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Gold(I)-Catalyzed Intramolecular Hydroamination of Alkyne with Trichloroacetimidates

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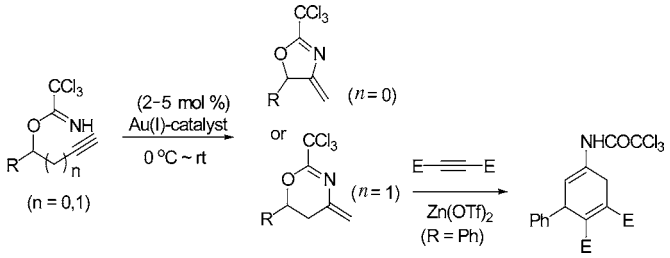
ABSTRACT



A study on the gold (I)-catalyzed intramolecular hydroamination of trichloroacetimidates derived from propargyl and homopropargyl alcohols is described. In the presence of 2–5 mol % of cationic Au(I) complex, a variety of trichloroacetimidates undergo efficient hydroamination under an exceptionally mild condition. An orthogonality of the current catalytic protocol with those using a stoichiometric electrophile as well as a preliminary synthetic application as a stable precursor of 2-acylamino-1,3-diene has been demonstrated.

A formal addition of an N−H bond across C−C multiple bonds, collectively known as hydroamination, has gained a great deal of attention as a simple and atom-economical protocol for N-functionalization.[1] While hydroamination catalyzed by lanthanide, alkali metal, and early transition metal complexes typically takes place through activation of an N−H bond,[2] those catalyzed by late transition metal complexes,[3] such as Pd, Ru, Pt, Ir, Rh, Ni, Ag, and Au, can occur through activation of C−C multiple bonds, followed by attack of the N-nucleophile. Recently, gold catalysts are emerging as efficient π-group activators,[4] and a number of N-nucleophiles have been reported for Au-catalyzed hydroamination of alkenes and alkynes,[5] including free amine,[5a] aniline,[5b] indole,[5c] sulfonamide,[5d] and carbamate.[5e] Considering that many late transition metals require high reaction temperature, we were prompted to explore new types of N-donors that react in mild reaction conditions under Au catalysis. Herein we report that trichloroacetimidates derived from propargyl and homopropargyl alcohols undergo an efficient Au(I)-catalyzed intramolecular hydroamination to alkyne under exceptionally mild conditions.

In continuation of our interest in gold-catalyzed activation of π-bonds as a catalytic alternative to using a stoichiometric electrophile, such as IBr,[6] we set out to explore the feasibility of imidate as a "soft" nucleophile that can N-functionalize an alkyne that is activated by a catalytic amount of Au(I)

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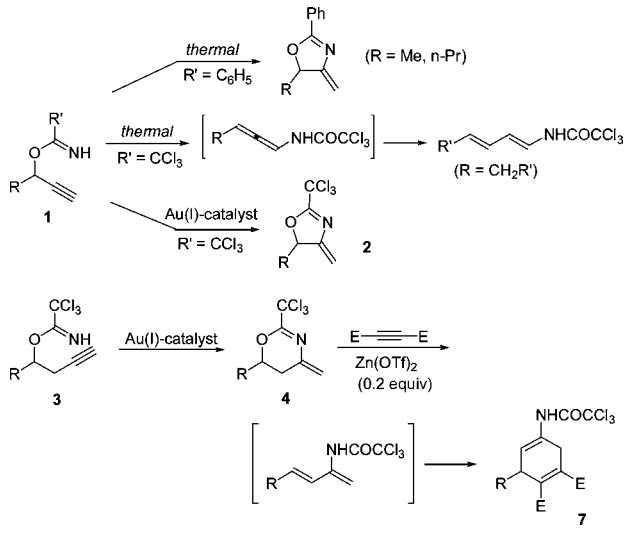
complex. Although cyclization of imidates of allyl and homoallyl alcohols promoted by a stoichiometric electrophile or mercuric salt is well documented,[7] the corresponding catalytic reaction of the triple bond has received little attention. Two most closely related examples are thermal 5-*exo-dig* cyclization of propargylic benzimidate into 4-methylene-4,5-dihydrooxazole and [3,3]-sigmatropic rearrangement of propargylic trichloroacetimidates, leading to 1-amino-1,3-diene (Scheme 1).[8]

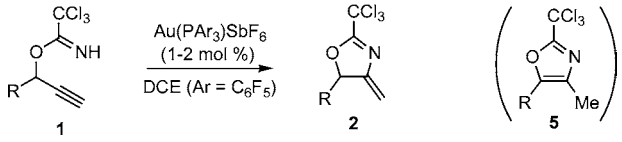
Scheme 1



In addition to their limited scope, these thermal reactions require a high temperature (~110 °C). On the other hand, current Au(I) catalysis occurs under exceptionally mild conditions (0 °C to room temperature) to give a Markovnikov product. Thus, trichloroacetimidates **1** and **3** cyclize in 5-*exo-dig* and 6-*exo-dig* mode to give **2** and **4**, respectively, having the usual 4-*exo*-methylene unit. Furthermore, we were intrigued by the possibility of **4** acting as a masked 2-acylamino-1,3-diene for subsequent Diels−Alder cycloaddition. The latter type of diene has scarce literature precedents, due to its thermal instability.[9]

We initiated our study by examining cyclization of propargylic trichloroacetimidates. Using $Au(PAr_3)SbF_6$ (Ar = C_6F_5) as a catalytic precursor prepared in situ,[6b] a variety of propargylic imidates cyclized efficiently without further necessity for optimization (Table 1). The 5-*exo-dig* process

Table 1. Cycloisomerization of **1**



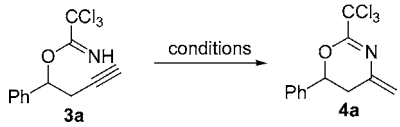
entry	**1**	R	catalyst loading	conditions[a]	yield (%)
1	**1a**	c−C_6H_{11}	1%	0 °C, 3 h	87
2	**1b**	*n*-C_7H_{15}	2%	0 °C, 5 h	92
3	**1c**	*i*-Pr	2%	0 °C, 8 h	74
4	**1d**	*t*-Bu	2%	0 °C, 2 h	89
5	**1e**	$PhCH_2$	2%	0 °C, 5 h	97
6	**1f**	H	2%	0 °C, 9 h	98

[a] Catalyst was prepared by mixing $Au[P(C_6F_5)_3]Cl$ (5 mol %) and $AgSbF_6$ (5 mol %) in situ.

proceeded with remarkable efficiency and only 1−2 mol % of catalyst was sufficient to give 4-methylene-4,5-dihydrooxazoles **2a**−**f** in good yields. Internal alkynes or aryl substrates (R = Ar in **1**), however, were not viable substrates (not shown). It is noteworthy that thermodynamically more stable oxazole compounds **5** (i.e., double bond isomerization) were not observed in the course of the reaction and purification.[10] The lack of isomerization to the oxazole is in sharp contrast to the related cycloisomerizations,[11] clearly demonstrating the mildness of the current protocol.

Next, we examined the reaction parameters for the cyclization of homopropargylic trichloroacetimidates using substrate **3a**. Selected optimization data are shown in Table 2. Using $Au(PPh_3)NTf_2$ (5%) as catalyst precursor, various

Table 2. Optimization of Cyclization of **3a**



catalyst[a]	solvent	temp (°C)	time	yield[b] (%)
$Au(PPh_3)NTf_2$	CH_3CN	40	24 h	29
$Au(PPh_3)NTf_2$	CH_3NO_2	40	12 h	15
$Au(PPh_3)NTf_2$	DCE	40	4 h	49
$AuCl_3$	DCE	40	12 h	37
$Au(PAr_3)SbF_6$	DCE	40	24 h	NR
$Au(PAr_3)NTf_2$	DCE	40	12 h	messy
$Au(PPh_3)OTf$	DCE	40	30 min	7
$Au(PPh_3)BF_4$	DCE	40	10 min	57 (62)
$Au(PPh_3)BF_4$	DCE	0	30 min	91
$Au(PPh_3)BF_4$ (2%)	DCE	0	12 h	79

[a] Catalyst was prepared by mixing $Au(PAr_3)Cl$ (5 mol %) with appropriate AgX salt in situ. [b] Isolated yields (brsm in parentheses).

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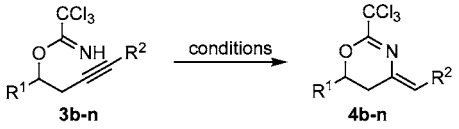
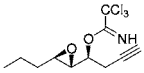
solvents were tested and 1,2-dichloroethane was found to be the best suited for the current cyclization, giving **4a** in 49% yield. We then screened a variety of catalysts. Use of PAr_3 (Ar = C_6F_5) ligand that was advantageously used in the formation of enol carbonates and the cycloisomerization of **1** was not effective at all. Interestingly, we found there is a significant counteranion effect in this reaction. While NTf_2, SbF_6, and OTf as counteranions were ineffective, change of counteranion to BF_4 led to 62% (brsm) yield of **4a** in just 10 min at 40 °C. Cooling the reaction mixture resulted in a cleaner conversion, giving 91% of **4a**. Lowering the catalyst loading to 2% still led to a reasonable yield, albeit in a prolonged reaction time.

The generality of the current method using the above optimized protocol is demonstrated in Table 3. Aliphatic and

Table 3. Cyclization of Homopropargylic Imidates



3b-n **4b-n**

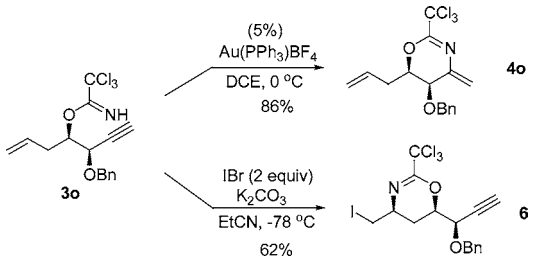
entry	sub	R^1	R^2	conditions[a]	yield[b] (%)
1	**3b**	*m*-CH_3-C_6H_4	H	0 °C, 3 h	84
2	**3c**	*m*-MeO-C_6H_4	H	0 °C, 2 h	88
3	**3d**	*p*-CN-C_6H_4	H	0 °C, 1.5 h	99
4	**3e**	*p*-Cl-C_6H_4	H	0 °C, 3 h	91
5	**3f**	H	H	0 °C, 10 min	84
6	**3g**	c-C_6H_{11}	H	0 °C, 2 h	85
7	**3h**	*n*-C_3H_7	H	0 °C, 30 min	74
8	**3i**	*t*-Bu	H	0 °C, 30 min	78
9	**3j**	Ph	Ph	0 °C, 4 h	95
10	**3k**	Ph	$SiMe_3$[c]	rt, 24 h	84
11	**3l**			0 °C, 2 h	80
12	**3m**			0 °C, 2 h	85
13	**3n**			0 °C, 2 h	73

[a] $Au(PPh_3)BF_4$ (5 mol %) in DCE (0.2 M). [b] Isolated yield. [c] [$Au(^nBu_3P)$]-BF4 (5 mol %) was used instead.

aromatic groups at R^1 having various steric and electronic demand were well accommodated (entries 1−8). An internal alkyne having a phenyl group at R^2 was also a viable substrate providing (*Z*)-**4j** in 95% isolated yield (entry 9).[12] Substrate **3k** having a TMS group at R^2 required change of ligand to P(*n*-Bu)$_3$ and gave a clean conversion to **4k** (entry 10). Substrate having a propargylic substituent, **3l** or **3m**, also underwent smooth reaction (entries 11 and 12). Excellent functional group tolerance is exemplified in the formation of **4n**, where the epoxide ring remained intact, underscoring high chemoselectivity of the current Au(I) catalysis (entry 13).

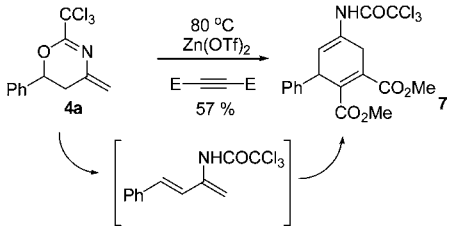
Chemoselectivity is a prime issue in organic chemistry, and we prepared substrates **3o** derived from homoallyl homopropargyl alcohol to further test this selectivity.[13] We found that IBr (2.5 equiv at −78 °C) and $Au(PPh_3)BF_4$ (5 mol % at 0 °C) showed completely orthogonal reactivities in the activation of alkene and alkyne, providing **4o** and **6**, respectively. This implies that the two reaction conditions could be employed complementarily (Scheme 2).

Scheme 2



Finally, we demonstrate the utility of heterocyclic product **4a** as a precursor for 2-acylamino-1,3-diene as the Diels−Alder cycloaddition partner. A preliminary result toward this goal is shown in Scheme 3. Treating **4a** with dimethylacetylenedicarboxylate in the presence of $Zn(OTf)_2$ (0.2 equiv) in toluene at 70 °C after 2 days provided cycloadduct **7** in 57% yield after chromatography.

Scheme 3



In summary, we have demonstrated that trichloroacetimidates derived from propargyl and homopropargyl alcohols undergo exceptionally mild cycloisomerization under Au(I) catalysis to provide 4,5-dihydrooxazoles or 5,6-dihydro-1,3-oxazine with an unusual *exo*-methylene unit. A preliminary application of the 5,6-dihydro-1,3-oxazine as a

(10) Upon keeping **2a** at room temperature for ~3 days, we started to observe formation of **5**. However, the dihydrooxazoles **2** could be kept for ca. 3 weeks at −20 °C without any decomposition.

(11) In a closely related cycloisomerization of propargyl amide, the intermediate dihydrooxazole with *exo*-methylene was observed only as an intermediate by NMR spectroscopy. See: Hashmi, A. S. K.; Weyrauch, J. P.; Frey, W.; Bats, J. W. *Org. Lett.* **2004**, *6*, 4391 and references therein.

(12) Based on NOE experiments. See Supporting Information.

(13) Maddess, M. L.; Lautens, M. *Org. Lett.* **2005**, *7*, 3557 and references therein.

stable 2-acylamino-1,3-diene precursor is presented. A study directed at applying this N-functionalization protocol in the context of total synthesis of natural product is currently underway in this laboratory.

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Supporting Information Available: Representative experimental procedures for the formation **2** and **4** as well as characterization of compounds **2a**−**f**, **4a**−**o**, **6**, and **7**. This material is available free of charge via the Internet at http://pubs.acs.org.

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