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Gold(I)-Catalyzed Regioselective Cyclizations of Silyl Ketene Amides and Carbamates with Alkynes

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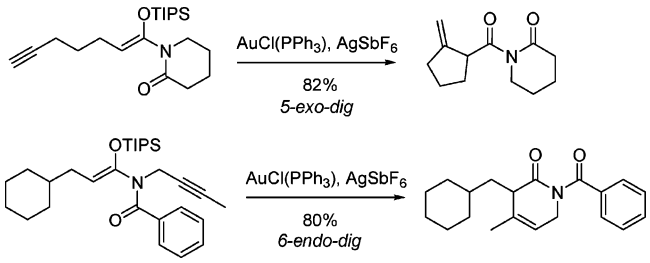
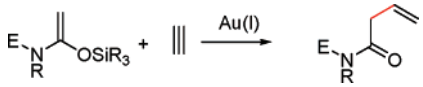
Received May 14, 2007



The gold(I)-catalyzed regioselective cyclizations of silyl ketene amides or carbamates with alkynes were utilized to construct cyclopentanes or dehydro-δ-lactams.

Gold-catalyzed cyclization reactions involving an alkyne have emerged as a powerful methodology to construct carbocycles,[1] as well as oxygen-[2] and nitrogen-containing heterocycles.[3] In these transformations, through the interaction of the alkyne with a cationic gold catalyst serving as a π-acid, the electron density of the triple bond is reduced, thereby rendering it electrophilic. A pendant carbon or heteroatom nucleophile may undergo nucleophilic addition followed by subsequent transformations to furnish carbocycles or heterocycles. Prior to our work, the Iwasawa group utilized tungsten[4] or rhenium[5] catalysts to accomplish a similar type of transformation. However, the active tungsten catalyst needs to be prepared by photoirradiation prior to the reaction. Alternatively, a reaction mixture containing the tungsten precatalyst needs to be photoirradiated throughout the reaction course. In addition, a typical reaction takes several days to complete even for 0.1 equiv of catalyst loading. The rhenium-catalyzed reactions need to be degassed and photoirradiated for multiple hours. Recently, it has been reported that palladium[6] or gold[1f] can catalyze the cyclization of the ketone-derived silyloxy-1,6-enynes to generate methylenecyclopentanes. For the tungsten-, rhenium-, palladium-, and gold-catalyzed reactions, the reported carbon nucleophiles that directly attack the metal−alkyne complex are mainly limited to silyl enol ethers derived from ketones. To develop more practical and convenient C−C bond formation with respect to the tungsten and rhenium chemistry mentioned above and to expand the scope of the nucleophiles, herein we report the gold(I)-catalyzed regioselective cyclization of silyl ketene amide or carbamate nucleophiles (Scheme 1) to form cyclopentanes and dehydro-δ-lactams.

SCHEME 1



All the substrates except **3d** shown in Tables 1 and 2 were prepared following the literature procedures reported by Kozmin et al.[7] With a variety of silyl ketene amide or carbamate substrates in hand, we screened the gold(III) catalysts **1a** and **1b** and gold(I) catalysts **1c**−**f**, with or without the silver cocatalysts **2a** or **2b** (Scheme 2). After the optimization of the reaction conditions using **3b** as a substrate, we found that the combination of **1e** and **2a** or **2b** in a 10:1 mixture of dichloromethane and methanol gave the best results. The methanol cosolvent serves as a proton source. For all cases reported in Tables 1 and 2, the major side reaction is the

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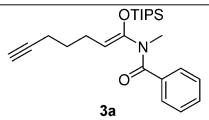
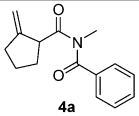
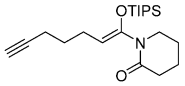
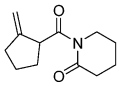
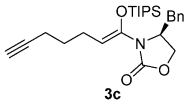
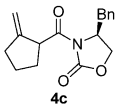
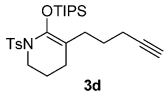
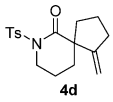
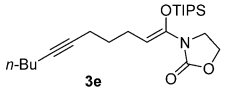
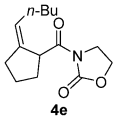
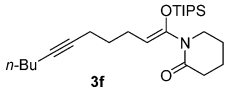
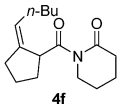
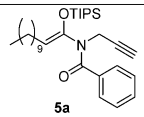
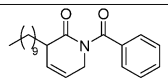
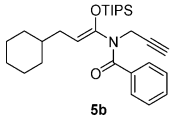
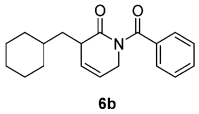
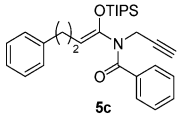
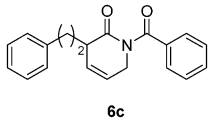
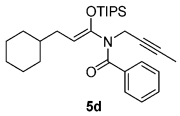
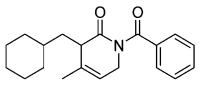
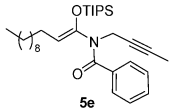
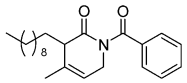
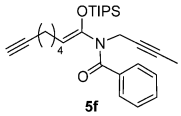
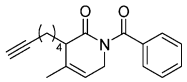
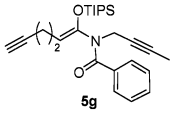
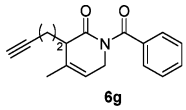
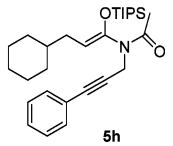
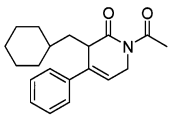
10.1021/jo071014r CCC: $37.00
Published on Web 07/11/2007

TABLE 1. Reactions of Silyl Ketene Amides and Carbamates[a]

entry	substrate	product	yield[b] (%)
1	 **3a**	 **4a**	68
2	 **3b**	 **4b**	82
3	 **3c**	 **4c**	30 (dr> 20:1)
4c[1f]	 **3d**	 **4d**	75
5	 **3e**	 **4e**	24
6	 **3f**	 **4f**	35

[a] General procedure unless otherwise noted: At 23 °C to a solution of substrate in dichloromethane/methanol (10:1) were added 5 mol % of **1e** and 5 mol % of **2a**. The reaction mixture was directly purified by column chromatography after 1 h. [b] Isolated yield.

TABLE 2. Reactions of Silyl Ketene Amides and Carbamates[a]

entry	substrate	product	yield[b] (%)
1	 **5a**	 **6a**	60
2	 **5b**	 **6b**	41
3	 **5c**	 **6c**	32
4	 **5d**	 **6d**	80
5	 **5e**	 **6e**	77
6[c]	 **5f**	 **6f**	62
7[c]	 **5g**	 **6g**	44
8	 **5h**	 **6h**	82

[a] General procedure unless otherwise noted: At 23 °C to a solution of substrate in dichloromethane/methanol (10:1) were added 5 mol % of **1e** and 5 mol % of **2a**. The reaction mixture was directly purified by column chromatography after 1 h. [b] Isolated yield. [c] 10 mol % of **2e** and 10 mol % of **3a** were used. Reaction was complete within 2 h.

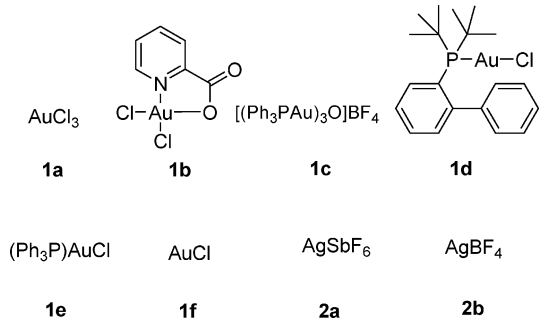
hydrolysis of silyl ketene amides or carbamates. Under the reaction conditions, it appeared that silyl ketene carbamates hydrolyzed faster than silyl ketene amides and thus gave much lower yields (30 and 24%, respectively, Table 1, entries 3 and 5). The use of water gave inferior results due to an increased protodesilylation side reaction. The reactions shown in Tables 1 and 2 were complete within 2 h at ambient temperature in air. Interestingly, only 5-*exo-dig* cyclization is observed for this 1,6-enyne system (Table 1). Conversely, 6-*endo-dig* cyclization products were formed exclusively for the enyne substrates containing a C−N linker (Table 2). In comparison, the tungsten-promoted cyclization of *ω*-acetylenic silyl enol ethers mainly worked in the *endo* mode. Iwasawa did discover a profound solvent effect to favor the *exo* regioselectivity.[4b] Interestingly, the regioselectivity in the gold-catalyzed cyclizations are substrate-dependent versus the tungsten-catalyzed cyclizations which are solvent-dependent. It should be noted that the double bond present in all of the products does not readily undergo isomerization into conjugation with the carbonyl group at ambient temperature.

Substrate **3c** bearing a chiral auxiliary gave a single diastereomer **4c**, indicating complete stereochemical control in C−C bond formation (Table 1, entry 3). Substrate **3d** efficiently underwent cyclization to generate a spirocycle.

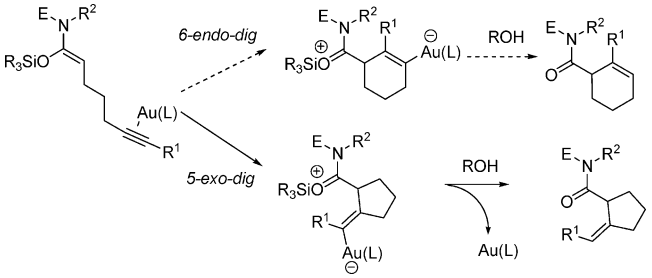
Substrates bearing internal alkynes shown in Table 1 generally gave lower yields (Table 1, entries 5 and 6) than those with terminal alkynes. In contrast, the internal alkyne substrates shown in entries 4 and 5 of Table 2 offered better yields than terminal alkyne counterparts (Table 2, entries 2 and 3). NOE studies established the geometry of the trisubstituted alkene in the products (Table 1, entries 5 and 6). This is in accord with the proposed mechanism, which involves a *trans* addition of the nucleophile to the alkyne with respect to the gold catalyst (Scheme 3).

For substrates **5f** and **5g** bearing two alkynes (Table 2, entries 6 and 7), the cyclization reactions were completely regioselective, in that only one of the two alkynes present in each substrate reacted, and only the *6-endo-dig* cyclization products were obtained as opposed to the *6-exo-dig* (Table 2, entry 6) or *5-endo-dig* cyclizations (Table 2, entry 7) involving the other alkyne to form carbocycles. In these cases, the reactions proceeded more slowly and thus 10 mol % of catalysts was used. In comparison to substrate **5d** and **5e**, the relatively lower

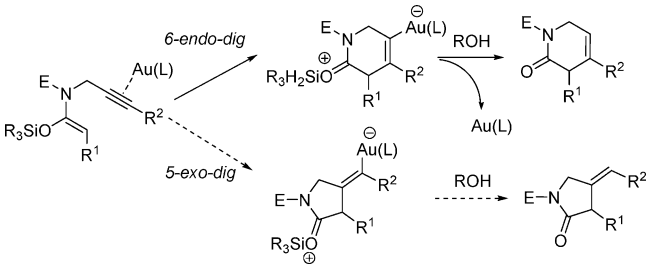
SCHEME 2



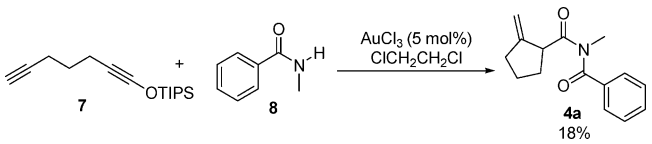
SCHEME 3



SCHEME 4



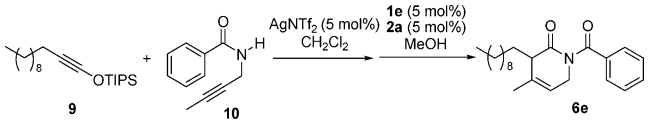
SCHEME 5



yields for entries 6 and 7 were due to the formation of competitive protodesilylation byproducts. Presumably, the desired cyclization rate is slower due to the coordination of the catalyst with the unreactive alkyne. In addition to methyl-substituted internal alkynes, a rather bulky phenyl-substituted alkyne substrate **5h** can also undergo facile cyclization to form the desired dehydro-δ-lactam **6h** in excellent yield (Table 2, entry 8). The proposed reaction mechanisms of substrates in Tables 1 and 2 are shown in Schemes 3 and 4.

Inspired by Kozmin's report that gold(III) catalysis can promote the hydroamidation of alkynyl ether, albeit in lower yields,[7] we attempted a tandem reaction involving a hydroamidation of **7** followed by cyclization (Scheme 5). Indeed the desired product **4a** was formed. Low yield may be attributed to the competing desilylation reaction. We then performed a stepwise one-pot reaction of alkynyl ether **9** with propargyl amide **10**, employing $AgNTf_2$ (Tf = CF_3SO_2) as the catalyst, followed by the addition of catalysts **1e**, **2a**, and methanol. We were pleased to obtain product **6e** in 41% overall yield (Scheme 6).

SCHEME 6



In conclusion, we have developed gold(I)-catalyzed cyclizations of alkynes using silyl ketene amides and carbamates as novel nucleophiles. The mild reaction conditions, convenient procedures, and complete control of regiochemistry are major advantages of applying this method for the generation of cyclopentane and dehydro-δ-lactam derivatives. Additionally, the recently reported palladium system has not yet worked for the substrates leading to dehydro-δ-lactams by the gold catalysis. We further demonstrated a tandem reaction using gold(III) chloride as a sole catalyst for both hydroamination and cyclization to form a cyclopentane and a one-pot procedure involving a sequential silver(I)-catalyzed hydroamination and gold(I)-catalyzed cyclization to assemble the dehydro-δ-lactam products.

Experimental Section

General Procedures for Tables 1 and 2. To a solution of substrate in dichloromethane/methanol (10:1, 0.01−0.1 M) were added the gold and silver catalysts at ambient temperature. The mixture immediately turned white cloudy and slowly changed into a light purple black solution. After 1 h, the mixture was directly purified by flash chromatography eluting with 2−10% ethyl acetate in hexanes to give the desired product.

Procedure for Tandem Reaction (Scheme 5): To a solution of **7** (50 mg, 0.19 mmol) and **8** (21 mg, 0.16 mmol) in 1,2-dichloroethane (1.5 mL) were added $AuCl_3$ (2.4 mg, 0.079 mmol) and 1 drop of methanol. The mixture was stirred at rt overnight and then purified by flash chromatography eluting with 3−8% of ethyl acetate in hexanes to give **4a** (7 mg, 0.029 mmol, 18%) as a colorless oil. **4a**: ^{1}H NMR (600 MHz, CD_2Cl_2) δ 7.64 (d, J = 7.8 Hz, 2 H), 7.57 (t, J = 7.8 Hz, 1 H), 7.48 (t, J = 7.8 Hz, 2 H), 4.99 (s, 1 H), 4.89 (s, 1 H), 3.83 (m, 1 H), 3.23 (s, 3 H), 2.41 (m, 1 H), 2.38 (m, 1 H), 2.03 (m, 1 H), 1.84 (m, 2 H), 1.53 (m, 1 H); ^{13}C NMR (150 MHz, CD_2Cl_2) δ 178.8, 174.3, 152.9, 135.9, 132.5, 128.9, 128.7, 107.3, 50.7, 34.6, 34.0, 31.5, 25.2; LC/MS *m*/*z* 244.30, 266.68 (M + H, M + Na).

Procedure for Sequential Reaction (Scheme 6): To a solution of **9** (150 mg, 0.44 mmol) and **10** (78 mg, 0.44 mmol) in 2 mL of dichloromethane was added silver bis(trifluoromethanesulfonyl)-imide (9 mg, 0.022 mmol). After 1.5 h, to this mixture was added 0.2 mL of methanol followed by the addition of **1e** (11 mg, 0.022 mmol) and **2a** (8 mg, 0.022 mmol). The mixture immediately turned white cloudy and slowly changed into a light purple black solution. After 1 h, the mixture was directly purified by flash chromatography eluting with 2−10% ethyl acetate in hexanes to give **6e** (64 mg, 0.18 mmol, 41%) as a colorless oil. **6e**: ^{1}H NMR (600 MHz, CD_2Cl_2) δ 7.51 (d, J = 7.8 Hz, 2 H), 7.49 (t, J = 7.8 Hz, 1 H), 7.40 (t, J = 7.8 Hz, 2 H), 5.68 (br s, 1 H), 4.43 (dt, J = 3.0, 18 Hz, 1 H), 4.18 (dq, J = 2.4, 17.4 Hz, 1 H), 2.91 (br s, 1 H), 1.91 (m, 2 H), 1.81 (d, J = 0.6 Hz, 3 H), 1.02−1.40 (m, 16 H), 0.90 (t, J = 7.2 Hz, 3 H); ^{13}C NMR (125 MHz, CD_2Cl_2) δ 174.2, 174.1, 136.8, 134.3, 131.3, 128.2, 127.8, 116.6, 49.1, 45.9, 39.9, 32.1, 31.4, 29.8, 29.7, 29.5, 26.3, 22.9, 20.5, 17.7, 12.5; LC/MS *m*/*z* 356.45, 378.42 (M + H, M + Na).

Acknowledgment. We thank Dr. George Doss for the NMR support.

Supporting Information Available: Representative experimental procedures and spectroscopic data for new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

JO071014R