Gold(I)-Catalyzed Conia-Ene Reaction of β-Ketoesters with Alkynes

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Enolate alkylation represents one of the most powerful and widely employed methods for the formation carbon−carbon bonds.[1] The efficiency of this process would be greatly enhanced by the ability to directly α-functionalize a carbonyl group without requiring enolate formation. The thermal cyclization of ketones onto alkynes (Conia-ene reaction) provides access to α-vinylated ketones without the need for deprotonation; however, the high temperature needed severely limits its synthetic utility.[2] On the other hand, transition metal-catalyzed[3] versions of this reaction generally operate at lower temperatures. Unfortunately, these catalytic reactions require enolate generation,[4] strong acid[5] or photochemical activation.[6] A catalytic version of the Conia-ene reaction that proceeds at ambient temperatures and under neutral conditions[7] would dramatically increase the utility of this reaction. Herein, we report the realization of this goal by employing phosphinegold(I) complexes as catalysts.

Carbon−carbon bond formation promoted by homogeneous gold catalysts is extremely rare.[8−10] However, recent reports of group 11 metal-catalyzed addition of heteroatom nucleophiles to alkynes,[11,12] encouraged us to examined the viability of these complexes as catalysts for the intramolecular addition of a β-ketoester to an unactivated alkyne (Table 1). In the event, treatment of ketoester 1 with 10% silver(I) triflate did afford some of the desired cyclopentene (2), but the reaction did not proceed to completion even after a day at room temperature (entry 1). On the other hand, gold-(III) chloride rapidly consumed the starting alkyne (2), but produced only a small amount of the desired adduct (entry 3). While triphenylphosphinegold(I) chloride was unreactive (entry 4), the triphenylphosphinegold(I) cation rapidly and cleanly converted 1 into 2 in less than 15 min at room temperature (entry 5). In sharp contrast to the phosphine inhibition of the silver(I)-catalyzed reaction (entry 2), a cationic gold(I) complex lacking phosphines did not catalyze the reaction (entry 6). In accord with the hypothesis that cationic triphenylphosphinegold(I) is the active catalyst, generation of this species by protonation[12a] of [(PPh₃Au)₃O]BF₄ also resulted in a viable catalysts system (entries 7 and 8).

Further optimization revealed that 1 mol % of the gold(I) catalyst, in dichloromethane[13] rapidly converted ketoester 1 into 2 in 94% yield at room temperature (Table 2, entry 1). Notably, the catalyst operates under "open-flask" conditions in which no precautions were taken to exclude air and moisture from the reaction mixture. Under these conditions a wide range of β-ketoester substrates participated in the gold(I)-catalyzed cycloisomerization. A longer reaction time was required with an increase in the steric size of the ketone substituent (entry 2), while changing the ester group from methyl to *tert*-butyl had only a slight impact on the rate of the reaction (entry 3). Notably, when a propargyl ester was employed, the reaction was completely chemoselective for formation of the *exo*-methylenecyclopentane at the expense of competing lactone formation (entry 4).

The gold(I)-catalyzed reaction also allows for the synthesis of bicyclic ring systems. *Cis*-fused 5,5-bicyclic ketone 10 was

Table 1. Efficiency of Group XI Metal Catalysts in the Conia-Ene Reaction


entry	conditions	time	% conv. to 2[a]
1	10 mol % AgOTf, DCE, rt	18 h	50
2	10 mol % AgOTf, 10 mol% PPh₃, DCE, rt	18 h	0
3	10 mol % AuCl₃, DCE, R.T.	30 min	30[b]
4	10 mol % (PPh₃)AuCl, DCE, 60 °C	6 h	0
5	10 mol % (PPh₃)AuOTf, DCE, rt	<15 min	>95
6	10 mol % [(CyNC)₂Au]PF₆, DCE, rt	14 h	0
7	1 mol % [PPh₃Au)₃O]BF₄, DCE, 60 °C	1 h	0
8	1 mol % [PPh₃Au)₃O]BF₄, 5% HOTf, DCE, rt	<15 min	>95

[a] As judged by ¹H NMR. [b] No starting material (1) remained.

produced from cyclopentanone 9 as a single diastereomer in excellent yield (entry 5). When the ester was located in the ring, such as lactone 13, longer reaction times were required but the yield remained excellent (entry 7). The Au-catalyzed reaction was also employed in the synthesis of *cis*-6,5-bicylic ring systems by annulating a six-membered ring onto a cyclopentanone (entry 6) or a five-membered ring onto a cyclohexanone (entry 8); the former requiring an increase in catalyst loading to 5 mol % in order to proceed to completion in 18h. Similarly, 5 mol % triphenylphosphinegold(I)-catalyst was needed for the diastereoselective construction of *cis*-7,5-bicyclic ketone 20 (entry 10). Notably, the gold-catalyzed reaction was also employed in the construction of a ketone (18) containing *vicinal*-quaternary carbons (entry 9). Additionally, bicyclo-[3.2.1]-octanone 22 was prepared, in excellent yield, by the Au-catalyzed cycloisomerization of β-ketoester 21 (entry 11).

Having established that the Au-catalyzed reaction shows excellent levels of diastereoselectivity in the creation of bicyclic systems, we examined the diastereoselectivity of the cyclopentane formation. Compared to other catalyst systems,[6] significantly better 1,2-diastereoselectivity was observed when 2-ethyl- (23) and 2-phenyl-(24) substituted β-ketoesters were subjected to the Au-catalyzed Conia reaction (entries 12 and 13). Additonally, *exo*-methlyenecyclopentanes 28 and 30 were prepared with good control of 1,3-diastereoselectivity starting from 3- or 4-substituted ketoesters (entries 14 and 15).

We envisioned two possible mechanisms for the Au-catalyzed addition of β-ketoesters to alkynes (eq 1). Mechanism A involves nucleophilic attack on a Au(I)-alkyne complex by the enol form of
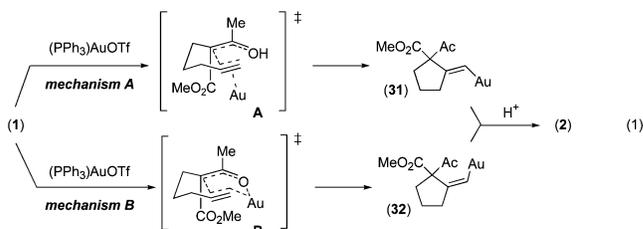
Table 2. Gold(I)-Catalyzed Conia-Ene Reaction[a]

entry	substrate		time	product		yield (d.r.)
1		R = Me, R' = Me (1)	15 min		(2)	94%
2		R = Ph, R' = Et (3)	18 h		(4)	93%
3		R = Me, R' = ᵗBu (5)	30 min		(6)	81%
4		R = Me, R' = CH₂CCH (7)	60 min		(8)	79%
5		n = 1 (9)	1 h		(10)	90%
6		= 2 (11)	18h		(12)	90%[b]
7		(13)	16 h		(14)	88%
8		R = H, R' = Et (15)	2.5 h		(16)	90%
9		R = Me, R' = Me (17)	8 hrs		(18)	83%
10		(19)	30 min		(20)	86%[b]
11		(21)	5 min		(22)	99%
12		R = Et (23)	50 min		(24)	95% (17:1)
13		R = Ph (25)	24 h		(26)	86% (4.2:1)
14		(27)	1 h		(28)	96% (4.0:1)
15		(29)	1 h		(30)	97% (2.9:1)

[a] **Reaction Conditions**: 1 mol % (PPh₃)AuCl, 1 mol % AgOTf, 0.4 M (ketoester) in dichloromethane, rt. [b] 5 mol % (PPh₃)AuCl and 5 mol % AgOTf.

the ketoester, affording vinyl-Au intermediate **31** that is protonated to form the product. An alternative mechanism (**B**) proceeds by formation of a Au-enolate, by direct auration[14] of the β-ketoester, followed by a *cis*-carboauration[12a] of the alkyne to produce vinyl-Au intermediate **32**.

To probe these mechanistic hypotheses, selectively deutrated β-ketoesters **33** and **34** were prepared. The Au-catalyzed Conia-ene reaction of deutroacetylene **33** furnished cyclopentane **35** selectively deuterated (90%) syn to the ketoester (eq 2). On the other hand, **34** afforded adduct **36** in which the *exo*-methylene was selectively (48%) deuterated anti to the ketoester. These deuterium-labeling experiments support a mechanism involving enol[15] addition to a Au-alkyne complex (mechanism **A**).[16]

(2)
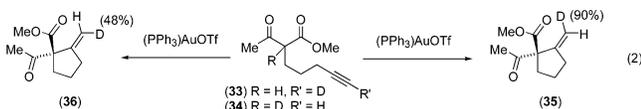
In conclusion, we have developed a Au(I)-catalyzed Conia-ene reaction that proceeds under neutral conditions at room temperature. In most cases, the reaction requires low catalyst loadings, short reaction times and proceeds under "open-flask" conditions. The high diastereoselectivities and mildness of these reaction conditions should make this reaction a valuable tool for synthesis of quaternary carbon centers[17] and *exo*-methylenecycloalkanes. Additionally, these

result underscore the potential of Au(I) as a homogeneous catalyst for the formation of carbon−carbon bonds.[9] Studies extending the range of Au(I)-catalyzed C−C bond forming reactions are currently underway in our laboratories.

Supporting Information Available: Experimental procedures and compound characterization data (PDF). This material is available free of charge via the Internet at http://pubs.acs.org

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(15) In accord with this hypothesis diester **37** and ketoamide **38** (enol form destabilized by 1,3-allylic strain) fail to participate in the reaction.
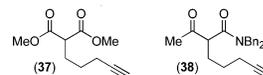
(16) This mechanism also provides an explanation for the poor reactivity (<10% conversion) of non-terminal alkynes, since severe 1,3-allylic strain develops in the transition state (**A**) for cyclization.

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