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Direct Carbocyclization of Aldehydes with Alkynes: Combining Gold Catalysis with Aminocatalysis

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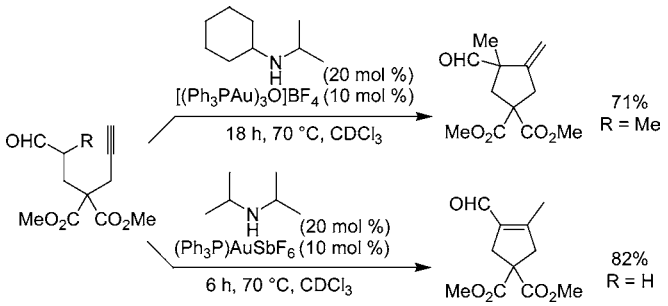
ABSTRACT



A combination of gold(I) complexes and amine bases catalyzes the 5-*exo-dig* cyclization of formyl alkynes. This direct α-functionalization of aldehydes with unactivated alkynes does not involve the use of preformed enol equivalents.

Cyclization reactions involving homogeneous gold catalysts as carbophilic Lewis acids have emerged as a powerful strategy to construct complex carbocyles.[1] Among the many different C−C bond formations that proceed through a gold(I)-catalyzed activation of alkynes toward nucleophilic attack, the addition of activated methylene compounds such as malonates and β-ketoesters to an unactivated alkyne (Scheme 1) has been particularly well-studied.[2] However, less enolizable carbonyls lack the required nucleophilicity to react directly with gold(I)-complexed alkynes under C−C bond-forming α-functionalization, instead suffering an initial C−O bond formation.[3,4] As an alternative strategy, a variety of enol equivalents derived from ketones and aldehydes were employed in gold(I)-catalyzed cyclization reactions. For instance, electron-rich alkyl enol ethers,[5] silyl enol ethers,[6] silyl ketene amides,[7] and enamines[8] efficiently attack gold(I)−alkyne complexes, although their synthetic utility is

Scheme 1. Combining Gold Catalysis with Enamine Catalysis

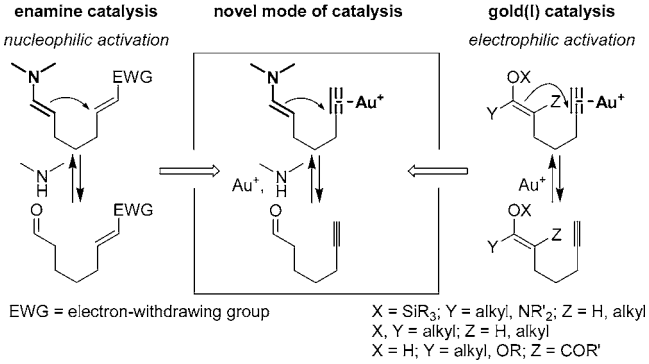


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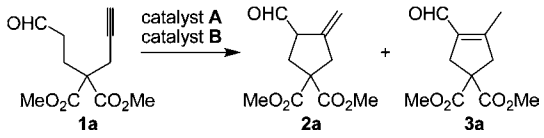
Table 1. Effect of Catalysts on the Cyclization of **1a**



entry	catalyst **A** (mol %)	catalyst **B** (mol %)	conditions	yield [%][a] **1a**:**2a**:**3a**
1			120 °C, toluene, 24 h	100:0:0[b]
2	$(Ph_3P)AuSbF_6$ (10)		70 °C, $CDCl_3$, 6 h	0:0:0[b]
3	$[(Ph_3PAu)_3O]BF_4$ (10)		70 °C, $CDCl_3$, 6 h	82:0:0
4		$HN(i\text{-}Pr)_2$ (20)	70 °C, $CDCl_3$, 6 h	100:0:0[b]
5	$(Ph_3P)AuSbF_6$ (10)	$HN(i\text{-}Pr)_2$ (20)	70 °C, $CDCl_3$, 6 h	0:0:82
6	$(Ph_3P)AuSbF_6$ (2)	$HN(i\text{-}Pr)_2$ (20)	70 °C, $CDCl_3$, 10 h	0:0:75
7	$(Ph_3P)AuSbF_6$ (10)	$HN(i\text{-}Pr)_2$ (20)	70 °C, CH_3NO_2, 6 h	0:0:80
8	$[(Ph_3PAu)_3O]BF_4$ (10)	$HN(i\text{-}Pr)_2$ (20)	70 °C, $CDCl_3$, 3 h	0:0:86
9	$[(Ph_3PAu)_3O]BF_4$ (10)	$HN(i\text{-}Pr)(c\text{-}Hex)$ (20)	70 °C, $CDCl_3$, 3 h	0:0:83
10	$[(Ph_3PAu)_3O]BF_4$ (10)	$H_2N(i\text{-}Pr)$ (20)	70 °C, $CDCl_3$, 3 h	0:0:74
11	$LAuSbF_6$ (10)[c]	$HN(i\text{-}Pr)_2$ (20)	70 °C, $CDCl_3$, 6 h	0:0:74
12	$(Ph_3P)AuNTf_2$ (10)	$HN(i\text{-}Pr)_2$ (20)	70 °C, $CDCl_3$, 2 h	0:0:13
13	$AgSbF_6$ (10)	$HN(i\text{-}Pr)_2$ (20)	70 °C, $CDCl_3$, 24 h	0:0:16
14	AgOTf (10)	$HN(i\text{-}Pr)_2$ (20)	70 °C, $CDCl_3$, 2 h	0:0:59
15	$PtCl_2$ (10)	$HN(i\text{-}Pr)_2$ (20)	120 °C, toluene, 24 h	0:0:50

[a] Yield of pure product after column chromatography unless otherwise indicated. [b] The ratios were determined by ^1H NMR spectroscopy. [c] L = 2-(biphenyl)di-*tert*-butylphosphine. [d] Traces of **3a** (<5%) were detected by capillary gas chromatography in the absence of $HN(i\text{-}Pr)_2$.

somewhat diminished due to the fact that the synthesis of these preformed enol equivalents involves an additional synthetic step.

On the other hand, simple aldehydes react in an intramolecular Michael reaction with enones by using amines as organocatalysts.[9,10] In this reaction, the catalytically generated enamine is the actual nucleophilic carbanion equivalent, which promotes α-carbonyl functionalization with the appropriate electrophile. Given the established capacity of preformed enamines to cyclize onto gold(I)−alkyne complexes,[8] we questioned whether it might be possible to utilize for the first time catalytically generated enol equivalents in a gold(I)-catalyzed cyclization reaction and thereby to access a mode of reaction that leads to the direct α-functionalization of aldehydes with unactivated alkynes. More specifically, we hypothesized that the combined use of an amine as a Lewis base catalyst and a gold(I) complex as a Lewis acid catalyst should activate formyl alkynes toward a C−C bond formation not currently possible without employing preformed enol equivalents.[11] Herein, we describe the direct cyclization of formyl alkynes catalyzed by the combined action of an amine and a cationic gold(I) complex.

Since previous studies demonstrated that soft noble-metal cations catalyze cascade reactions, of which one step is an intermolecular amine condensation,[8d,12] gold(I) π-acids were likely to maintain their chemoselectivity toward the alkyne moiety even in the presence of amines and water. To test this activation concept, the catalyzed cyclization was first evaluated with use of formyl alkyne **1a** (Table 1). In fact, treatment of formyl alkyne **1a** with both $(Ph_3P)AuSbF_6$ (10 mol %) and $i\text{-}Pr_2NH$ (20 mol %) in $CDCl_3$ at 70 °C resulted in the formation of the cyclization product **3a** in 82% isolated yield, but the reaction did not produce the double bond isomer **2a** that was expected to be initially formed through

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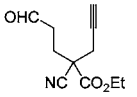
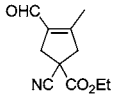
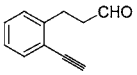
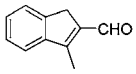
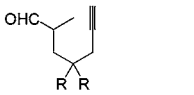
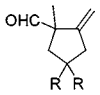
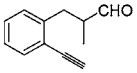
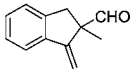
5-*exo-dig* cyclization.[13,14] The reaction can be run at low catalyst loadings for $(Ph_3P)AuSbF_6$ (2 mol %), while lowering the amine percentage led to a significant loss in reaction efficiency. In the presence of *i*-Pr_2NH (20 mol %), $[(Ph_3PAu)_3O]BF_4$ is slightly superior in terms of practicability due to the fact that competing decomposition was not observed. This cyclization reaction is accomplished by using a wide variety of transition metal catalysts other than $(Ph_3P)AuSbF_6$ and $[(Ph_3PAu)_3O]BF_4$ including several gold(I) complexes as well as silver(I) and platinum(II) salts, albeit in significantly reduced yields. The identity of the base catalyst proved to be less relevant as other bases such as *i*-$PrNH_2$, pyrrolidine, and (*c*-C_6H_{11})(*i*-Pr)NH gave the desired cyclization product with similar yields.

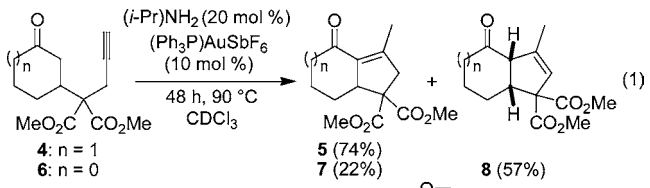
Table 2. Catalyzed Cyclization of Formyl Alkynes

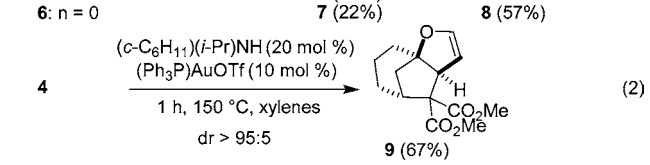
entry	substrate	product	time (h)	yield [%][a]
1	**1b**: R = CH_2OSiPh_2tBu	**3b**	4	78[b]
2	**1c**: R = CH_2OCH_3	**3c**	2	81[b]
3	**1d**: R = CH_2OCH_2Ph	**3d**	2	55[b]
			3	74[c]
4	**1e**: R = $C(O)CH_3$	**3e**	4	71[b]
5	**1f** 	**3f** 	4	97[b]
6	**1g** 	**3g** 	1	96[b]
7	**1h**: R = CO_2Me 	**2h** 	18	71[c]
			18	71[d]
			18	65[e]
			4	33[b]
8	**1i**: R = CH_2OCH_3	**2i**	18	68[c]
9	**1j**: R = CH_2OCH_2Ph	**2j**	18	72[c]
10	**1k** 	**2k** 	18	50[c]

[a] Yield of pure product after column chromatography. Reaction mixture was stirred in a sealed vial until TLC analysis (or ^1H NMR of the crude reaction mixture) indicated full conversion. [b] Conditions: substrate, 10 mol % $(Ph_3P)AuSbF_6$, 20 mol % $HN(i\text{-}Pr)_2$, 70 °C, $CDCl_3$. [c] Conditions: substrate, 7.5 mol % $[(Ph_3PAu)_3O]BF_4$, 20 mol % HN(*i*-Pr)(*c*-Hex), 70 °C, $CDCl_3$. [d] Conditions: substrate, 7.5 mol % $[(Ph_3PAu)_3O]BF_4$, 20 mol % $H_2N(i\text{-}Pr)$, 70 °C, $CDCl_3$. [e] Conditions: substrate, 10 mol % AgOTf, 20 mol % $HN(i\text{-}Pr)_2$, 70 °C, $CDCl_3$.

As revealed in Table 2, a range of formyl alkynes underwent cycloisomerization catalyzed by a gold(I) complex and an amine.[15] Reaction of α-unbranched aldehydes through cyclization followed by double bond migration gave 2-methylcyclopent-1-enecarbaldehyde products **3** (Table 2, entries 1−6). To create all-carbon quaternary stereocenters, we then employed substrates that bear an additional substituent in the α-position. In general, α-branched aldehydes were found to be less reactive in these direct α-functionalizations with unactivated alkynes. Consequently, a longer reaction time was required to achieve complete consumption of **1** (Table 2, entries 7−10). As exemplified for the reaction of **1h**, reactions of α-branched aldehydes should be conducted utilizing $[(Ph_3PAu)_3O]BF_4$ as π-acid catalyst; in the case of $(Ph_3P)AuSbF_6$, a significant decrease in yield was observed due to decomposition.

Treatment of cyclic ketones such as **4** with $(Ph_3P)AuSbF_6$ (10 mol %) and $H_2N(i\text{-}Pr)$ (20 mol %) in $CDCl_3$ at 90 °C in a sealed tube gave the desired cyclization products as well (eq 1), but the reaction was slowed markedly. In the case of the five-membered cyclic ketone **6** ($n = 0$), cyclization gave the double bond isomer **8** as the major product.[6c] Unexpectedly, slightly different reaction conditions [10 mol % $(Ph_3P)AuOTf$, 20 mol % (*c*-C_6H_{11})(*i*-Pr)NH, 150 °C, xylenes] resulted in a formal [3+2]-cycloaddition[16] to produce **9** as a single diastereoisomer in 67% isolated yield (eq 2). The structure of compound **9** was established by analysis of $^1H-^1H$ COSY, HMBC, and NOESY data.[17]





Since the presence of the amine base was required for cyclization in all cases, this outcome is in accord with the hypothesis that a combination of a Lewis acidic gold(I) complex and a Lewis basic amine can act as a viable catalyst system for the dual activation of formyl alkynes. At least two conceivable mechanisms can be proposed for this gold-catalyzed cyclization. In one, product formation may be rationalized by nucleophilic attack of an enamine intermedi-

(13) We assume that initially formed **2a** isomerizes directly into the more stable conjugated compound **3a** in the presence of $HN(i\text{-}Pr)_2$ at 70 °C.

(14) All reactions reported herein can be conducted with 1,2-DCE or $CHCl_3$ as solvent to provide the cyclization products in mostly identical yields as accomplished in $CDCl_3$. The use of $CDCl_3$ facilitates the realization of complete conversion by ^1H NMR analysis of the crude reaction mixtures.

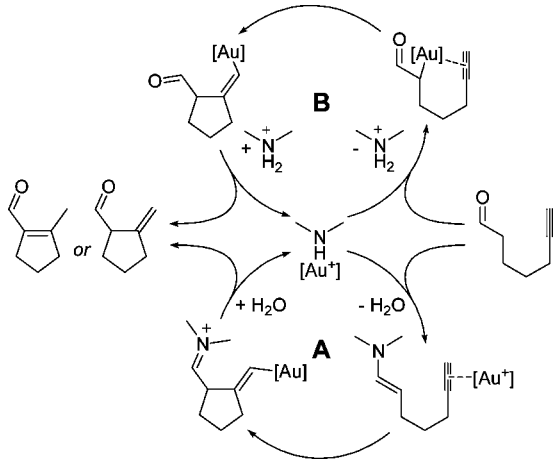
(15) **General Procedure.** Synthesis of **2h** (Table 2, entry 7): A solution of **1h** (100 mg, 0.42 mmol) and (*c*-C_6H_{11})(*i*-Pr)NH (20 mol %, 12 mg) in $CDCl_3$ (0.4 mL) was added to $[(Ph_3PAu)_3O]BF_4$ (7.5 mol %, 45 mg), and the reaction vial was sealed, protected from light, and stirred at 70 °C for 18 h (until ^1H NMR analysis of the reaction mixture indicated complete conversion). The mixture was concentrated under reduced pressure. Purification of the residue by flash chromatography on silica gel (pentanes/EtOAc = 95/5) gave **2h** as a colorless oil (71 mg, 0.30 mmol, 71%). R_f 0.48 (pentanes/EtOAc = 90/10); ^1H NMR (360 MHz, $CDCl_3$) δ 1.26 (s, 3 H), 2.23 (d, $J = 14.0$ Hz, 1 H), 2.92−3.07 (m, 3 H), 3.73 (s, 3 H), 3.74 (s, 3 H), 4.95 (app. t, $J = 2.2$ Hz, 1 H), 5.22 (app. t, $J = 1.9$ Hz, 1 H), 9.29 (s, 1 H); ^{13}C NMR (90.6 MHz, $CDCl_3$) δ 21.8, 40.5, 41.2, 53.1, 53.1, 56.9, 58.1, 110.9, 149.5, 171.7, 171.9, 199.8; LRMS (EI) 209 (19%) [$M^+ - CH_3O$], 180 (18%), 152 (95%), 93 (100%); HRMS 209.0815 [209.0814 calcd for $C_{11}H_{13}O_4$ ($M^+ - CH_3O$)].

(16) Huang, X.; Zhang, L. *J. Am. Chem. Soc.* **2007**, *129*, 6398.

(17) This ring system has not been previously described in the literature.

ate onto a Au(I)−alkyne complex as envisaged at the outset of the project (Scheme 2, **A**). This hypothesis is supported

Scheme 2. Possible Mechanism



by the fact that aldehydes such as *i*-PrCHO were found to undergo condensation with amines under the reaction conditions. An alternative mechanism involves the initial formation of an aldehyde-derived Au(I)−enolate[18] in the presence of the amine base (Scheme 2, **B**). In the gold-catalyzed case, this mechanism appears less likely since the use of tertiary amines such as EtN(*i*-Pr)$_2$ fails to give significant amounts of the corresponding cyclization products after 7 d at 70 °C in $CDCl_3$ utilizing $[(Ph_3PAu)_3O]BF_4$ as π-acid catalyst. On the other hand, it merits note that treatment of formyl alkyne **1h** with EtN(*i*-Pr)$_2$ (20 mol %) in $CDCl_3$ at 70 °C gave the cyclization product **2h** in 73% isolated yield when AgOTf (10 mol %) is used as the Lewis acid catalyst. This observation may indicate that the silver-catalyzed cyclization occurs through an in situ enolate generation.

In conclusion, we have shown that formyl alkynes undergo previously unknown cyclizations on activation with catalytic amounts of a Au(I) complex and an amine, thus opening a new entry into the direct α-functionalization of aldehydes with unactivated alkynes. Therefore, this protocol constitutes a valuable supplement to existing methodology for the Au(I)-catalyzed cyclization of enol equivalents onto alkynes.

Acknowledgment. This project was supported by the DFG and the FCI.

Supporting Information Available: Representative experimental procedures for catalytic formation of **2** and **3**, and copies of ^{1}H and ^{13}C NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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