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

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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 CO₂ 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.

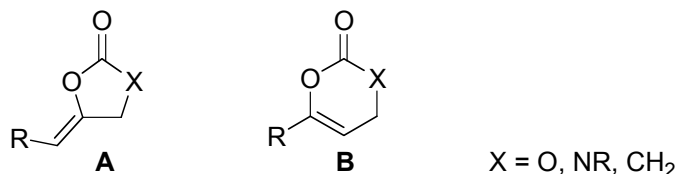
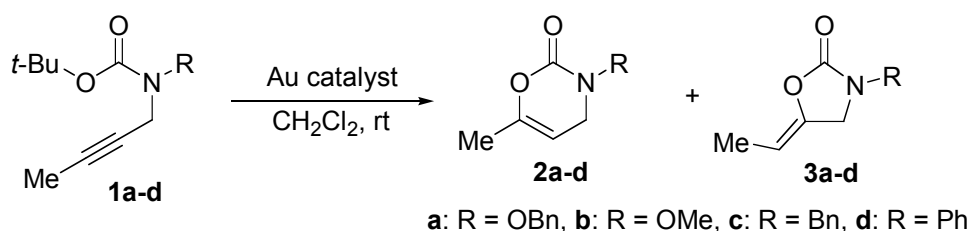


Figure 1. Cyclic enols **A** and **B**

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 CH₂Cl₂ at room temperature. Representative results are shown in Table 1. Gold (III) catalyst using AuCl₃ and AgOTf accelerated the cyclization of **1a** to give the 6-*endo* cyclized product **2a** in 82% yield (entry 1). Although the combination of AuCl₃ and AgNTf₂ decreased the cyclization rate (entry 2), the selective formation of

endo-product **2a** was also observed in reaction using gold (I) catalyst using AuCl(PPh₃) and AgNTf₂ (entry 3). Additionally, AuNTf₂(PPh₃), prepared from AuCl(PPh₃) and AgNTf₂, 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).



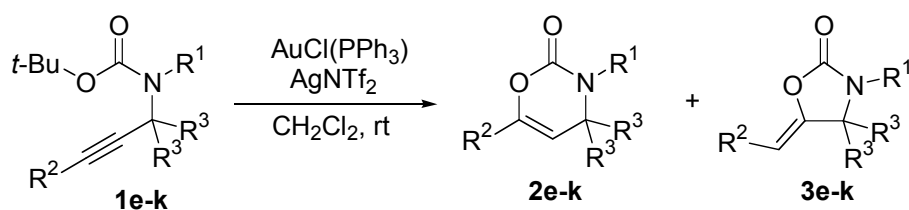
Scheme 1. Gold-Catalyzed Reaction of **1a-d**

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)

^aReaction carried out with AuCl₃ (6 mol%) and AgOTf (18 mol%) for 1 h. ^bReaction carried out with AuCl₃ (6 mol%) and AgNTf₂ (18 mol%) for 1 h. ^cReactions carried out with AuCl(PPh₃) (6 mol%) and AgNTf₂ (6 mol%) for 1 h. ^dReaction carried out with AuNTf₂(PPh₃) (6 mol%) for 24 h.

We next studied the effect of substituents (R¹, R² and R³) 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 (R²) (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).

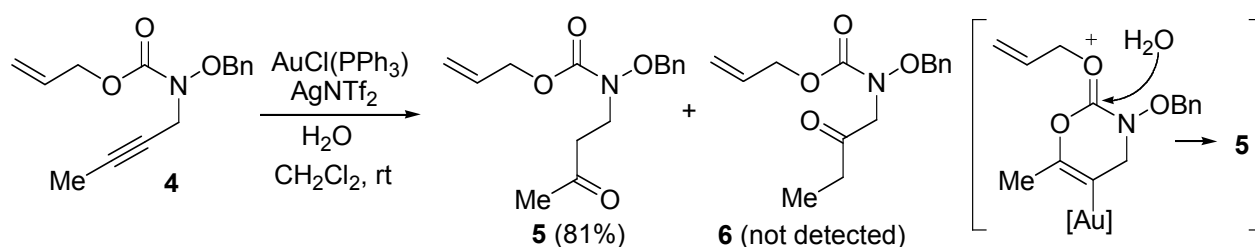


Scheme 2. Gold (I)-Catalyzed Reaction of **1e-k**

Table 2 Cyclization of Carbamates **1e-k** Using AuCl(PPh₃) and AgNTf₂^a

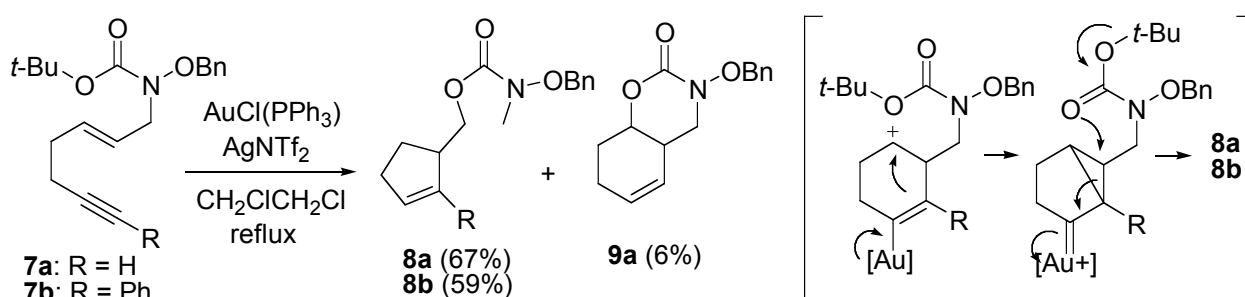
Entry	Substrate	R ¹	R ²	R ³	Product (% Yield)
1	1e	OBn	Ph	H	2e (62) + 3e (8)
2	1f	OBn	CH ₂ OH	H	2f (71)
3	1g	OMe	Ph	H	2g (63) + 3g (11)
4	1h	Bu	Ph	H	2h (14) + 3h (83)
5	1i	OBn	H	H	3i (79)
6	1j	Bn	H	H	3j (93)
7	1k	Bn	H	Me	3k (67)

^aAll reactions were carried out with AuCl(PPh₃) (6 mol%) and AgNTf₂ (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(PPh₃) (0.06 eq) and AgNTf₂ (0.06 eq) in CH₂Cl₂ (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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