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Highly Efficient Au(I)-Catalyzed Intramolecular Addition of β-Ketoamide to Unactivated Alkenes

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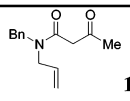
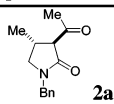
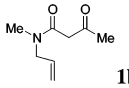
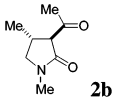
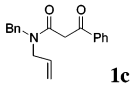
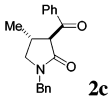
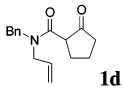
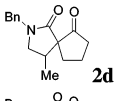
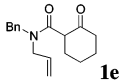
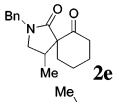
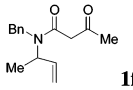
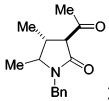
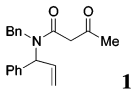
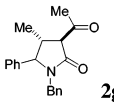
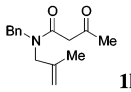
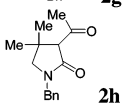
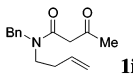
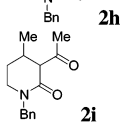
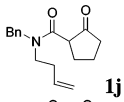
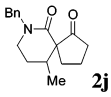
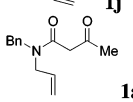
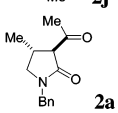
The addition of a C−H bond across alkenes constitutes a particularly valuable method for C−C bond formation. The addition of a carbon nucleophile to alkenes conjugated to an electron-withdrawing group (Michael reaction) is usually employed in organic synthesis.[1] In contrast, addition of a 1,3-dicarbonyl compound to an unactivated alkene remains a difficult task for chemists.[2,3] Recently, efficient palladium-catalyzed intramolecular hydroalkylation of alkenes with β-diketones has been reported, but the reactions often proceed via the 6-*endo-trig* cyclization pathway.[2] Thermal alkene hydroalkylation without a catalyst normally requires high temperature (230 °C), and substrate scope is limited.[3b]

It has recently been shown that Au(I) and Au(III) complexes can efficiently catalyze a variety of organic reactions.[4−7] Au(I) is a soft Lewis acid, which can coordinate and activate unsaturated C−C bonds toward nucleophilic attack, and indeed, Au(I)-catalyzed intermolecular and intramolecular additions of a heteroatom to unactivated alkenes are documented in the literature.[6] We envisioned that Au(I) complexes might be able to catalyze C−C bond formation through activation of alkenes toward attack by a carbon nucleophile. An example of Au(III)-catalyzed intermolecular addition of β-diketone to alkenes was reported, but the scope of the alkenes was confined to electron-rich ones.[7] To our knowledge, there has been no report concerning gold-catalyzed intramolecular C−C bond formation through hydroalkylation of unactivated alkenes by 1,3-dicarbonyl compounds. Here, we first describe that Au(I) complexes efficiently catalyze intramolecular addition of β-ketoamide to unactivated alkenes to afford highly substituted lactams; the latter are commonly found in natural products and biologically active molecules.

In preliminary experiments, we treated **1a** with a catalytic amount of a mixture of $Au(PPh_3)Cl$ (5 mol %) and AgOTf (5 mol %) at 90 °C for 10 h to give lactam **2a** in 87% yield (see Supporting Information), whose benzyl group could be easily removed by hydrogenolysis. The *trans* stereochemistry of **2a** was proposed by comparison with that of related compounds (see Supporting Information). The metal salts AgOTf, $Au(PPh_3)Cl$, and $AuCl_3$ alone, and $AuCl_3$/AgOTf, failed to catalyze the cyclization. The effect of solvent was examined; 1,4-dioxane, dichloroethane, and acetonitrile led to the desired products in lower yields. When the bulky complex Au[P(*t*-Bu)$_2$(*o*-biphenyl)]Cl/AgOTf (mol ratio = 1:1), which was previously reported by Echavarren and co-workers to have useful applications in gold catalysis,[8] was used as catalyst, the product yield increased to 97%. After optimization of reaction conditions, the protocol with 5 mol % of Au[P(*t*-Bu)$_2$(*o*-biphenyl)]Cl/AgOTf at 50 °C for 5 h gave the product in 99% yield (Table 1, entry 1).

With the optimized condition, we examined the substrate scope of Au(I)-catalyzed cyclization of *N*-alkenyl β-ketoamides (Table 1). *A variety of substrates underwent Au(I)-catalyzed exo-trig cyclization to give highly substituted lactams. In all cases, no endo cyclization was observed.* Variation at the amide and ketone moieties had only a slight impact on the reaction time and the product yield (Table 1, entries 2 and 3). This Au(I)-catalyzed reaction allows for the synthesis of spirolactams. Treatment of **1d** with Au[P(*t*-Bu)$_2$(*o*-biphenyl)]Cl/AgOTf furnished a 3:1 mixture of the diastereoisomeric 5,5-bicyclic spirolactams **2d** in 99% yield (entry 4). 5,6-Bicyclic spirolactams **2e** were similarly obtained as a 3:1 mixture of two diastereomers in excellent yield (entry 5). β-Ketoamides

Table 1. Intramolecular Addition of β-Ketoamide to Unactivated Alkenes Catalyzed by Au[P(*t*-Bu)$_2$(*o*-biphenyl)]Cl/AgOTf [a]

entry	substrate	time	product	yield (%)[b]
1	 **1a**	5 h	 **2a**	99
2	 **1b**	12 h	 **2b**	94
3	 **1c**	4 h	 **2c**	99
4	 **1d**	4 h	 **2d**	99 dr=3:1[c]
5	 **1e**	4 h	 **2e**	99 dr=3:1[c]
6	 **1f**	5 h	 **2f**	99 dr=4:1[c]
7	 **1g**	5 h	 **2g**	91 dr=1.5:1[c]
8[d]	 **1h**	12 h	 **2h**	95
9[e]	 **1i**	5 h	 **2i**	98
10[e]	 **1j**	6 h	 **2j**	97 dr=1.3:1[c]
11[f]	 **1a**	3 day	 **2a**	90

[a] Reactions were performed in toluene with ratio of gold catalyst/substrates = 5:100 at 50 °C. [b] Isolated yield. [c] Determined by ^{1}H NMR of the crude reaction mixture. [d] Reaction temperature = 90 °C. [e] Reaction temperature = 60 °C. [f] The reaction was run with 5 g of **1a**.

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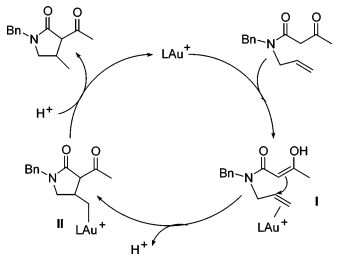
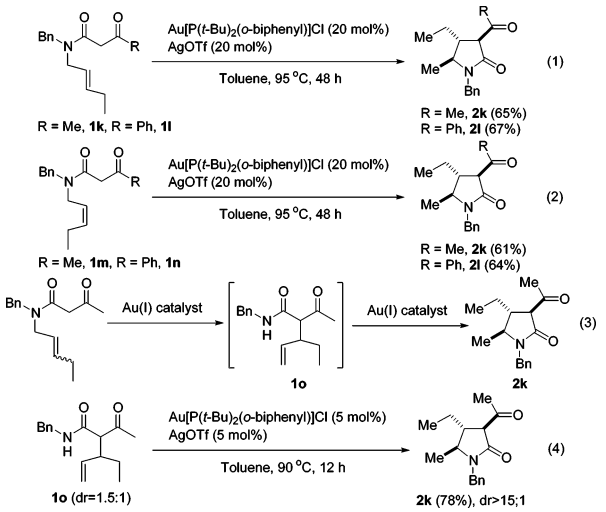
Scheme 1. Proposed Reaction Mechanism

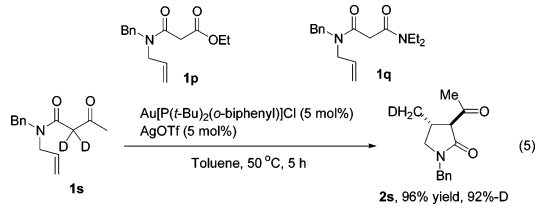


with substituent at the allyl position also gave the products with modest to a good level of diastereoselectivity and high isolated yields (entries 6 and 7). Substitution at the internal alkenyl carbon atoms led to a longer reaction time and higher temperature, but the product yield remained excellent (entry 8). The β-ketoamide containing a butenyl chain underwent Au(I)-catalyzed cyclization to furnish six-membered ring lactams. For example, reactions of β-ketoamides **1i** and **1j** in the presence of Au[P(*t*-Bu)$_2$(*o*-biphenyl)]-Cl/AgOTf at 60 °C led to corresponding piperidone **2i** and spiropiperidone **2j** in high yields (entries 9 and 10). *The catalysis also could be performed in a preparative-scale and in aqueous media as demonstrated by the following experiments: The reaction using 5 g of substrate **1a** and with 1 mol % of catalyst loading gave product **2a** (4.5 g) in 90% yield (Table 1, entry 11). The reaction of **1a** (0.4 mmol) using 5 mol % catalyst in aqueous media (H$_2$O/dioxane=10:1) for 7 h afforded **2a** in 94% yield.*

Interestingly, the Au(I)-catalyzed reactions of β-ketoamides **1k** and **1m** having *trans* and *cis* internal alkenyl chains, respectively, afforded the highly substituted lactam **2k** as a single diastereomer (eqs 1 and 2). Similarly, cyclization of **1l** and **1n** with the benzoyl moiety led to **2l**. No *exo* cyclization product was observed in these cases. These reactions probably proceeded through intramolecular tandem Claisen rearrangement and a hydroamination pathway[6,9] via intermediate **1o** (eq 3). In accordance with this hypothesis, Au(I)-catalyzed cyclization of **1o** led to **2k** in 78% yield (eq 4).



A proposed reaction mechanism is depicted in Scheme 1. The cationic gold(I) coordinates to alkene to give intermediate **I**, which is followed by *exo-trig* addition of the enol form of β-ketoamide to generate intermediate **II**. In accord with enol addition to alkene, no cyclization of amide ester **1p** and diamide **1q** was observed, presumably the presence of ester and amide functionality decreases the enol concentration.[10] ^{1}H NMR measurements of a mixture of **1a** and Au[P(*t*-Bu)$_2$(*o*-biphenyl)]Cl/AgOTf in CDCl$_3$ under various conditions support the feasibility of coordination of the alkene moiety of **1a** to Au(I) (see Supporting Information). Analysis of a solution of **1p** and Au[P(*t*-Bu)$_2$(*o*-biphenyl)]Cl/AgOTf (20 mol %) in toluene after stirring for 2 h at 50 °C by MALDI-TOF MS showed a peak at *m*/*z* 756.287, attributable to the adduct formed between Au$^+$[P(*t*-butyl)$_2$(*o*-biphenyl)] and **1p** and hence suggests the possibility of coordination of cationic Au(I) to **1p**. The result of a deuterium-labeled experiment is also consistent with the proposed step **I** to **II** of Scheme 1 (eq 5).



In conclusion, we have demonstrated that a Au(I) complex can efficiently catalyze the intramolecular addition of β-ketoamide to unactivated alkenes to produce highly substituted lactams with excellent product yields and regioselectivities under mild conditions.

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Supporting Information Available: Experimental procedures and characterization data for compounds **2a**−**2k**. This material is available free of charge via the Internet at http://pubs.aca.org.

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