

Highly Efficient Addition of Activated Methylene Compounds to Alkenes Catalyzed by Gold and Silver

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The alkylation of 1,3-dicarbonyl compounds represents one of the most common methodologies in organic synthesis. The standard protocol requires the usage of a stoichiometric amount of base and an organic halide (Figure 1, route a). On the other hand, the development of carbon–carbon bond formation via an overall structural isomerization such as the hydroalkylation of alkenes (Figure 1, route b) represents the most atom-economical approach for chemical synthesis.¹ Since the landmark report of the ruthenium-catalyzed hydroarylation of alkenes by Murai and co-workers,² there has been great interest in hydrocarbonylation of alkenes involving other organic substrates such as electron-deficient alkenes.³ However, most recent developments in the field have been limited to the addition of arenes onto alkenes.⁴ Recently, Widenhoefer and co-workers reported an elegant intramolecular hydroalkylation of alkenes by carbonyl compounds catalyzed by palladium.⁵ To the best of our knowledge, the intermolecular hydroalkylation of alkenes involving such activated methylene C–H bonds has not been reported. Herein, we wish to describe such an intermolecular reaction catalyzed by gold and silver.

Compared to other late transition metals, gold has not been a common catalyst of choice in synthesis. However, recently Ito,⁶ Hashmi,⁷ and others⁸ have shown unique catalytic properties of gold in several reactions. Previously, we reported the highly efficient three-component coupling of aldehyde, alkyne, and amine (A³ Coupling) catalyzed by gold⁹ and silver¹⁰ in water. The reaction was rationalized involving the activation of the sp hybridized terminal alkyne by gold. On the other hand, Hashimi,¹¹ Reetz,¹² and Arcadi¹³ have recently reported the activation of sp² hybridized aryl C–H bonds by gold. Our continued interests in developing C–C bond formation based on the reactivity of C–H bonds and the unique catalytic activity of gold toward sp and sp² C–H bonds led us to explore the hydroalkylation of alkenes with 1,3-dicarbonyl compounds via the reactivity of the sp³ hybridized C–H bond.¹⁴ In our initial study, 2,4-pentanedione was reacted with styrene under a variety of conditions (Table 1) with the following conclusions: (1) AgOTf or AuCl₃ alone (entries 7 and 8, respectively) provided only trace amounts of the desired product, (2) the combination of AuCl₃ and AgOTf provided the desired product in good yields, (3) changing the counterion on the silver salt from OTf lowers the yield (entries 3–5), but there is no difference when the counterion for gold is changed (entries 2 and 6), and (4) CH₂Cl₂ is the solvent of choice relative to DCE and nitromethane, and there is no amount or trace amounts of product in THF and water (entries 9–12, respectively). The use of (PPh₃)AuCl or cyclo-hexNCAuCl, instead of AuCl₃, decreased the reactivity considerably. Therefore, the use of catalytic AuCl₃/AgOTf in CH₂Cl₂ (entry 2) with a slight excess of styrene provided the best yield.

Subsequently, the reaction was examined on various substrates (Scheme 1). Various diketones were effectively added to styrene and styrene derivatives under the current reaction conditions (Table 2). Note that the addition of 1,3-diketones to indene is also highly

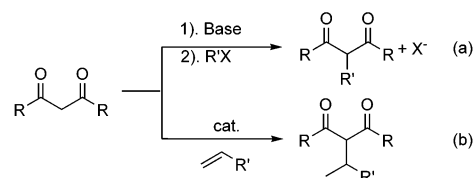
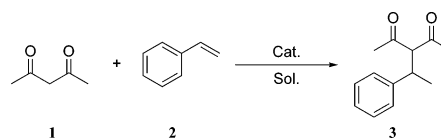


Figure 1. Alkylation of 1,3-Dicarbonyl Compounds.

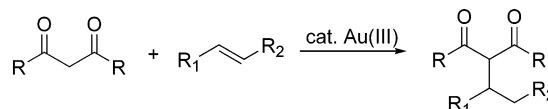
Table 1. Addition of Pentane-2,4-dione to Styrene Catalyzed by Gold



entry	catalyst ^a	solvent	1:2 (mol:mol)	yield (%) ^c
1	AuCl ₃ /AgOTf	CH ₂ Cl ₂	1:1	49
2	AuCl ₃ /AgOTf	CH ₂ Cl ₂	1:1.5	74
3	AuCl ₃ /AgBF ₄	CH ₂ Cl ₂	1:1.5	12
4	AuCl ₃ /Ag(O ₂ CCF ₃)	CH ₂ Cl ₂	1:1.5	0
5	AuCl ₃ /AgSbF ₆	CH ₂ Cl ₂	1:1.5	65
6	AuBr ₃ /AgOTf	CH ₂ Cl ₂	1:1.5	74
7	AgOTf ^b	CH ₂ Cl ₂	1:1.5	trace
8	AuCl ₃	CH ₂ Cl ₂	1:1.5	5
9 ^d	AuCl ₃ /AgOTf	DCE	1:1.5	61
10 ^d	AuCl ₃ /AgOTf	MeNO ₂	1:1.5	64
11	AuCl ₃ /AgOTf	THF	1:1.5	— ^e
12	AuCl ₃ /AgOTf	H ₂ O	1:1.5	0

^a 5 mol % gold salt and 15 mol % silver salt. ^b 15 mol % silver triflate. ^c Isolated yield. ^d Under reflux. ^e THF decomposed during the reaction.

Scheme 1. Addition of Activated Methylene to Alkenes



effective. The use of β -ketone esters is also effective; however, it gave a complicated mixture that is still under investigation. Additionally, simple terminal alkenes are also reactive under the current conditions; however, only very low conversion is observed at the present time. The use of norbornene provided a 81% yield of the corresponding product under the same reaction conditions (entry 15). Esters such as dimethyl malonate and β -ketoesters decomposed possibly because of the high Lewis acidity of the system. The use of cyclic 1,3-diketones led to low conversions under the present conditions.

A tentative mechanism is proposed involving the activation of the C–H bond of the activated methylene by a Au(I) species (generated in situ from the reduction of Au(III) by the activated methylene). The alkylgold hydride intermediate then reacts with the styrene to give the hydroalkylation product and regenerate the

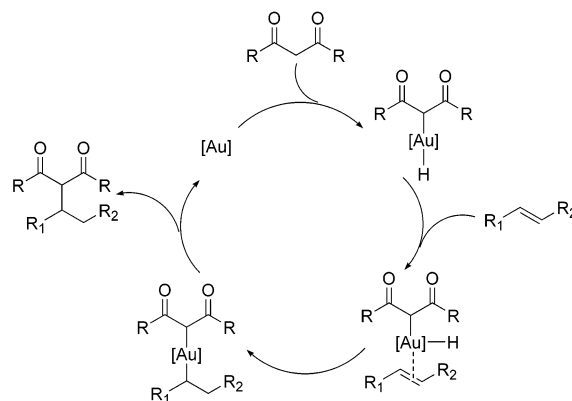
Table 2. Gold-Catalyzed Reaction of Alkenes with β -Diketone

entry	β -diketone	alkene ^a	product	yield(%) ^b
1				89
2				94
3				62
4				97
5 ^c				50
6				44
7				70 (1:1) ^d
8				55 (1:1) ^d
9				89 (1:1) ^d
10				67 (1:1) ^d
11				93
12				98
13				91
14				39 ^e
15				81 ^f

^a Alkenes were added by syringe pump in 5 h. ^b Isolated yield. ^c The reaction was carried out in nitromethane under refluxing temperature. ^d The ratio of two diastereomers was determined by ¹H NMR. ^e 56% of diketone was recovered. ^f Only exo (determined by NOE) product was isolated.

Au(I) catalyst for further reactions (Scheme 2). Alternatively, it may occur through an enolate addition to alkenes as in alkynes.¹⁴

In conclusion, a highly effective intermolecular addition of activated methylene compounds to alkenes was developed by using AuCl₃/AgOTf. The scope, mechanism, and synthetic applications of this reaction is currently under investigation.

Scheme 2. Tentative Mechanism for the Gold-Catalyzed Addition Reaction

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Supporting Information Available: Representative experimental procedure and characterization of all new compounds (PDF). This material is available free of charge via the Internet at <http://pubs.acs.org>.

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