Carbocyclization

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Gold(I)-Catalyzed Cyclizations of Silyl Enol Ethers: Application to the Synthesis of (+)-Lycopladine A**

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The construction of carbocycles containing quaternary stereocenters continues to be an important synthetic challenge.[1] We recently described the gold(I)-catalyzed cyclizations of

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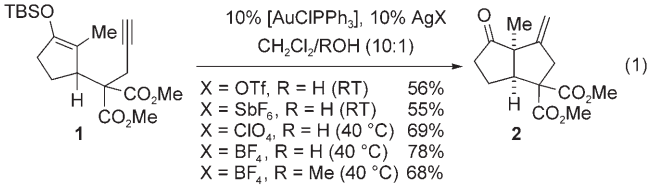
enolizable β-keto esters and β-diketones onto appended alkynes as a method for cyclopentene formation.[2] Although broadly applicable to the diastereoselective formation of a variety of cyclic and bicyclic systems, the method is limited to the synthesis of quaternary carbon atoms that bear two carbonyl functionalities. Our proposed mechanism for these transformations involves the addition of the enol tautomer of the keto ester to a gold(I)-complexed alkyne and the subsequent protonolysis of the resulting vinyl–gold(I) species. On the basis of this hypothesis, we envisioned taking advantage of the well-precedented nucleophilicity of silyl enol ethers as "frozen enol equivalents" in gold(I)-catalyzed cyclization reactions.[3,4] Described herein is the development of the gold(I)-catalyzed cyclization of silyl enol ethers onto alkynes and allenes and the application of this carbon–carbon bond-forming reaction to an expedient total synthesis of (+)-lycopladine A.[5]

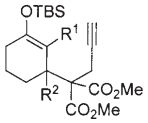
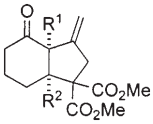
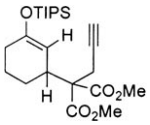
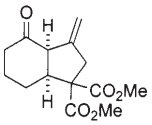
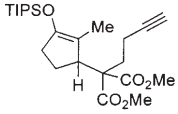
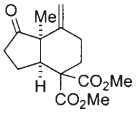
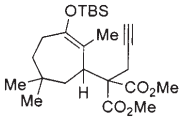
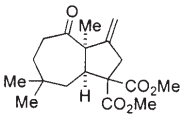
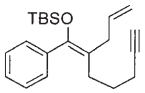
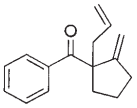
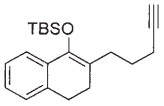
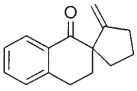
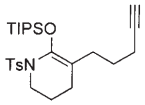
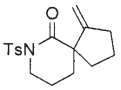
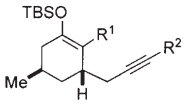
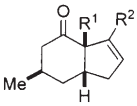
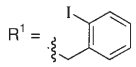
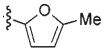
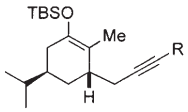
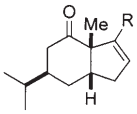
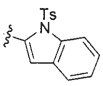
Several issues must be confronted in employing silyl enol ethers in gold(I)-catalyzed reactions. First, unlike enol nucleophiles, the silylated counterparts lack the proton source necessary for the protonolysis of the vinyl–gold(I) intermediate. Thus, an external proton source is required to complete the catalytic cycle. The competitive reaction of this proton source[6,7] and the electrophilic cationic gold(I) species[8] with the highly nucleophilic silyl enol ether must be avoided. With this in mind, we examined the feasibility of the gold(I)-catalyzed 5-*exo* cyclization of silyl enol ether **1** with water as the external proton source. A catalytic amount of $[Ph_3PAuCl]/AgBF_4$ in a 10:1 dichloromethane/water mixture at 40 °C for 30 minutes provided bicyclic ketone **2** in 78% yield of the isolated product [Eq. (1); OTf = trifluoromethanesulfonate]. The identity of the counterion proved to be key as other complexes (namely, ClO_4, SbF_6, and OTf salts) produced the desired cyclized product with varying amounts of hydrolyzed enol ethers. Additionally, we found that methanol could be substituted as the proton source with only a slight deterioration in the yield of the isolated product **2**.



(1)

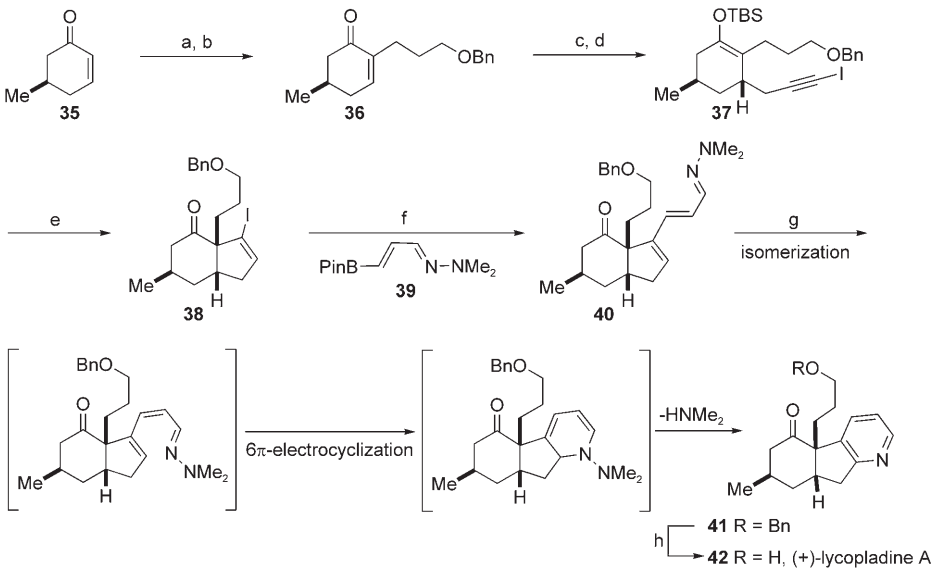
Under these conditions, the gold(I)-catalyzed *exo*-dig cyclization proved to be general in scope (Table 1, entries 1–8). Alkyl, aryl, and hydrogen substitution was tolerated at the α-position in the completely diastereoselective formation of bicyclic systems. For example, the gold(I)-catalyzed cyclization of enol ether **3** afforded bicyclic product **4**, which contains three consecutive all-carbon quaternary stereocen-

Table 1: Scope of Au^{I}-catalyzed carbocyclizations of silyl enol ethers and alkynes[a].

Entry	Substrate				Product	Yield [%]
1		**3**	R^1 = Me	R^2 = Me	 **4**	90
2		**5**	R^1 = Ph	R^2 = H	**6**	83
3		**7**			 **8**	83[b]
4		**9**			 **10**	94
5		**11**			 **12**	80
6		**13**			 **14**	77[c]
7		**15**			 **16**	91[c]
8		**17**			 **18**	75[c]
9		**19**	R^1 = allyl	R^2 = H	 **20**	77
10		**21**	R^1 = 	R^2 = Ph	**22**	85
11		**23**	R = 		**24**	73
12		**25**	R = 		 **26**	75
13		**27**	R = 		**28**	91

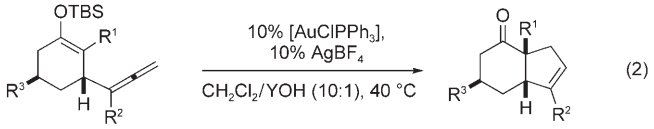
[a] Reaction conditions: $[AuClPPh_3]$ (10 mol%), $AgBF_4$ (10 mol%), silyl enol ether (0.4 M) in CH_2Cl_2/H_2O (10:1), 40 °C. [b] Reaction carried out in toluene/MeOH (10:1, 0.4 M) at room temperature, and the product was isolated as a 9:1 mixture with the corresponding enone. [c] Reaction conditions: $[AuClPPh_3]$ (10 mol%) and AgOTf (10 mol%) in CH_2Cl_2/MeOH (10:1), 0 °C. TIPS = triisopropylsilyl, Ts = *p*-toluenesulfonyl.

ters, in 90% yield (Table 1, entry 1). Furthermore, the mildness of the reaction conditions is highlighted by the fact that non-quaternary α-stereocenters can be created diastereoselectively with minimal isomerization of the *exo*-methylene unit into conjugation with the ketone function (Table 1, entry 3). Furthermore, *exo*-methylene cyclohexane **10** was prepared in 94% yield through a gold(I)-catalyzed 6-*exo*-dig cyclization (Table 1, entry 4). The gold(I)-catalyzed reaction also operates effectively with acyclic silyl enol ether **13**, thus affording *exo*-methylene cyclopentane **14** in 77% yield (Table 1, entry 6). Moreover, the reaction can be employed to construct spirocyclic ketone **16** and amide **18** in 91 and 75% yield, respectively (Table 1, entries 7 and 8).

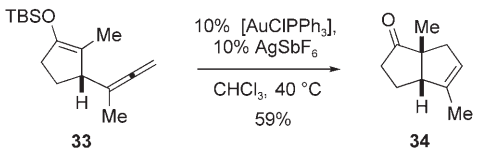


Scheme 1. Synthesis of (+)-lycopladine A. Reagents and conditions: a) I_2 (0.6 equiv), $PhI(OCOCF_3)_2$ (0.6 equiv), pyridine, CH_2Cl_2, room temperature (85%); b) $(BnOCH_2CH_2CH_2)_3B$, $[PdCl_2(dppf)]$ (5 mol%), $AsPh_3$ (5 mol%), Cs_2CO_3, DMF, THF, H_2O (72%); c) tributylallenylstannane, TBSOTf, CH_2Cl_2, −78→−10°C (93%); d) NIS, $AgNO_3$, DMF, 0°C→RT (82%); e) $[AuClPPh_3]/AgBF_4$ (10 mol%), CH_2Cl_2/MeOH (10:1), 40°C (95%); f) **39**, $[Pd(PPh_3)_4]$ (5 mol%), NaOMe, MeOH/PhH (83%); g) $PhCH_3$, 190°C, 4 h (60%); h) 10% Pd/C, 1,4-cyclohexadiene, EtOH (75%). Bn = benzyl, DMF = dimethylformamide, dppf = 1,1′-bis(diphenylphosphino)ferrocene, NIS = *N*-iodosuccinimide, Pin = pinacol.

We envisioned that this catalyst system might be extended to allow the construction of cyclopentenes, with control of the location of the double bond, simply by varying the electrophilic component. Gratifyingly, silyl enol ethers also participated as nucleophiles in gold(I)-catalyzed 5-*endo*-dig additions to alkynes, which allows for the production of a variety of systems bearing endocyclic olefins (Table 1, entries 9–13). Notably an aryl iodide, a functional group susceptible to oxidative addition by other d^{10}-transition-metal catalysts, remains untouched in the Au^I-catalyzed process (Table 1, entry 10). Additionally, a variety of heteroaromatic groups were well tolerated at the acetylenic position (Table 1, entries 11–13). Moreover, similar conditions can be employed for the use of allenes as the electrophilic partner in a 5-*endo*-trig cyclization [Eqs. (2) and (3); TBS = *tert*-butyldimethylsilyl].[9] For example, allene **31** smoothly underwent a gold(I)-catalyzed cyclization to afford bicylic cyclopentenes **32** in 72% yield. Therefore, the combination of the gold(I)-catalyzed alkyne and allene cyclization reactions allows for the construction of cyclopentenes with control of the position of the unsaturation (compare **20** with **32**).



(2)



(3)

The utility of the gold(I)-catalyzed method for the formation of non-ester-bearing all-carbon quaternary centers was immediately realized in an expedient total synthesis of the recently isolated fawcettimine alkaloid (+)-lycopladine A (**42**). Isolated from *Lycopodium complantum*, lycopladine A (**42**) shows modest but selective cytotoxicity against murine lymphoma L1210 cells and possesses an unprecedented $C_{16}N$-type alkaloid skeleton, including a novel pyridyl-fused hydrindanone core.[5] We envisioned that a gold(I)-catalyzed 5-*endo*-dig cyclization could be employed to construct the hydrindanone core of lycopladine A. To this end, cyclohexenone **36** was obtained through iodination[10] and subsequent B-alkyl Suzuki–Miyaura coupling[11] of readily obtainable (*R*)-(+)-5-methyl-2-cyclohexen-1-one (**35**;[12] Scheme 1). Conjugate propargylation of tributylallenylstannane promoted by *tert*-butyldimethylsilyl trifluoromethanesulfonate (TBSOTf)[13] followed by iodination of the resultant terminal alkyne[14] diastereoselectively furnished iodoacetylene **37** and set the stage for the key gold(I)-catalyzed 5-*endo*-dig cyclization. Reaction of silyl enol ether **37** under our optimized conditions gave hydrindanone vinyl iodide **38** in 95% yield as a single diastereomer. Vinyl iodide **38** underwent Suzuki coupling with boronic ester **39**[15] to afford *N*,*N*′-dimethylhydrazone **40** in 83% yield. Notable is the consecutive use of two catalytic reactions mediated by d^{10} metals with orthogonal reactivity (Au^I and Pd^0), thus allowing rapid and convergent access to all of the carbon atoms of lycopladine. Thus, heating **40** promoted a cascade sequence involving double-bond isomerization, 6π electrocyclization, and elimi-

nation of dimethylamine to generate pyridyl-fused product **41** in 60% yield.[16] The benzyl ether protecting group was removed under conditions for transfer hydrogenation to complete the asymmetric total synthesis of (+)-lycopladine A (**42**) and thereby establish the absolute stereochemistry of this alkaloid.

In summary a gold(I)-catalyzed addition of silyl enol ethers to alkynes and allenes has been developed. The reaction allows for the diastereoselective synthesis of a variety of bicyclic frameworks containing all-carbon quaternary centers. Taken together, the gold(I)-catalyzed 5-*exo*-dig, 5-*endo*-dig, and 5-*endo*-trig pentannulation reactions provide access to cyclopentenes with control of the position of the double bond. The utility of these reactions was demonstrated by an efficient total synthesis of (+)-lycopladine A (8 steps, 17% overall yield from enone **35**) which takes advantage of the orthogonal reactivity of the Au^I and Pd^0 centers towards unsaturated iodides.[17] Further demonstration of the utility of these cyclopentene annulation reactions, including additional application to the fawcettimine alkaloids, is in progress and will be reported in due course.

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Keywords: alkaloids · carbocyclization · gold · homogeneous catalysis · silyl enol ethers

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