2. MS (ESI): 200 $(M + H^+)$, 230 $(M + K^+)$.

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Supporting Information Available: Experimental procedures and characterization data for all previously unreported compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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