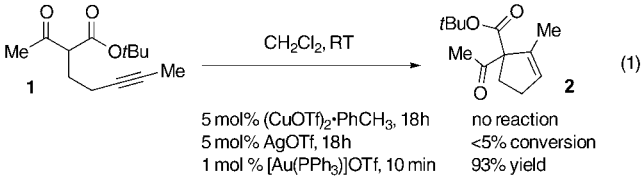
Synthetic Methods

Gold(I)-Catalyzed 5-*endo-dig* Carbocyclization of Acetylenic Dicarbonyl Compounds**

*Steven T. Staben, Joshua J. Kennedy-Smith, and F. Dean Toste**

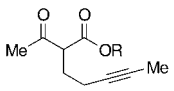
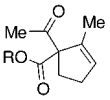
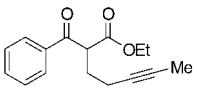
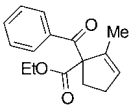
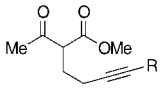
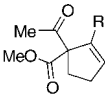
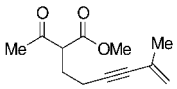
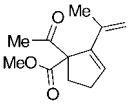
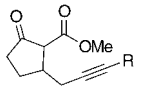
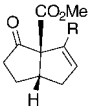
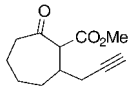
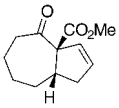
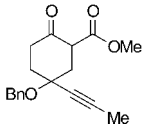
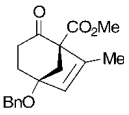
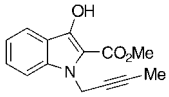
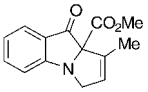
The importance of cyclopentanoid natural products[1] continues to inspire the development of methods for the synthesis of 5-membered rings.[2] For example, the Conia–ene reaction provides an atom-economical synthesis of methylenecyclopentanes by the thermal cyclization of ε-acetylenic carbonyl compounds.[3] While the classic thermal reaction is limited to the exocyclic cyclization mode, group 6 metal complexes catalyze the formal 5-*endo-dig* addition of β-ketoesters[4] and silyl enol ethers[5] to alkynes. These reactions proceed via intermediate metal vinylidenes and therefore are limited to substrates containing a terminal acetylene moiety. The scope and utility of this reaction would be greatly increased if nonterminal alkynes could be employed as electrophiles.[6] However, while examples of the transition-metal-catalyzed 5-*endo-dig* addition of heteroatom nucleophiles to nonterminal alkynes are common,[7–9] this class of cyclization employing carbon nucleophiles is rare.[10]

We have recently demonstrated that cationic gold(I) complexes catalyze the Conia–ene reaction by a mechanism that appears to involve formation of a gold(I) alkyne complex.[11] Thus, we reasoned that an endocyclic Conia–ene reaction might be feasible with group 11 metal complexes as catalysts for alkyne activation.[8,9] Furthermore, while the gold(I)-catalyzed Conia–ene reaction is limited to terminal alkynes, we anticipated that a 5-*endo-dig* variant would allow for carbocyclization onto nonterminal alkynes. To this end, we surveyed several cationic group 11 metal triflates as catalysts for the cyclization of β-ketoesters **1** with nonterminal α-3′-alkynyl substituents [Eq. (1)]. Reaction of **1** with Cu^I and Ag^I triflate



(1)

Table 1: Scope of Au^I-catalyzed 5-*endo-dig* carbocyclization.[a]

Entry	Substrate		Time	Product		Yield
1		R = allyl **3**	10 min		**4**	90%
2		R = propargyl **5**	5 min		**6**	96%
3		**7**	5 h		**8**	90%
4		R = Et **9**	5 min		**10**	83%
5		R = CH_2OTHP **11**	45 min		**12**	80%
6		**13**	1 h		**14**	88%[b]
7		R = H **15**	1 h		**16**	83%
8		R = Me **17**	15 min		**18**	74%
9		R = Ph **19**	10 min		**20**	94%
10		**21**	20 h		**22**	80%[c]
11		**23**	6 min		**24**	99%
12		**25**	6 h		**26**	99%[c]

[a] Reaction conditions: see Experimental Section. [b] Together with about 15% of a 1,3-diene isomer. [c] 2 mol% $[(PPh_3)Au]Cl$, 2 mol% AgOTf.

complexes did not produce the desired cyclopentene adduct **2**. On the other hand, triphenylphosphinegold(I) triflate rapidly (10 min) converted alkyne **1** into cyclopentene **2** in 93% yield. Notably, these reactions were run under "open-flask" conditions at room temperature without the necessity for dry solvents or inert atmosphere.

Under these experimentally simple conditions, a wide range of substrates underwent rapid 5-*endo-dig* cycloisomerization to give cyclopentene products (Table 1, entries 1–6). In all cases no *exo*-cyclization was observed, including a substrate (**5**) having the opportunity to undergo competitive 5-*exo-dig* cyclization onto a propargyl ester (entry 2). Variation at the ester (entries 1 and 2) and ketone (entry 3)

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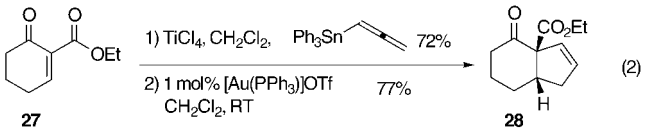
moieties is tolerated, although cyclization of aryl ketones requires increased reaction times. The reaction is also amenable to a wide range of alkynyl substituents including alkyl, aryl (entry 9), vinyl (entry 6), and proton (entry 7), although the latter appears to react more sluggishly. Importantly, the mild reaction conditions allow for the use of acid-labile groups such as *tert*-butyl ester [Eq. (1)], tetrahydropyranyl ether (entry 5), and tertiary propargyl ether (entry 11). This cycloisomerization provides an alternative synthesis of 1,3-dienes often prepared by enyne metathesis.[12] For example, 1,3-enyne **13** underwent rapid cyclization to give 1,3-diene **14** in good yield (entry 6).

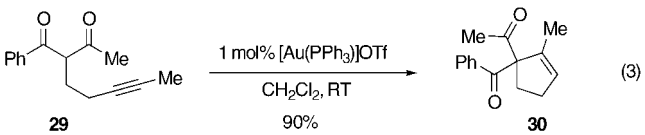
Having established the feasibility of the endocyclic carbocyclization, we sought to apply this method to the synthesis of bicyclic structures by a cyclopentene annulation[13] onto α,β′-unsaturated β-ketoesters. Thus, conjugate addition of allenyltriphenylstannane[14] to **27**, followed by gold(I)-catalyzed cyclization afforded cyclopentene **28** as a single diastereomer [Eq. (2)]. This cyclopentene annulation



(2)

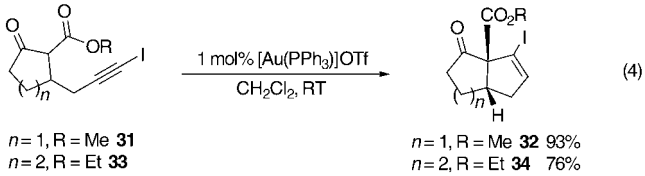
can also be applied to the diastereoselective formation of 5,5- (Table 1, entries 7–9) and 7,5-fused (entry 10) bicyclic ring systems. Additionally, bicyclo[3.2.1]octane **24** is available in excellent yield from the 5-*endo-dig* cyclization of β-ketoester **23** (entry 11). Lewis-basic groups, such as a tertiary amine, are tolerated and thus the gold-catalyzed reaction allows for the synthesis of heterocyclic ring systems. For example, the benzo-fused pyrrolizidine core of the mitosanes (**26**)[15] is available in excellent yield from a gold(I)-catalyzed cyclization of 3-hydroxyindole **25** (entry 12).

We have found that β-diketones[6] are also viable nucleophiles under the optimized reaction conditions. For example, 1 mol% triphenylphosphinegold(I) triflate rapidly and efficiently catalyzes the conversion of 1,3-dione **29** into cyclopentene **30** [Eq. (3)].



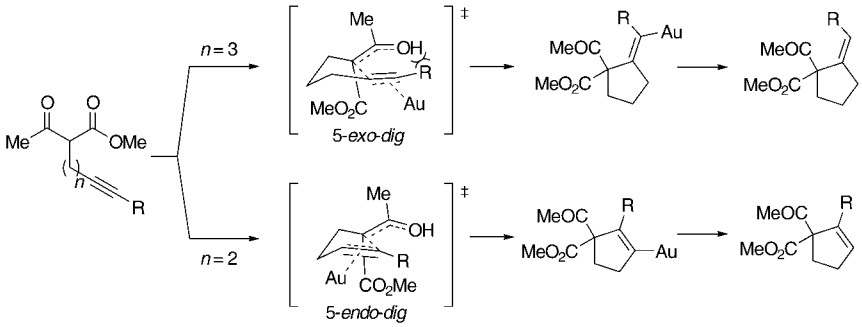
(3)

Carbocyclization onto 1-halo-1-alkynes would provide a facile entry into cyclopentenyl halides, however, transition-metal-catalyzed addition reactions to alkynyl halides are exceptionally rare.[16] We were, therefore, very pleased to find that 1-iodoalkynes **31** and **33** underwent rapid cyclization to give cyclopentenyl iodides **32** and **34** as single diastereomers in 93 and 76% yield, respectively [Eq. (4)].



(4)

We propose that these reactions proceed by a mechanism involving nucleophilic addition of an enol to a gold(I) alkyne complex (Scheme 1). Based on this mechanistic hypothesis, one of the potential explanations for the lack of reactivity of nonterminal alkynes in the gold-catalyzed 5-*exo-dig* cyclization[11] is that placement of the catalyst near an alkyl-substituted carbon atom is sterically unfavorable. However, in the transition state for the endocyclic reaction the gold center is located near an alkyl-substituted carbon atom without inhibiting the cyclization. We propose that the 5-*exo-dig* Conia–ene reaction is limited to terminal alkynes because of the development of 1,3-allylic strain in the transition state. This strain is absent in the transition state for the gold(I)-catalyzed 5-*endo-dig* cyclization allowing for the participation of nonterminal alkynes.



Scheme 1. Proposed mechanism for the gold(I)-catalyzed 5-*endo-dig* carbocyclization.

In conclusion, we have developed a gold(I)-catalyzed 5-*endo-dig* carbocyclization of dicarbonyl compounds onto appended alkynes. The reaction is carried out under open-flask conditions and shows excellent tolerance for variation in the ketone, ester, and alkyne substituents. As such, it provides entry into a wide range of cyclopentanoid structures including those containing 1,3-diene, vinyl iodide, and heterocyclic moieties. These results further highlight the potential of gold(I) complexes[17] to serve as catalysts for the formation of carbon–carbon bonds by alkyne activation. Applications of this strategy, including an asymmetric variant, are underway in our laboratory and will be reported in due course.

Experimental Section

General synthetic procedure: To a small screw-cap scintillation vial equipped with a magnetic stir bar and charged with a solution of the α-3′-alkynyl-substituted β-dicarbonyl compound (~150 mg, 1 equiv)

in CH_2Cl_2 (0.4 M) was added [Au(PPh_3)]Cl (1 mol%) followed by AgOTf (1 mol%). The cloudy white reaction mixture was then stirred at room temperature and monitored periodically by thin layer chromatography. Upon completion of the reaction, the mixture was loaded directly onto a silica gel column and chromatographed with the appropriate mixture of hexanes and ethyl acetate to give the cycloisomerized products.

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