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Short Note

(Z)-5-Benzylidene-4-phenyl-2-(*p*-tolyl)-4,5-dihydrooxazole

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Abstract: By strategic use of the valence difference between hard gold(III) and soft gold(I) catalysts, one-pot synthesis of (*Z*)-5-benzylidene-4-phenyl-2-(*p*-tolyl)-4,5-dihydrooxazole (**15**) from propargylic alcohol (**9**) and *p*-toluamide (**13**) was achieved via gold(III)-catalyzed propargylic substitution followed by gold(I)-catalyzed cyclization. The structure of **15** was confirmed by X-ray crystallographic analysis.

Keywords: gold catalysts; propargylic substitution; cyclization

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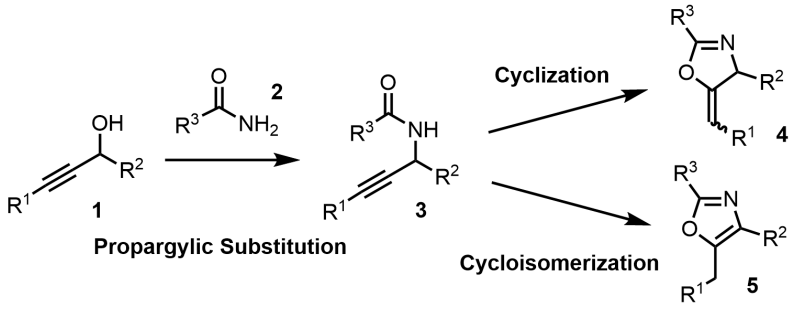
1. Introduction

Oxazoline and oxazole are frequently found as structural constituents of natural products and biologically active compounds [1,2] and are also useful as reagents and intermediates in organic synthesis [3–5]. Therefore, many synthetic methods have been developed, most of which are based on cyclization to oxazolines **4** or cycloisomerization to oxazoles **5** from propargylic amides **3** in the presence of transition metals [6,7] or other reagents [8,9] (Scheme 1). On the other hand, there are no reports of oxazoline **4** synthesis and only a few reports [10–12] of oxazole **5** synthesis by propargylic substitution-cyclization/cycloisomerization sequences from propargylic alcohol **1** and amide **2**, making this sequential transformation a challenging task because both propargylic substitution and subsequent cyclization/cycloisomerizarion should proceed effectively (Scheme 1).

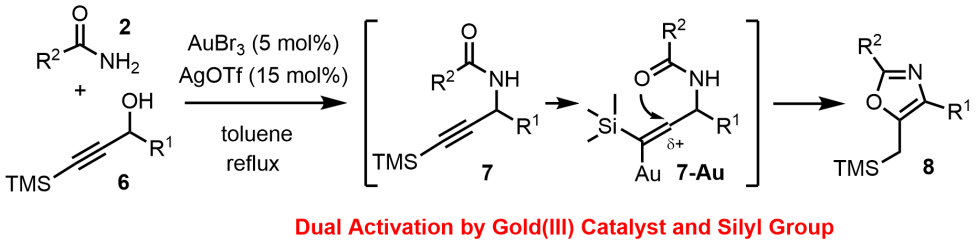


Scheme 1. Synthesis of oxazoline and oxazole.

So far, oxazoles **5** have been synthesized via propargylic substitution/cycloisomerization from propargylic alcohols **1** and amides **2** by using a combination of two transition metals ($Cp^*RuCl(\mu_2\text{-}SMe)_2RuCp^*Cl/AuCl_3/NH_4BF_4$ [10]) or ($Zn(OTf)_2/TpRuPPh_3(CH_3CN)_2PF_6$ [11]). However, these methods are applicable only to terminal propargylic alcohols **1** (R^1 = H), affording oxazoles **5** (R^1 = H) with a methyl group at the 5-position. Zhan et al. reported a one-pot synthesis of oxazoles **5** from propargylic alcohols **1** and amides **2** in the presence of *p*-toluenesulfonic acid monohydrate (PTSA) [12]. Although this procedure has a wide scope for the preparation of oxazoles **5** and is superior to the former two methods in that it requires only a single kind of catalyst, a stoichiometric amount of PTSA is required

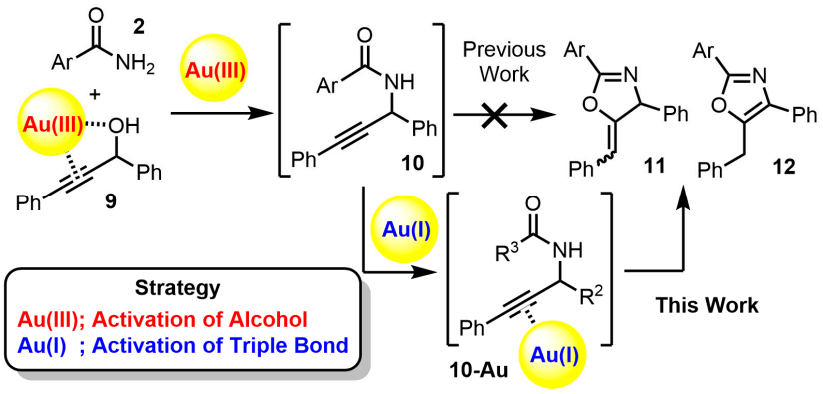
in the reaction. Thus, the development of an efficient procedure for the construction of oxazoline **4** and oxazole **5** from propargylic alcohol **1** and amide **2** is still required.

We have developed an efficient synthesis of heterocyclic compounds (cyclic ethers [13]/piperidines [14]/azepanes [15]) from propargylic alcohols by strategic use of oxophilic (hard) gold(III) and π-philic (soft) gold(I) catalysts. We also extended this procedure to the gold-catalyzed intermolecular reaction of propargylic alcohols with carbon nucleophiles, affording cyclic compounds (indenes [16]/dihydropyrans [17]). In addition, we developed a gold-catalyzed synthesis of substituted oxazoles **8** from 3-trimethylsilylpropargylic alcohols **6** and amides **2** via propargylic substitution followed by cycloisomerization in one pot [18] (Scheme 2). Activation of the triple bond by the gold catalyst and the β-cation-stabilizing effect (**7-Au**) of the silicon atom in the propargylic amide **7** are both important for the cycloisomerization process.



Scheme 2. One-pot synthesis of substituted oxazoles via gold(III)-catalyzed propargylic substitution followed by cycloisomerization.

We also found that the propargylic substitution reaction proceeds to give propargylic amide **10** as an intermediate when the silyl group at the terminal position of alkyne in propargylic alcohol is changed to a phenyl group, but the cyclization/cycloisomerization process to furnish oxazoline **11**/oxazole **12** from propargylic amide **10** does not proceed. To overcome this problem, we planned to dramatically accelerate the cyclization/cycloisomerization from propargylic amide **10** through the activation of the triple bond (**10-Au**) by a soft gold(I) catalyst [19] (Scheme 3). Here, we present a one-pot synthesis of (*Z*)-5-benzylidene-4-phenyl-2-(*p*-tolyl)-4,5-dihydrooxazole (**15**) from propargylic alcohol **9** and *p*-toluamide (**13**) via a gold(III)-catalyzed propargylic substitution followed by gold(I)-catalyzed cyclization.



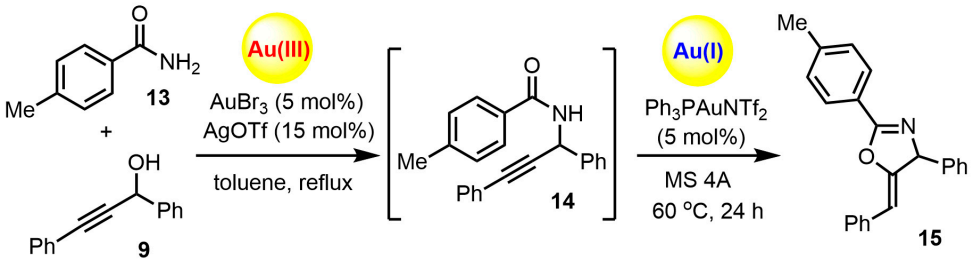
Scheme 3. Strategic use of the valence of gold catalysts. Gold(III)-catalyzed propagylic substitution followed by gold(I)-catalyzed cyclization/cycloisomerization.

2. Results and Discussion

2.1. Chemistry

The reaction conditions in the first propargylic substitution reaction of propargylic alcohol **9** and *p*-toluamide (**13**) were those identified in our previous work (5 mol% $AuBr_3$/15 mol% AgOTf in toluene, reflux, 20 min). For the cyclization of propargylic amide **14**,

we investigated the soft gold(I) catalyst $Ph_3PAuNTf_2$ (Scheme 4). Finally, treatment of propargylic alcohol **9** with *p*-toluamide (**13**) in the presence of $AuBr_3$ (5 mol%) and AgOTf (15 mol%) in toluene at reflux for 20 min afforded propargylic amide **14**, and then addition of $Ph_3PAuNTf_2$ (5 mol%) and MS 4A resulted in cyclization to furnish oxazoline **15** in 52% yield in one pot. The NMR spectroscopic data supported the formation of oxazoline **15**, and the expected structure was confirmed by means of X-ray crystallographic analysis [20].



Scheme 4. Gold(III)-catalyzed propargylic substitution followed by gold(I)-catalyzed cyclization.

2.2. X-ray Structure Analysis

X-Ray analysis for a single crystal of oxazoline **15** grown via slow diffusion of dichloromethane solvent at room temperature revealed a triclinic crystal structure and a P-1 space group (Table 1, Figure 1A, the Supplementary Material). The torsional angle between the *p*-tolyl ring and the oxazoline ring is 0.30° and that between the oxazoline ring and the phenyl ring is 0.01°, indicating that these three rings are nearly co-planar. The crystal packing was driven by the combination of the intermolecular π−π stacking interaction (3.4 Å) (Figure 1, (B) green line) between the tolyl group and two intermolecular CH-π interactions (2.8 Å) (Figure 1, (B) yellow line) between the methyl group and sp^2–carbon of the carbon–carbon double bond.

Table 1. Summary of the crystallographic data and refinement statistics for **15**.

Parameter	Data
Identification code	$C_{23}H_{19}NO$
Formula weight	325.29
Temperature/K	293(2)
Crystal system	triclinic
Space group	P-1
Unit cell dimensions	a/Å 8.0541(4) α/° 81.010(4)
	b/Å 9.3301 (5) β/° 89.182(4)
	c/Å 11.8454(6) γ/° 72.271(5)
Volume/Å3	836.91(8)
Z	2
ρcalc g/cm^3	1.291
μ/mm^{-1}	0.611
F(000)	344.0
Crystal size/mm^{-1}	0.25 × 0.15 × 0.20
Radiation	Cu Kα (λ = 1.54184)
2Θ range for data collection/°	16.83 to 102.658
Index ranges	$-8 \leq h \leq 8$, $-9 \leq k \leq 9$, $-5 \leq l \leq 11$
Reflections collected	1752

Table 1. *Cont.*

Parameter	Data
Independent reflections	1462 [R_{int} = 0.0045, R_{sigma} = 0.0121]
Data/restraints/parameters	1462/0/227
Goodness-of-fit on F^2	1.056
Final R indexes [I $\geq 2\sigma$ (I)]	R_1 = 0.0301, wR_2 = 0.0781
Final R indexes [all data]	R_1 = 0.0316, wR_2 = 0.0793
Largest diff. peak/hole/e Å^{-3}	0.17/−0.17

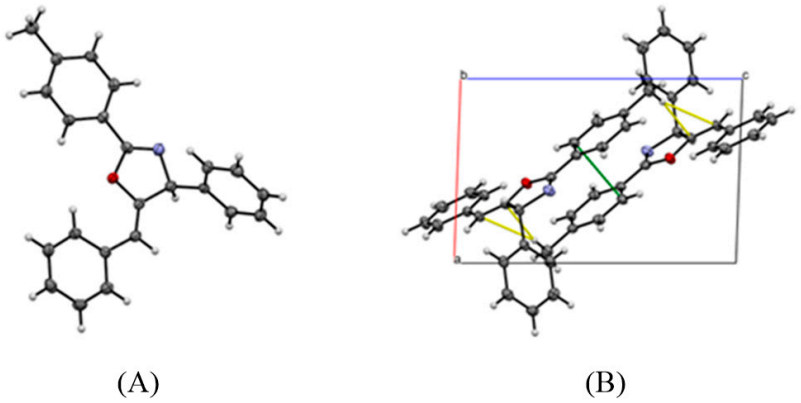


Figure 1. (A) ORTEP diagram of (*Z*)-5-benzylidene-4-phenyl-2-(*p*-tolyl)-4,5-dihydrooxazole (**15**) with thermal ellipsoids at the 50% probability level. (B) Packing diagram of **15** along the b axis. Atom colors: (a) blue = nitrogen, (b) white = hydrogen, (c) red = oxygen, (d) grey = carbon. Interaction colors: (e) green line = $\pi-\pi$ stacking interaction, and (f) yellow line = CH-π interaction.

3. Materials and Methods

3.1. General Information

^{1}H and ^{13}C NMR spectra were recorded with a BRUKER AV-300 spectrometer (Bruker, Billerica, MA, USA) at room temperature, with tetramethylsilane as an internal standard ($CDCl_3$ solution). Chemical shifts were recorded in ppm, and coupling constants (*J*) in Hz. Infrared (IR) spectra were recorded with a Shimadzu IRSpirit-T. Mass spectra (Shimadzu, Kyoto, Japan) were recorded on JEOL JMS-700 spectrometers (JEOL, Tokyo, Japan). Merck silica gel 60 (1.09385) and Merck silica gel 60 F254 were used for column chromatography and thin layer chromatography (TLC), respectively.

3.2. Synthesis of (Z)-5-benzylidene-4-phenyl-2-(p-tolyl)-4,5-dihydrooxazole (15)

$AuBr_3$ (5.3 mg, 0.012 mmol, 5 mol%) and AgOTf (9.4 mg, 0.036 mmol, 15 mol%) were added at room temperature to a solution of 1,3-diphenylprop-2-yn-1-ol (**9**) (50 mg, 0.24 mmol) and *p*-toluamide (**13**) (33 mg, 0.24 mmol) in toluene (4 mL), and the mixture was heated at reflux for 20 min. After confirming consumption of the starting alcohol **9** and the production of propargylic amide **14**, $Ph_3PAuNTf_2$ (19 mg, 0.012 mmol, 5 mol%) and MS 4A (100 mg) were added at room temperature. The reaction mixture was stirred at 60 °C for 24 h, then filtered, and the filtrate was concentrated *in vacuo*. The crude product was subjected to column chromatography on silica gel (hexane:AcOEt = 20:1) to give the oxazoline **15** (41 mg, 52%).

Mp. 152-153 °C; IR (ATR) 3085, 3061, 3028, 2921, 1695, 1647, 1611, 1493, 1452, 1278, 1179, 1059, 1019 cm^{-1}; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 8.05 (2H, d, *J* = 8.4 Hz), 7.59 (2H, d, *J* =8.4 Hz), 7.40-7.29 (9H, m), 7.25-7.18 (1H, m), 5.93 (1H, d, *J* = 2.4 Hz), 5.52 (1H, d, *J* = 2.4 Hz), 2.45 (3H, s); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 163.0, 155.5, 142.8, 140.4, 134.8, 129.4, 128.9, 128.5, 128.4, 128.1, 128.0, 127.6, 126.3, 123.6, 102.8, 74.1, 21.7; HRMS (EI) *m*/*z* calcd for $C_{23}H_{19}NO$

325.1467, found 325.1473. The supporting ^{1}H-NMR, ^{13}C-NMR, IR and mass spectra are presented in the Supplementary Material Files.

4. Conclusions

By the strategic use of the valence difference between hard gold(III) and soft gold(I) catalysts, we were able to synthesize (*Z*)-5-benzylidene-4-phenyl-2-(*p*-tolyl)-4,5-dihydrooxazole (**15**) by gold(III)-catalyzed propargylic substitution, followed by gold(I)-catalyzed cyclization in one pot. We are currently examining the application of this method to the synthesis of various (*Z*)-5-benzylidene-4-phenyl-2-(*p*-tolyl)-4,5-dihydrooxazole derivatives.

Supplementary Materials: The following materials are available online. Figure S1. ^{1}H, ^{13}C-NMR, IR, HRMS and X-ray data (CCDC-2239857) of (*Z*)-5-benzylidene-4-phenyl-2-(*p*-tolyl)-4,5-dihydrooxazole (**15**).

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Sample Availability: Samples of the compounds are not available from the authors.

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