ORGANIC LETTERS

2006
Vol. 8, No. 16
3537−3540

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

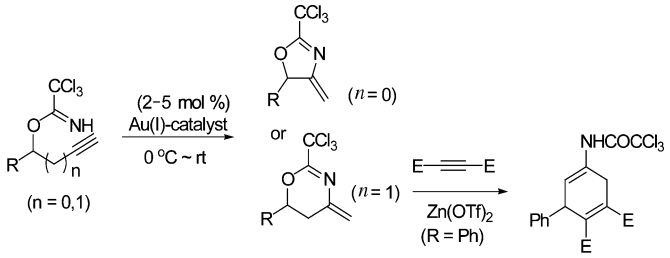
Ji-Eun Kang, Hak-Beom Kim, Jin-Woo Lee, and Seunghoon Shin*

Department of Chemistry, Hanyang University, 17 Haengdang-dong, Seongdong-gu, Seoul 133-791, Korea

sshin@hanyang.ac.kr

Received May 29, 2006

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)

(1) (a) Beller, M.; Seayad, J.; Tillack, A.; Jiao, H. *Angew. Chem., Int. Ed.* **2004**, *43*, 3368 and references therein. (b) Muller, T. E.; Beller, M. *Chem. Rev.* **1998**, *98*, 675. (c) Hong, S.; Marks, T. J. *Acc. Chem. Res.* **2004**, *37*, 673.

(2) (a) Aspinall, H. C. *Chem. Rev.* **2002**, *102*, 1807. (b) Tzalis, D.; Koradin, C.; Knochel, P. *Tetrahedron Lett.* **1999**, *40*, 6193. (c) Ackermann, L.; Bergman, R. G.; Loy, R. N. *J. Am. Chem. Soc.* **2003**, *125*, 11956.

(3) (a) Utsunomiya, M.; Hartwig, J. F. *J. Am. Chem. Soc.* **2003**, *125*, 14286. (b) Shimada, T.; Yamamoto, Y. *J. Am. Chem. Soc.* **2003**, *125*, 6646. (c) Karshtedt, D.; Bell, A. T.; Tilley, T. D. *J. Am. Chem. Soc.* **2005**, *127*, 12640. (d) Ahmed, M.; Seayad, A. M.; Jackstell, R.; Beller, M. *J. Am. Chem. Soc.* **2003**, *125*, 10311.

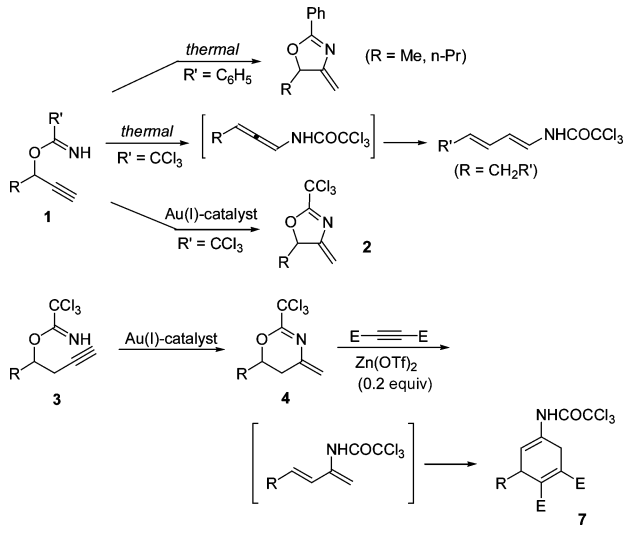
(4) For recent reviews, see: (a) Hashmi, A. S. K. *Gold Bull.* **2004**, *37*, 51. (b) Hoffmann-Roder, A.; Krause, N. *Org. Biomol. Chem.* **2005**, *3*, 387.

(5) (a) Morita, N.; Krause, N. *Org. Lett.* **2004**, *6*, 4121. (b) Mizushima, E.; Hayashi, T.; Tanaka, M. *Org. Lett.* **2003**, *5*, 3349. (c) Li, Z.; Shi, Z.; He, C. *J. Organomet. Chem.* **2005**, *690*, 5049. (d) Zhang, J.; Yang, C.-G.; He, C. *J. Am. Chem. Soc.* **2006**, *128*, 1798. (e) Han, X.; Widenhoefer, R. A. *Angew. Chem., Int. Ed.* **2006**, *45*, 1747.

10.1021/ol061307r CCC: $33.50
Published on Web 07/11/2006

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]

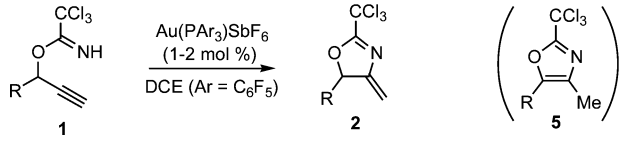
Scheme 1



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 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.

Table 1. Cycloisomerization of **1**

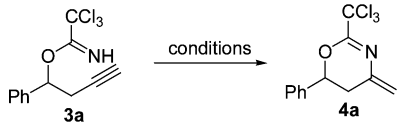


entry	1	R	catalyst loading	conditions[a]	yield (%)
1	**1a**	c−C_6H_{11}	1%	0 °C, 3 h	87
2	**1b**	*n*-C_7H_{15}	2%	0 °C, 5 h	92
3	**1c**	*i*-Pr	2%	0 °C, 8 h	74
4	**1d**	*t*-Bu	2%	0 °C, 2 h	89
5	**1e**	$PhCH_2$	2%	0 °C, 5 h	97
6	**1f**	H	2%	0 °C, 9 h	98

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

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).

(6) (a) Kang, J. E.; Lee, E. S.; Park, S. I.; Shin, S. *Tetrahedron Lett.* **2005**, *72*, 4334. (b) Kang, J. E.; Shin, S. *Synlett* **2006**, 717. (c) Shin, S. *Bull. Korean Chem. Soc.* **2005**, *26*, 1925. (d) Buzas, A.; Gagosz, F. *Org. lett.* **2006**, *8*, 515. For IBr-promoted reaction, see: (e) Marshall, J. A.; Yanik, M. M. *J. Org. Chem.* **1999**, *64*, 3798.

(7) (a) Cardillo, G.; Orena, M. *Tetrahedron* **1990**, *46*, 3321. (b) Kang, S. H.; Jun, H. S. *Chem. Commun.* **1998**, 1929. (c) Kang, S. H.; Kim, J. S. *Chem. Commun.* **1998**, 1353.

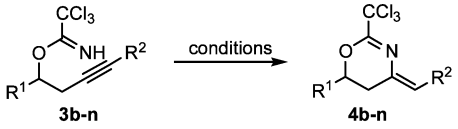
(8) (a) Overman, L. E.; Tsuboi, S.; Angle, S. *J. Org. Chem.* **1979**, *44*, 2323. (b) Overman, L. E.; Clizbe, L. A.; Freerks, R. L.; Marlowe, C. K. *J. Am. Chem. Soc.* **1981**, *103*, 2807. For application of 1-acylamino-1,3-diene in Diels−Alder reaction, see: (c) Overman, L. E.; Freerks, R.; Petty, C. B.; Clizbe, L.; Ono, R. K.; Taylor, G. F.; Jessup, P. J. *J. Am. Chem. Soc.* **1981**, *103*, 2816.

(9) (a) Chou, S.-S. P.; Chow, T. J.; Hsu, C.-H.; Yang, C.; Long, S.-H.; Lin, C.-D. *J. Chem. Soc., Chem. Commun.* **1997**, 1691. (b) McIntosh, J. M.; Pillon, L. Z. *Can. J. Chem.* **1984**, *62*, 2089. See also ref 8a.

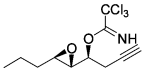
solvents were tested and 1,2-dichloroethane was found to be the best suited for the current cyclization, giving **4a** in 49% yield. We then screened a variety of catalysts. Use of PAr_3 (Ar = C_6F_5) ligand that was advantageously used in the formation of enol carbonates and the cycloisomerization of **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**

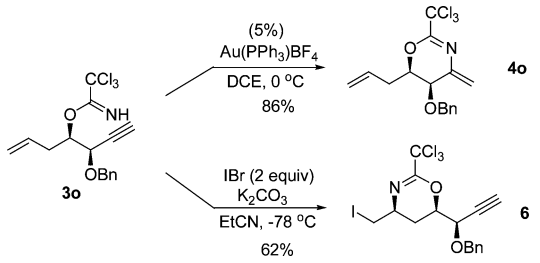
entry	sub	R^1	R^2	conditions[a]	yield[b] (%)
1	**3b**	*m*-CH_3-C_6H_4	H	0 °C, 3 h	84
2	**3c**	*m*-MeO-C_6H_4	H	0 °C, 2 h	88
3	**3d**	*p*-CN-C_6H_4	H	0 °C, 1.5 h	99
4	**3e**	*p*-Cl-C_6H_4	H	0 °C, 3 h	91
5	**3f**	H	H	0 °C, 10 min	84
6	**3g**	c-C_6H_{11}	H	0 °C, 2 h	85
7	**3h**	*n*-C_3H_7	H	0 °C, 30 min	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).

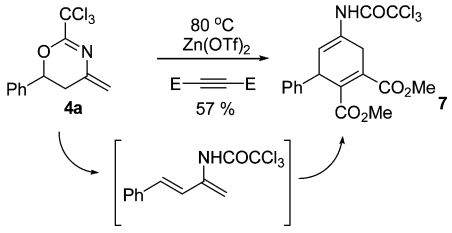
Chemoselectivity is a prime issue in organic chemistry, and we prepared substrates **3o** derived from homoallyl homopropargyl alcohol to further test this selectivity.[13] We found that IBr (2.5 equiv at −78 °C) and $Au(PPh_3)BF_4$ (5 mol % at 0 °C) showed completely orthogonal reactivities in the activation 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.

Acknowledgment. Financial support was provided by the Korean Science and Engineering Foundation (KOSEF, R01-2006-000-11283-0). J.E.K. and H.B.K. thank the BK21 program for a fellowship. The authors gratefully thank the reviewers for helpful comments on the manuscript organization.

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.

OL061307R