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GOLD-CATALYZED CYCLIZATION REACTION OF ALKYNYL *O-TERT*-BUTYLCARBAMATES

Hideto Miyabe,[a,b]* Yuichi Sami,[a] Takeaki Naito,[c] and Yoshiji Takemoto[a]*

[a]Graduate School of Pharmaceutical Sciences, Kyoto University, Yoshida, Sakyo-ku, Kyoto 606-8501, Japan. E-mail: takemoto@pharm.kyoto-u.ac.jp [b]School of Pharmacy, Hyogo University of Health Sciences, Minatojima, Kobe 650-8530, Japan. E-mail: miyabe@huhs.ac.jp [c]Kobe Pharmaceutical University, Motoyamakita, Higashinada, Kobe 658-8558, Japan. E-mail: taknaito@kobepharma-u.ac.jp

Abstract – Gold-catalyzed cyclization of alkynyl *O-tert*-butylcarbamates having *N*-benzyloxy group provided the 6-*endo* cyclized products selectively. Cascade reaction of *O-tert*-butylcarbamates having an enyne moiety was also examined.

Cyclic enols **A** and **B** are attractive synthetic intermediates. In general, the cyclic enol **A** can be prepared by the fixation of CO_2 with propargylic alcohols or amines via 5-*exo* cyclization.[1-3] In contrast, less is known about preparation of cyclic enol **B**;[4,5] thus, the development of effective 6-*endo* cyclization reaction of propargylic alcohol or amine derivatives remains a major challenge. Recently, mercuric triflate has been reported to promote the 6-*endo* cyclization of propargylic *O-tert*-butylcarbonates giving cyclic enol **B** by Nishizawa's group.[6] In this paper, we describe the gold (I)-catalyzed method for 6-*endo* cyclization of propargylic *O-tert*-butylcarbamates and the effect of *N*-substituents on nitrogen atom on 5-*exo*/6-*endo* selectivity.

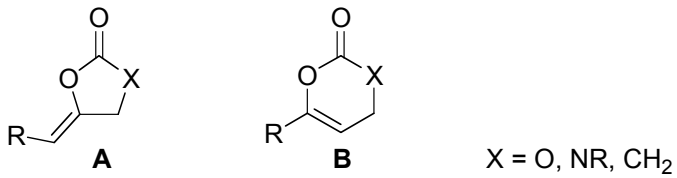
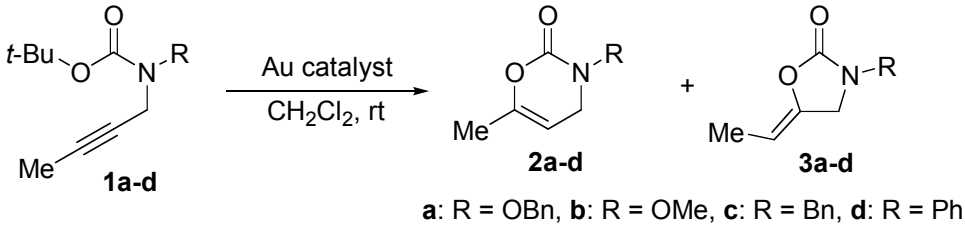


Figure 1. Cyclic enols **A** and **B**

To study the effect of gold catalysts on reactivity, our experiments began with the investigation of reaction of propargylic amine derivatives **1a-d** (Scheme 1).[7] All reactions were run in CH_2Cl_2 at room temperature. Representative results are shown in Table 1. Gold (III) catalyst using $AuCl_3$ and AgOTf accelerated the cyclization of **1a** to give the 6-*endo* cyclized product **2a** in 82% yield (entry 1). Although the combination of $AuCl_3$ and $AgNTf_2$ decreased the cyclization rate (entry 2), the selective formation of

endo-product **2a** was also observed in reaction using gold (I) catalyst using $AuCl(PPh_3)$ and $AgNTf_2$ (entry 3). Additionally, $AuNTf_2(PPh_3)$, prepared from $AuCl(PPh_3)$ and $AgNTf_2$, promoted the reaction with good activity to form the product **2a** in 93% yield after being stirred for 24 h (entry 4). The *N*-substituents (R) had an impact on 5-*exo*/6-*endo* selectivity. Hydroxylamine derivative **1b** (R = OMe) has also shown the good 6-*endo* selectivity (entry 5). In contrast, the reaction of **1c** (R = Bn) and **1d** (R = Ph) took place with lower 5-*exo*/6-*endo* selectivities (entries 6 and 7).



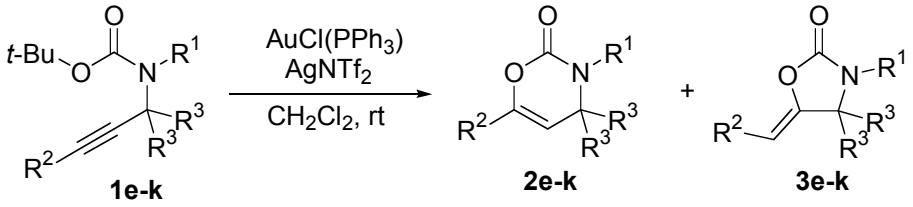
Scheme 1. Gold-Catalyzed Reaction of **1a-d**

Table 1 Gold-Catalyzed Reaction of Carbamates **1a-d**

Entry	Substrate	Catalyst	Product (% Yield)
1[a]	**1a**	$AuCl_3$, AgOTf	**2a** (82)
2[b]	**1a**	$AuCl_3$, $AgNTf_2$	**2a** (20)
3[c]	**1a**	$AuCl(PPh_3)$, $AgNTf_2$	**2a** (83)
4[d]	**1a**	$AuNTf_2(PPh_3)$	**2a** (93)
5[c]	**1b**	$AuCl(PPh_3)$, $AgNTf_2$	**2b** (49)
6[c]	**1c**	$AuCl(PPh_3)$, $AgNTf_2$	**2c** (82) + **3c** (10)
7[c]	**1d**	$AuCl(PPh_3)$, $AgNTf_2$	**2d** (46) + **3d** (23)

[a]Reaction carried out with $AuCl_3$ (6 mol%) and AgOTf (18 mol%) for 1 h. [b]Reaction carried out with $AuCl_3$ (6 mol%) and $AgNTf_2$ (18 mol%) for 1 h. [c]Reactions carried out with $AuCl(PPh_3)$ (6 mol%) and $AgNTf_2$ (6 mol%) for 1 h. [d]Reaction carried out with $AuNTf_2(PPh_3)$ (6 mol%) for 24 h.

We next studied the effect of substituents (R^1, R^2 and R^3) of carbamates **1e-k** on 5-*exo*/6-*endo* selectivity (Scheme 2). The 6-*endo* cyclized compounds **2e-g** were the predominant products in reaction of hydroxylamine derivatives **1e-g** having the phenyl or hydroxymethyl group as a substituent (R^2) (Table 2, entries 1-3). More interestingly, the effect of hydroxylamine moiety was confirmed by testing the reaction of butylamine derivative **1h**, which gave the 5-*exo* cyclized product **3h** as a major product (entry 4). The *Z*-configuration of **3h** was confirmed by NOE experiment.[6] In contrast to substrates **1e-h**, terminal alkyne derivatives **1i-k** gave the 5-*exo* cyclized products **3i-k** exclusively (entries 5-7).

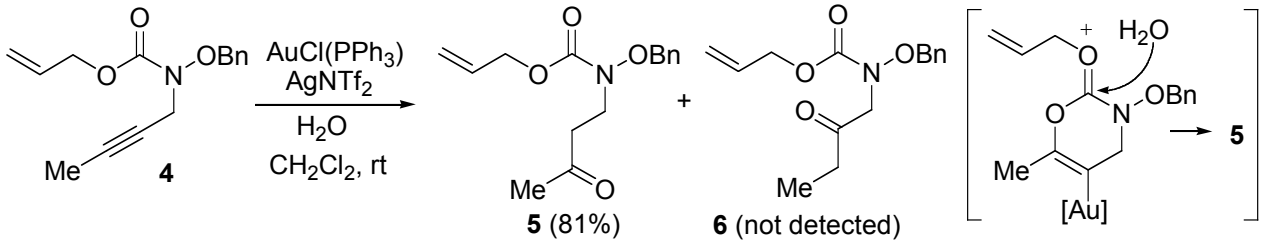


Scheme 2. Gold (I)-Catalyzed Reaction of **1e-k**

Table 2 Cyclization of Carbamates **1e-k** Using $AuCl(PPh_3)$ and $AgNTf_2$ [a]

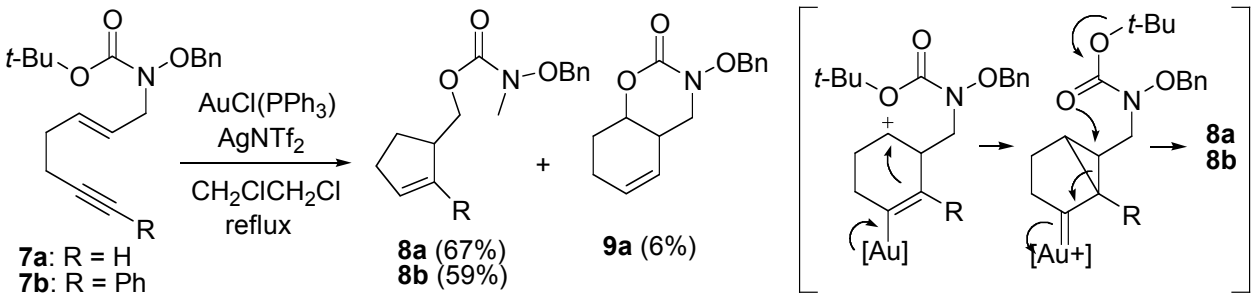
Entry	Substrate	R^1	R^2	R^3	Product (% Yield)
1	**1e**	OBn	Ph	H	**2e** (62) + **3e** (8)
2	**1f**	OBn	CH_2OH	H	**2f** (71)
3	**1g**	OMe	Ph	H	**2g** (63) + **3g** (11)
4	**1h**	Bu	Ph	H	**2h** (14) + **3h** (83)
5	**1i**	OBn	H	H	**3i** (79)
6	**1j**	Bn	H	H	**3j** (93)
7	**1k**	Bn	H	Me	**3k** (67)

[a]All reactions were carried out with $AuCl(PPh_3)$ (6 mol%) and $AgNTf_2$ (6 mol%) for 1 h.



Scheme 3. Regioselective Gold (I)-Catalyzed Hydration of Substrate **4**

The interest regioselectivity was also observed in the hydration of substrate **4** (Scheme 3). Ketone **5** was obtained in 81% yield without the formation of isomer **6**, probably due to 6-*endo* type assistance of carbamate moiety as shown in Scheme 3.



Scheme 4. Gold (I)-Catalyzed Cascade Reaction

Based on these studies, we finally explored the cascade reaction of enynes **7a** and **7b** (Scheme 4). As expected, the cyclized products **8a** and **8b** were isolated in 67% and 59% yields, respectively, through the cascade process involving 6-*endo* cyclization.

GENERAL EXPERIMENTAL PROCEDURE

A solution of starting material (0.04 mmol), $AuCl(PPh_3)$ (0.06 eq) and $AgNTf_2$ (0.06 eq) in CH_2Cl_2 (3.0 mL) was stirred for 1 h under argon atmosphere at rt. The organic solvent was removed under reduced pressure. Purification of the residue by column chromatography (hexane/AcOEt) afforded products.

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