Gold Catalysis

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Efficient Gold(I)-Catalyzed Direct Intramolecular Hydroalkylation of Unactivated Alkenes with α-Ketones**

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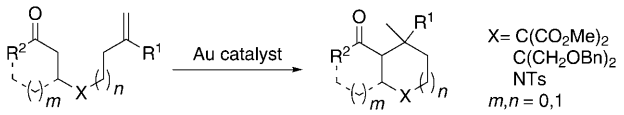
The direct addition of a stabilized carbon nucleophile to an unactivated alkene (such as hydroalkylation) is one of the most powerful and widely employed methods for the formation of carbon–carbon bonds, often with concomitant formation of rings and generation of stereocenters.[1] The efficiency of this process can be greatly enhanced by transition-metal catalysts, and broad substrate scope and intriguing selectivity are observed under mild reaction conditions,[2] which are advantageous relative to approaches using free-radical[3] and Lewis acid catalysts.[4] These transition-metal-catalyzed hydroalkylation methodologies commonly involve the use of metal enolates and related stabilized carbanions as the carbon nucleophile.[2] Despite the importance of these methods, they require synthesis of stabilized carbon nucleophiles, resulting in the generation of toxic metal salts as reaction by-products, often in stoichiometric amounts.[2] To address this issue, much effort has been devoted over the past decades to the development of direct α-functionalization of a carbonyl group without the need for enolate formation.[2,5] Through the use of such methodology, these direct hydroalkylation reactions with carbonyl compounds improve the overall atom economy of the reaction. In the reported direct hydroalkylation reactions with carbonyl compounds,[5] the carbon nucleophile substrates are limited to those containing activated methylene units, such as β-diketones or β-keto esters, which directly react with unactivated alkenes through their corresponding enol form. However, simple α-ketones remain a challenging class of substrates for hydroalkylation of unactivated alkenes, because they possess a less acidic C–H bond[6] and a significantly lower enol/ketone equilibrium constant ($K_{enol/ketone}$) than activated methylene compounds.[7] Indeed, there have been a few reports on palladium-catalyzed intramolecular hydroalkylation of alkenes with α-aryl or alkyl ketones by the 6-*endo-trig* cyclization pathway to build six-membered rings,[8] but all of these palladium-catalyzed reactions require substoichiometric or stoichiometric amounts of $CuCl_2$ and other external reagents, such as trimethylsilylchloride (TMSCl)/H_2O or the Brønsted acid HCl, to facilitate the enolization of ketones.

Recently, gold complexes have been shown to be versatile and efficient catalysts that promote a variety of organic transformations.[9] In particular, gold catalysts have been found to display an exceptional ability to activate C–C multiple bonds toward nucleophilic attack.[10] Based on this mode of activation, several methods for gold-catalyzed inter- and intramolecular addition of oxygen,[11] nitrogen,[12] or active methylene nucleophiles[5g–i] to unactivated alkenes[5i,13] have been reported. Moreover, gold complexes have been demonstrated to be useful in catalyzing the addition of a variety of enol equivalents such as electron-rich alkyl enol ethers,[14] silyl enol ethers,[15] silyl ketene amides,[16] and enamines[17] derived from ketones[18] to unactivated alkynes and allenes. However, to our knowledge, gold-catalyzed direct hydroalkylation of unactivated alkenes with simple α-ketones has not been reported. Owing to the propensity of gold complexes to promote the enolization of α-ketones,[19] thus rendering a possible increase of their nucleophilicity to react directly with gold-complexed alkenes, we envisioned that gold complexes might be able to catalyze direct C–C bond formation through hydroalkylation of unactivated alkenes through attack by simple α-ketones. We describe herein that gold(I) complexes, in the absence of additive reagents, efficiently catalyze direct intramolecular hydroalkylation of unactivated alkenes with simple α-ketone groups by *exo-trig* cyclization to build a variety of new five- and six-membered rings in excellent yields (up to 99%) and with good diastereoselectivity (Scheme 1).



Scheme 1. Synthesis of new cyclic compounds by gold-catalyzed hydroalkylation. Bn = benzyl, Ts = 4-toluenesulfonyl.

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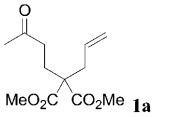
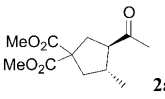
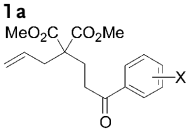
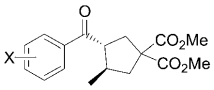
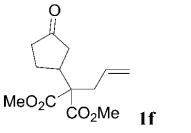
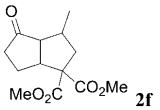
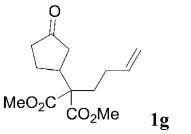
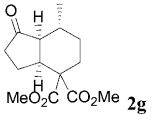
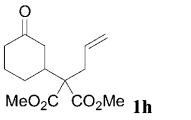
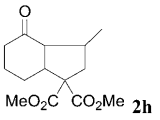
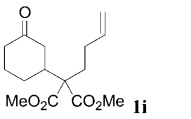
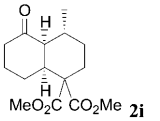
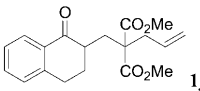
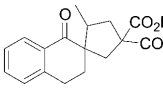
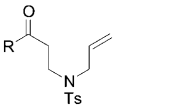
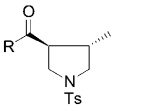
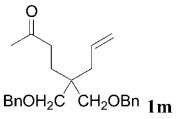
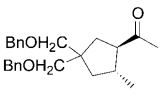
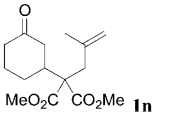
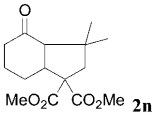
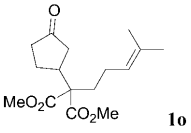
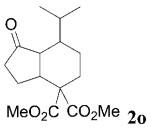
We first examined the cyclization reaction of alkenyl alkyl ketone **1a** using various electrophilic transition metal catalysts in toluene at 110 °C (see the Supporting Information, Table S1; the structure of **1a** is shown in Table 1, entry 1). The metal salts Cu(OTf)$_2$ (OTf = trifluoromethanesulfonate), AgOTf, and PicAuCl$_2$ (Pic = 2-picolinate) failed to catalyze this cyclization (Table S1, entries 1–3). However, the gold(I) cation derived from the reaction of [(*t*Bu)$_2$(*o*-diphenyl)PAuCl], a catalyst previously reported by Echavarren and co-workers,[20] with an equimolar amount of AgOTf in toluene at 110 °C for 15 hours cleanly converted **1a** to **2a** by a 5-*exo*-*trig* cyclization as a 7.9:1 mixture of diastereomers in 99 % yield (Table S1, entry 5). The relative *trans* configuration of the substituents of the ketone and the methyl groups of the product **2a** was established by NOE spectroscopy. Examination of other counteranions of the cationic complex [(*t*Bu)$_2$(*o*-diphenyl)PAu]$^+$ reveals that the non-coordinating anion ClO_4^- was the best for the reaction, affording the product **2a** in 99 % yield with a diastereomeric ratio of 8.5:1 for a reaction time of 3.5 hours (Table S1, entry 9). A panel of Au^I complexes with different ancillary ligands were screened for activity and diastereomeric induction in the cyclization reaction of **1a** (Table S1, entries 10–13). Among the complexes examined, [IPrAuCl]/$AgClO_4$ (molar ratio = 1:1, IPr = *N*,*N*′-bis(2,6-diisopropylphenyl)-imidazol-2-ylidene), which was reported by Nolan and co-workers to have useful applications in gold catalysis,[21] gave the best result (Table S1, entry 13). A further improvement in diastereoselectivity was achieved by conducting the reaction with a substrate concentration of 0.5 M at 90 °C, thereby furnishing **2a** with a diastereomeric ratio of 8.6:1 in 99 % yield (Table 1, entry 1). Further screening of solvents showed that the nonpolar solvent toluene gave the best result, while polar solvents methanol, THF, and acetonitrile gave low product yields and diastereoselectivities (see the Supporting Information, Table S2). Notably, this cyclization reaction was not catalyzed by trifluoromethanesulfonic acid (Table S1, entry 15).

With the optimal reaction conditions, we set out to explore the scope of this protocol with respect to other alkenyl α-ketone substrates. As shown in Table 1, changing the alkenyl alkyl ketone **1a** to alkenyl aryl ketones **1b–e** did not have a significant influence on the product yield and diastereoselectivity. For example, treatment of **1b** with a catalytic amount of [IPrAuCl]/$AgClO_4$ (5 mol %) at 90 °C for 9 hours gave the expected product **2b** in 91 % yield with a diastereomeric ratio of 7.3:1 (Table 1, entry 3). In addition to substrate **1b**, alkenyl aryl ketones with electron-donating or electron-withdrawing substituents on the phenyl ring underwent gold(I)-catalyzed direct intramolecular hydroalkylation to afford the corresponding products in 89–96 % yields (Table 1, entries 4–6). In all cases, the *trans* diastereomer was

Table 1: Scope of gold(I)-catalyzed intramolecular hydroalkylation of unactivated alkenes with α-ketones.[a]

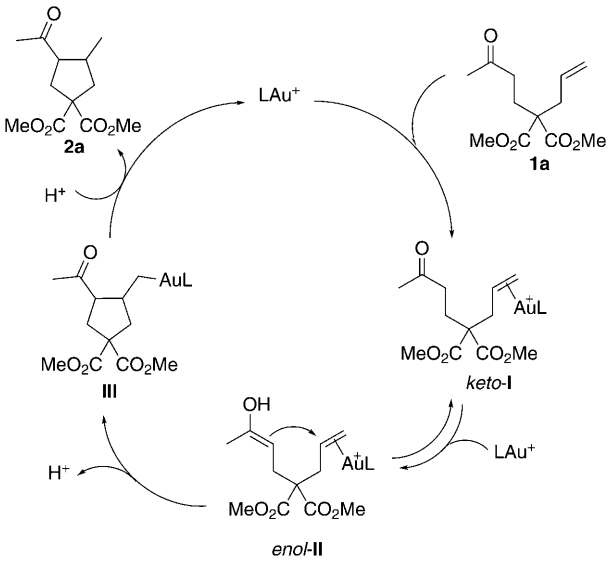
Entry	Substrate	*t* [h]	Product	Yield [%][b]	d.r.[c]
1	 **1a**	4.5	 **2a**	99	8.6:1
2[d]	**1a** 	16	**2a** 	97	8.6:1
3	X = H: **1b**	9	X = H: **2b**	91	7.3:1
4	4-OMe: **1c**	6	4-OMe: **2c**	96	7.2:1
5	4-NO_2: **1d**	10	4-NO_2: **2d**	89	8.0:1
6	2-Br: **1e**	9	2-Br: **2e**	89	9.0:1
7	 **1f**	5	 **2f**	99	4.0:1.5:1
8	 **1g**	13	 **2g**	99	10.3:1
9	 **1h**	5	 **2h**	91	2.1:1
10	 **1i**	9	 **2i**	90	9.5:1
11	 **1j**	5	 **2j**	81	1.7:1
					
12	R = Me: **1k**	17	R = Me: **2k**	78	6.7:1
13	Ph: **1l**	13	Ph: **2l**	71	1.5:1
14	 **1m**	3	 **2m**	71	3.0:1
15[e]	 **1n**	16	 **2n**	86	6.0:1
16[e]	 **1o**	48	 **2o**	–[f]	–

[a] Reaction conditions: substrate **1** (0.25 mmol), [IPrAuCl]/$AgClO_4$ (5 mol %), toluene (0.5 mL) at 90 °C. [b] Yield of isolated product. [c] Diastereomeric ratio determined by ^{1}H NMR spectroscopy; major isomer shown. [d] Reaction conditions: substrate **1a** (10 mmol), [IPrAuCl]/$AgClO_4$ (0.5 mol %), toluene (5 mL) at 90 °C. [e] Reaction conditions: substrate **1** (0.25 mmol), [IPrAuCl]/$AgClO_4$ (10 mol %), toluene (0.5 mL) at 110 °C. [f] No desired product was detected.

favored with good to excellent selectivity (Table 1, entries 1–6). This gold(I)-catalyzed hydroalkylation reaction also allows rapid synthesis of bicyclic ring systems. Treatment of cyclopentanone derivative **1f** in the presence of 5 mol% [IPrAuCl]/$AgClO_4$ gave the desired 5,5-bicyclic ketone **2f** in 99% yield, albeit with lower diastereoselectivity (Table 1, entry 7). This process has also been applied to the synthesis of 6,5-bicyclic ketones in excellent yields and with modest to good levels of diastereoselectivity by annealing a six-membered ring onto a cyclopentanone **1g** (Table 1, entry 8) or a five-membered ring onto a cyclohexanone **1h** (Table 1, entry 9). The 6,6-bicylic ketone **2i** was obtained as a 9.5:1 mixture of two diastereomers in excellent yield (Table 1, entry 10). The relative configuration of **2g** and **2i** was determined by X-ray crystallographic analysis (Figure S1 in the Supporting Information).[22] Notably, the gold(I)-catalyzed cyclization reaction could also be used to furnish spirocyclic ketone **2j** in 81% yield (Table 1, entry 11).

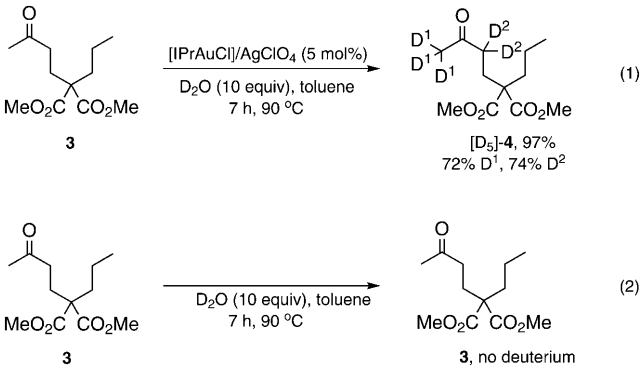
To further investigate the scope of application, we tested the use of N-tethered α-ketones as substrates. Good yields with moderate to good selectivity for the *trans* diastereomer were observed when substrates with an alkyl or aryl group attached to the ketone were used (Table 1, entries 12 and 13). The relative *trans* configuration of **2k** was established by NOE spectroscopy and by X-ray crystallographic analysis (Figure S1 in the Supporting Information).[22] The substrate **1m** containing benzyl ether functional groups in the tether was also cyclized to afford the corresponding product **2m** as a 3.0:1 mixture of two diasteromers in 71% yield (Table 1, entry 14). Furthermore, the α-ketone **1n** with substitution at the internal olefinic carbon atom was applicable to this Au^I-catalyzed system, giving 6,5-bicyclic ketone **2n** with a diastereomeric ratio of 6.0:1 and in 86% yield, although an increased catalyst loading (10 mol%), a higher reaction temperature (110°C), and a longer reaction time were required for full substrate conversion (Table 1, entry 15). However, the α-ketone **1o** having an internal alkene group did not yield the desired product **2o** (Table 1, entry 16), possibly owing to the large steric hindrance during the course of intramolecular hydroalkylation. Notably, the gold-catalyzed cyclization reaction could be scaled up (Table 1, entry 2). For example, 2.4 g of cyclic product **2a** was readily obtained in 97% yield with a diastereomeric ratio of 8.6:1, even using 0.5 mol% catalyst at 90°C for 16 h.

On the basis of the established reactivity of gold(I)-alkene complexes toward nucleophiles,[23] a reaction mechanism for the Au^I-catalyzed addition of α-ketone to unactivated alkene is proposed (Scheme 2). Coordination of the double bond of **1a** to the gold(I) complex to form *keto*-**I** enhances the electrophilicity of the alkene,[10] and the subsequent nucleophilic attack (as shown in *enol*-**II**) of the enol form of the α-ketone to the gold-coordinated alkene affords the alkyl Au intermediate **III**, which is protonated to give the final product **2a**. Enolization of intermediate *keto*-**I** to generate the reactive tautomer *enol*-**II** could be facilitated by the gold complex in this catalytic system, and it should be noted that the rate of enolization of simple α-ketone in the absence of an acid catalyst is slow.[6,7,24] This hypothesis is supported by the finding that [D_5]-**4** was obtained in 97% yield with approx-

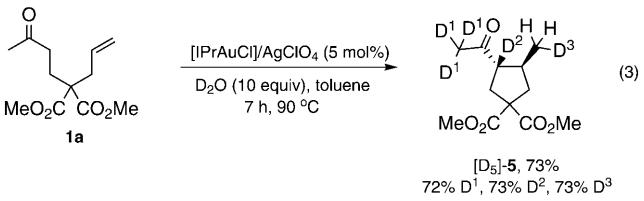


Scheme 2. Proposed mechanism.

imately 70% deuterium incorporation at the α-position of the ketone when alkyl ketone **3** was treated with a catalytic amount of [IPrAuCl]/$AgClO_4$ (5 mol%) in D_2O/toluene at 90°C for 7 hours [Eq. (1)].[25] No deuterium exchange occurred in the absence of gold catalyst under the same reaction conditions [Eq. (2)], thus indicating that the gold catalyst might play a crucial role for the keto–enol tautomerization between *keto*-**I** and *enol*-**II** in the proposed reaction pathway in Scheme 2. Moreover, the gold(I)-catalyzed reaction of **1a** furnished [D_5]-**5** in 73% yield with 73% deuterium incorporation at the newly formed methyl group in D_2O/toluene under the standard reaction conditions [Eq. (3)], revealing that D atoms incorporated into the methyl group of [D_5]-**5** mainly come from D_2O through the protonolysis of alkyl Au intermediate **III** depicted in Scheme 2. On the other hand, an alternative dual catalyst mechanism, which proceeds by the formation of a gold(I) enolate intermediate[5g,26] with subsequent nucleophilic attack on a gold(I) alkene complex,[23] would also be consistent with these observations.

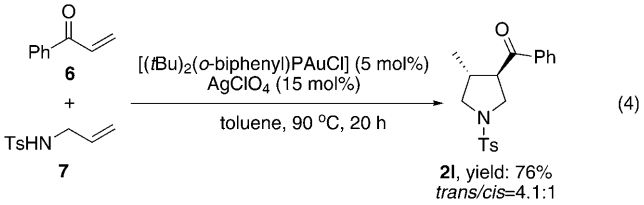


It is interesting to note that the protocol for the synthesis of highly substituted cyclic compounds could be extended to a



(3)

gold(I)-catalyzed cascade intermolecular N-Michael addition/intramolecular hydroalkylation reaction. Thus, when α,β-unsaturated ketone **6** was treated with *N*-tosyl allylic amine (**7**) in the presence of 5 mol% [(*t*Bu)$_2$(*o*-diphenyl)PAuCl] and 15 mol% $AgClO_4$ in toluene at 90 °C for 20 h, the cascade product **2l** was isolated in 76% yield as a 4.1:1 mixture of *trans*/*cis* isomers [Eq. (4)].



(4)

In summary, we have developed the first protocol for direct hydroalkylation of unactivated alkenes with simple α-ketone groups that can be performed with gold(I) complexes as catalysts in the absence of additive reagents. The protocol provides a highly efficient method for the synthesis of highly substituted cyclic compounds with excellent yields and good diastereoselectivity from simple starting materials. This operationally simple procedure not only provides a more straightforward alternative to the existing transition-metal-catalyzed hydroalkylation methods but also has the potential to open the door to novel gold(I)-catalyzed organic transformation.

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Keywords: cyclic compounds · gold · homogeneous catalysis · hydroalkylation · unactivated alkenes

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