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Au^I-Catalyzed Intramolecular Cyclization of 2-Alkenylphenyl Carbonyl Compounds: Exploring the Oxophilic Lewis Acidity of Au^I Species

Arun R. Jagdale[a] and So Won Youn*[a]

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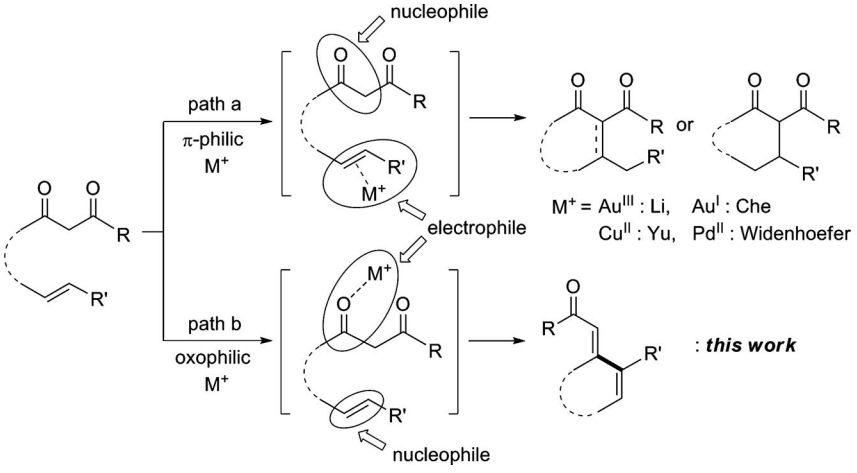
A Au^I-catalyzed intramolecular cyclization reaction of 2-alkenylphenyl carbonyl compounds to afford a variety of indene, indenol, and indanone ring systems was developed. In this process, Au^I serves to activate the carbonyl group of β-keto esters, aldehydes, and ketones, preferentially exhibiting oxophilicity in the presence of C–C multiple bonds. Furthermore, β-keto esters could participate as the electrophilic partner in reactions with carbon nucleophile such as alkenes.

Introduction

Transition-metal-catalyzed carbon–carbon bond formation reactions between 1,3-dicarbonyl compounds and alkenes have been of significant synthetic interest in recent years.[1] In general, such transformations operate through the nucleophilic character of the 1,3-dicarbonyl functionality, forging a carbon–carbon bond with the alkene component through π-philic transition-metal activations (Scheme 1, path a). Au^{III} and Au^I are both well documented soft π-philic Lewis acids that show a high degree of electrophilicity towards carbon–carbon multiple bonds, generating an activated species that is susceptible towards nucleophilic attack.[1c–1e,2] Meanwhile, it has also been reported that Au^{III} can exhibit oxophilic character towards the carbonyl group, thereby rendering an electrophilic nature to the latter functionality.[3–5] In stark contrast, synthetic applications that exploits the oxophilicity of Au^I remains scarce, especially in substrates bearing C=C bonds where the latter functionality is known to be more susceptible towards activation by Au^I catalysts.[6] As a pioneering example, Liu and co-workers reported a Au^I-catalyzed deoxygenative Nazarov cyclization of 2,4-dien-1-als in the preparation of cyclopentene derivatives, demonstrating the oxophilicity exhibited by Au^I catalysts towards the aldehyde functionality.[6b,6c] Herein, we report an unprecedented Au^I-catalyzed intramolecular cyclization reaction of 2-alkenylphenyl carbonyl compounds (Scheme 1, path b). In particular, for the first time, oxophilic activation of alkenyl β-keto esters has been demonstrated, thereby rendering the latter functionality susceptible to nucleophilic attack by the pendent



Scheme 1. Transition-metal-catalyzed reactions between β-keto carbonyl compounds and olefins.

[a] Department of Chemistry and Research Institute for Natural Sciences, Hanyang University,
Seongdong-Gu, Seoul 133-791, South Korea
Fax: +82-2-2299-0762
E-mail: sowony73@hanyang.ac.kr

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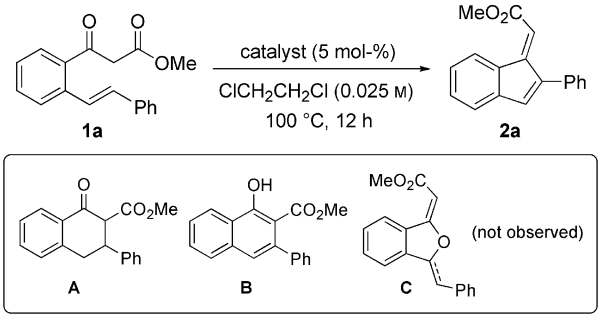
alkenyl moiety. This protocol enabled convenient entry to a variety of indenes,[7] indenols,[8] and indanones,[9] which are privileged structural motifs found in a diverse array of compounds possessing important physical and biological properties.[10]

Results and Discussion

Prompted by recent reports of Au-catalyzed addition of 1,3-dicarbonyl compounds to alkenes,[1c–1e,2] we initially anticipated a Au-catalyzed intramolecular cyclization of alkenyl β-keto esters **1a** to afford tetralone **A** and/or its oxidatively aromatized derivative naphthol **B** (Table 1).[11] Much to our surprise, treatment of **1a** with Ph_3PAuCl/AgOTf (1:1, 5 mol-%) in $ClCH_2CH_2Cl$ (0.025 M) at 100 °C led to, exclusively, the formation of indene **2a** in 70% yield (Table 1, Entry 1). We speculated this unexpected outcome originates from initial nucleophilic attack at the ketone moiety by the stilbene olefin, followed by subsequent dehydration. Expected products **A** and **B**, or **C**,[1h,1i] resulting from intramolecular nucleophilic addition of the β-keto ester to the alkene functionality through either C or O attack, respectively, could neither be isolated nor detected. Inspired by this serendipitous discovery, we set out to examine the reaction of **1a** in the presence of other Lewis acidic metal salts (Table 1; for details, see the Supporting Information). Au^{III}, Pt^{II}, Ru^{III}, Ag^{I}, and Cu^{II} triflate salts gave product **2a** in moderate yields, whereas other metal triflates were ineffective (Table 1, Entries 1–9). Considering the well-known π-philic Lewis acidity of Au^{I} that activates the alkene moiety towards nucleophilic attack by 1,3-dicarbonyls, and recognizing that Au^{III} is more oxophilic than Au^{I},[1c–1e,2–5] our findings are particularly noteworthy. The combination of AuCl and AgOTf also promoted the reaction in the absence of a phosphane ligand, albeit in lower yield (Table 1, Entry 2). Among a variety of Ag salts examined, AgOTf proved to be uniquely effective and essential as a cocatalyst (Table 1, Entries 10–14). On the other hand, a selection of Lewis and Brønsted acids examined did not promote the reaction at all (Table 1, Entries 20–34).[12] It is noteworthy that the reaction did not take place in the absence of cationic Au^{I} catalyst (Table 1, Entry 19). Control experiments employing protic acid that could conceivably be generated in situ to thereby catalyze the reaction did not give any products (Table 1, Entry 31), ruling out the possibility of protic acid catalysis. $ClCH_2CH_2Cl$ proved to be the solvent of choice (Table 1, Entries 16 and 17), and the reaction yield showed little dependence on concentration (Table 1, Entry 15). Finally, reducing either the reaction temperature or catalyst loading led to a lower yield of **2a** (Table 1, Entries 16 and 18).

With the optimized reaction conditions in hand, we set out to explore the substrate scope of this process. As shown in Table 2, the reaction showed little dependence on the nature of the ester group (Table 2, Entries 1–4), and both aryl (Table 2, Entries 1–11) and alkyl (Table 2, Entries 13–15) substituted styrenes were well tolerated. Furthermore, substrates bearing electron-deficient aryl groups (Table 2, Entries 7 and 8) as well as a sterically hindered alkyl group (Table 2, Entry 14) underwent the cyclization reaction successfully, whereas a terminal alkene afforded a much inferior yield of product (Table 2, Entry 16). Interestingly, reactions of substrates bearing a 4-methoxyphenyl-substituted alkene (R^4 = 4-$MeOC_6H_4$) afforded the corresponding tetralones **2f′** and **2l′** in high yields (exist in tautomeric forms; Table 2, Entries 6 and 12), where the structure of the

Table 1. Catalyst screening for the intramolecular cyclization of **1a**.

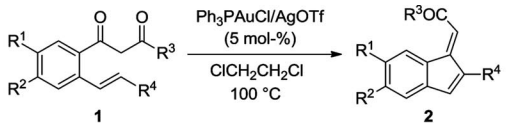


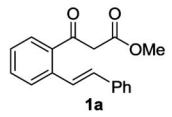
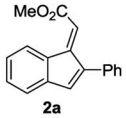
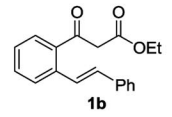
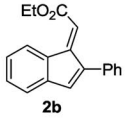
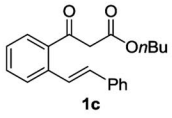
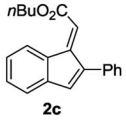
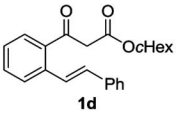
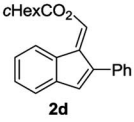
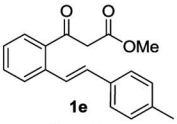
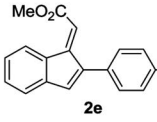
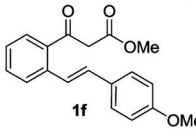
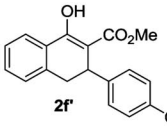
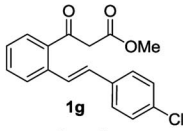
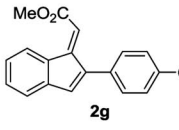
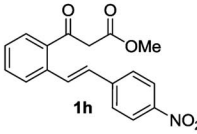
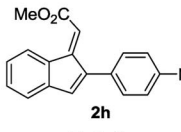
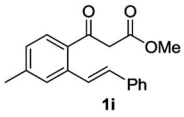
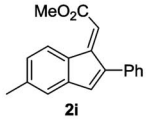
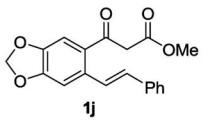
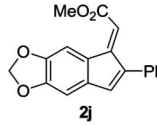
Entry	Catalyst (mol-%)	Yield [%][a]
1	Ph_3PAuCl (5)/AgOTf (5)	70
2	AuCl (5)/AgOTf (5)	50
3	$AuCl_3$ (5)/AgOTf (10)	45
4	$PtCl_2$ (5)/AgOTf (10)	40
5	$RuCl_3$ (5)/AgOTf (10)	45
6	AgOTf (5)	45
7	$Cu(OTf)_2$ (5)	45
8	$In(OTf)_3$ (5)	10
9	$Sc(OTf)_3$ (5)	0
10[b]	Ph_3PAuCl (5)/AgOTf (5)	70 (66)
11[b]	Ph_3PAuCl (5)/$AgBF_4$ (5)	0
12[b]	Ph_3PAuCl (5)/$AgSbF_6$ (5)	0
13[b]	Ph_3PAuCl (5)/AgOTs (5)	0
14[b]	Ph_3PAuCl (5)/$Ag(O_2CCF_3)$ (5)	0
15[c]	Ph_3PAuCl (5)/AgOTf (5)	50–60
16[d]	Ph_3PAuCl (5)/AgOTf (5)	40
17[e]	Ph_3PAuCl (5)/AgOTf (5)	0–trace
18	Ph_3PAuCl (3 or 4)/AgOTf (3 or 4)	45–60
19	Ph_3PAuCl (5)	0
20	$PdCl_2$ (5)	0
21	$Pd(OAc)_2$ (5)	0
22	$PdCl_2(MeCN)_2$ (5)	0
23	AuCl (5)	0
24	$AuCl_3$ (5)	0
25	$PtCl_2$ (5)	0
26	$RuCl_3$ (5)	0
27	$AlCl_3$ (5)	0
28	$ZnCl_2$ (5)	0
29	$FeCl_3$ (5)	0
30	$BF_3{\cdot}Et_2O$ (5)	0
31	TfOH(5)	trace
32	*p*TsOH (5)	trace
33	AcOH (5)	0
34	CF_3CO_2H (5)	0

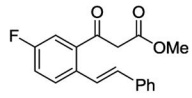
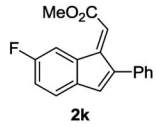
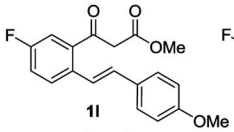
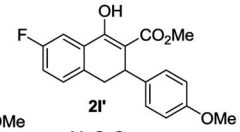
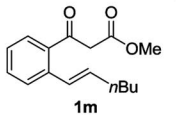
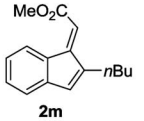
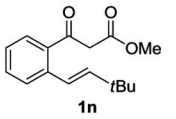
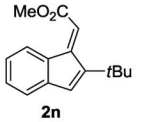
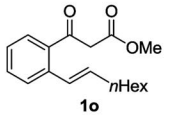
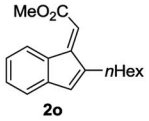
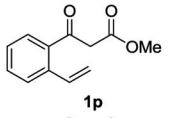
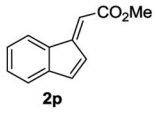
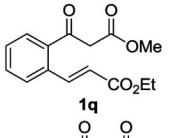
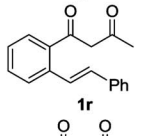
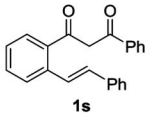
[a] Yield determined by ^1H NMR spectroscopy using trichloroethylene as an internal standard. Value in parentheses indicates isolated yield. [b] For 4 h. [c] In 0.05 or 0.017 M $ClCH_2CH_2Cl$. [d] At 80 °C. [e] Using THF, DMF, DMSO, MeCN, or toluene as the solvent at 80 °C for 48 h.

latter compound was unambiguously validated through X-ray analysis of its *O*-acetylated derivative (for details, see the Supporting Information).[13] The exact reason for the unexpected formation of tetralones **2f′** and **2l′** remains to be investigated; however, a working hypothesis involving electrophilic activation of the alkene moiety could be conceived where a species resonance-stabilized by an electron-releasing OMe group renders the β carbon (carbon bonded

Table 2. Au^{I}-catalyzed intramolecular cyclization of alkenyl β-keto esters **1**.[a]

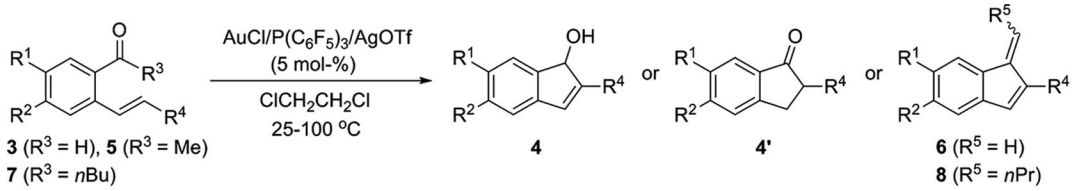


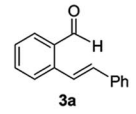
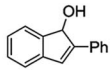
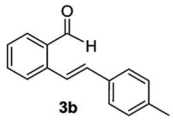
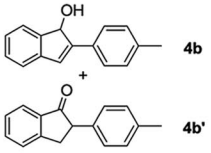
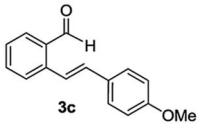
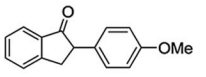
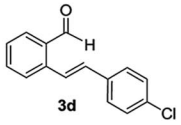
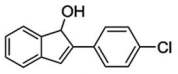
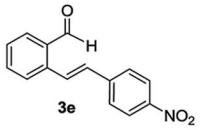
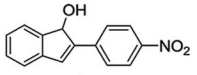
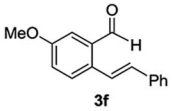
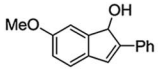
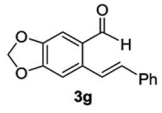
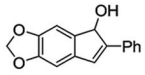
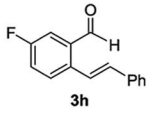
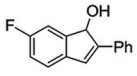
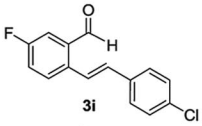
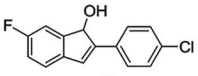
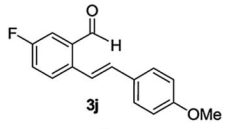
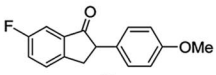
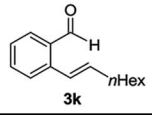
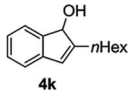
Entry	Substrate	Product	Yield [%][b]
1	 **1a**	 **2a**	66
2	 **1b**	 **2b**	80
3	 **1c**	 **2c**	72
4	 **1d**	 **2d**	65
5	 **1e**	 **2e**	65
6	 **1f**	 **2f′**	93 (enol/keto, 5:3)
7	 **1g**	 **2g**	73[c]
8	 **1h**	 **2h**	63[c]
9	 **1i**	 **2i**	57
10	 **1j**	 **2j**	40

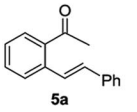
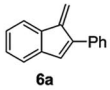
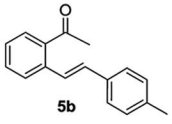
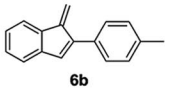
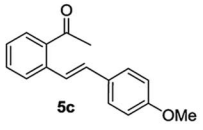
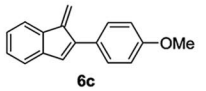
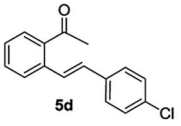
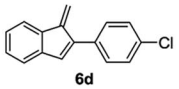
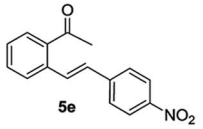
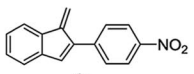
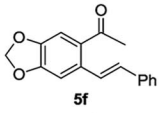
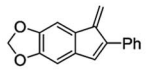
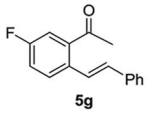
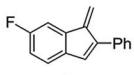
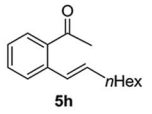
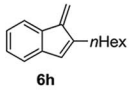
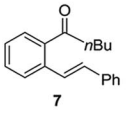
Entry	Substrate	Product	Yield [%][b]
11	 **1k**	 **2k**	69
12	 **1l**	 **2l′**	86 (enol/keto, 5:1)
13	 **1m**	 **2m**	73
14	 **1n**	 **2n**	62
15	 **1o**	 **2o**	76
16	 **1p**	 **2p**	31 (37)[d]
17	 **1q**	–	0[e]
18	 **1r**	–	0[e]
19	 **1s**	–	0[e]

[a] Reaction conditions: **1** (1 equiv.), Ph_3PAuCl (5 mol-%), and AgOTf (5 mol-%) in $ClCH_2CH_2Cl$ (0.025 M) at 100 °C for 1–6 h, unless otherwise noted. [b] Isolated yield. [c] Performed with Ph_3PAuCl/AgOTf (10 mol-%). [d] Performed with $AuCl/P(C_6F_5)_3$/AgOTf (5 mol-%) at 70 °C for 10 h. [e] No reaction occurred using either Ph_3PAuCl/AgOTf (5 mol-%) at 100 °C or $AuCl/P(C_6F_5)_3$/AgOTf (5 mol-%) at 60–80 °C for 9–24 h, and starting materials were recovered in 60–90% yield.

Table 3. Au^{I}-catalyzed intramolecular cyclization of 2-alkenylbenzaldehydes **3** and 2-alkenylaryl ketones **5** & **7**.[a]



Entry	Substrate	Product	Yield [%][b]
1	 **3a**	 **4a**	85
2	 **3b**	 **4b** + **4b'**	62 (**4b**) 23 (**4b′**)
3	 **3c**	 **4c'**	64
4	 **3d**	 **4d**	89
5	 **3e**	 **4e**	75
6	 **3f**	 **4f**	59
7	 **3g**	 **4g**	65
8	 **3h**	 **4h**	84
9	 **3i**	 **4i**	86
10	 **3j**	 **4j'**	72
11	 **3k**	 **4k**	91

Entry	Substrate	Product	Yield [%][b]
12	 **5a**	 **6a**	64
13	 **5b**	 **6b**	64[c]
14	 **5c**	 **6c**	38[c]
15	 **5d**	 **6d**	65
16	 **5e**	 **6e**	86
17	 **5f**	 **6f**	60[c]
18	 **5g**	 **6g**	66
19	 **5h**	 **6h**	92[c]
20	 **7**	**8** + **8'**	66[c] (**8**/**8′** = 63:37)
21	**9**	–	0[d]

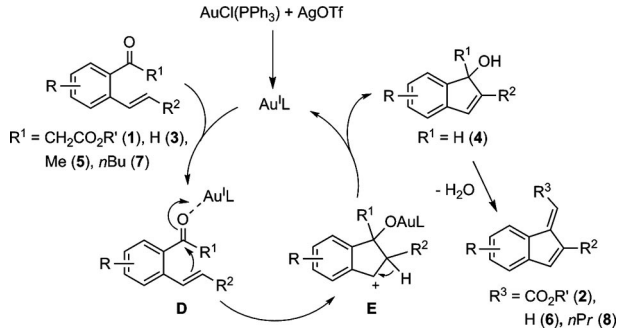
[a] Reaction conditions: **3**, **5**, or **7** (1 equiv.), AuCl (5 mol-%), $P(C_6F_5)_3$ (5 mol-%), and AgOTf (5 mol-%) in $ClCH_2CH_2Cl$ (0.025 M) at 25–100 °C for 0.5–8 h. [b] Isolated yield. [c] Performed with Ph_3PAuCl/AgOTf (5 mol-%). [d] No reaction occurred using either Ph_3PAuCl/AgOTf (5 mol-%) at 100 °C for 24 h or AuCl/$P(C_6F_5)_3$/AgOTf (5 mol-%) at 60 °C for 14 h, and starting materials were recovered in 90–95% yield.

to R^4) more electrophilic to nucleophilic attack by the proximal 1,3-dicarbonyl. Substituent effects of R^1 and R^2 were also examined, and in general, reaction yields were higher for substrates bearing electron-neutral or electron-withdrawing substituents than for substrates bearing electron-donating substituents (Table 2, Entries 9–11).[14] With the exception of **2p** (Table 2, Entry 16), only *E* isomers were obtained stereoselectively. The structure of all indene products were supported by ^{1}H NMR and NOESY spectroscopy experiments of compound **2a**,[15] and X-ray crystallographic analysis of product **2k**.[13] Lastly, this cyclization reaction failed to take place with β-keto esters bearing an enoate (R^4 = CO_2Et) or 1,3-diketones (R^3 = Me, Ph) (Table 2, Entries 17–19), findings supported by the preferential Au^I activation of the dicarbonyl moiety and propensity of diketones to exist in their less-reactive enol tautomeric forms,[16] respectively.

Encouraged by the Au^I-mediated cyclizations of alkenyl β-keto esters, we turned our attention to alkenyl benzaldehyde and aryl ketone substrates. We speculated a similar reaction pathway may take place leading to a variety of indenols and indenes. The results of our findings are shown in Table 3. Compared to the β-keto ester substrates, simple monocarbonyl substrates generally required longer reaction times. To circumvent this decreased reactivity, an electron-deficient ligand was employed to enhance the electrophilicity of the Au^I catalyst.

Much to our delight, although the Ph_3PAuCl/AgOTf-mediated reaction required a longer reaction time at a higher temperature (100 °C, 21 h, 72%), the combination of AuCl, AgOTf, and $P(C_6F_5)_3$ rapidly converted **3a** into **4a** at a lower temperature with an improved chemical yield (60 °C, 4 h, 85%; Table 3, Entry 1). The same catalyst blend also permitted the reaction to take place at room temperature with comparable yield, albeit a longer reaction time was required (25 °C, 24 h, 75%). The efficiency of this transformation is remarkable, considering that the related Au^I-catalyzed reaction of *cis*-2,4-dien-1-als resulted in a complex reaction mixture in the absence of the external nucleophile.[6b] Furthermore, cycloisomerization of *cis*-2,4-dien-1-als with other Lewis acids in the absence of a nucleophile only afforded cyclopentenones.[17] Under the optimized reaction conditions, 2-alkenylbenzaldehydes **3** and 2-alkenylaryl methyl ketones **5** proceeded smoothly to form the corresponding indenols **4** (Table 3, Entries 1–2, 4–9, and 11) and indenes **6** (Table 3, Entries 12–19), respectively. Aryl butyl ketone **7** also proved to be an effective substrate for this transformation (Table 3, Entry 20), whereas diaryl ketone **9** (R^3 = Ph) was unsuccessful (Table 3, Entry 21). Similar to the reactions with alkenyl β-keto esters **1** described earlier, substrates **3** and **5** bearing either aryl- or alkyl-substituted styrenes (R^4 = aryl or alkyl) were once again well tolerated. 2-Alkenylbenzaldehydes bearing electron-rich aromatic substituents (R^4 = 4-Me-C_6H_4, 4-MeO-C_6H_4) were found to undergo extensive isomerization of the initially formed indenols **4** into indanones **4′**, an observation also reported by other research groups (Table 3, Entries 2, 3, and 10).[10d,10f,18]

Scheme 2 outlines a plausible mechanism for the cyclization reaction described herein.[19] Activation of the carbonyl group through its coordination with the Lewis acidic Au^I center (**D**) precedes intramolecular nucleophilic attack by the pendant alkene moiety, thereby generating a newly formed carbon–carbon bond (**E**). Subsequent proton transfer regenerates the Au^I catalyst and produces indenol product **4**, which undergoes further dehydration for substrates where $R^1 \neq H$. Alternatively, a mechanistic explanation that invokes a Nazarov-type cyclization of activated species **D** could also be conceived.[6b,6c,17]



Scheme 2. Proposed mechanism for the Au^I-catalyzed intramolecular cyclization of 2-alkenylphenyl carbonyl compounds.

Conclusions

We have developed a Au^I-catalyzed intramolecular cyclization reaction of 2-alkenylphenyl carbonyl compounds to afford a variety of indenes, indenols, and indanones. In this process, Au^I served to activate the carbonyl group of β-keto esters as well as aldehydes and ketones, preferentially exhibiting oxophilicity in the presence of C–C multiple bonds. In parallel, β-keto esters could participate as the electrophilic component in reactions with carbon nucleophiles, for example, alkenes. On both accounts, the unique reactivities of both the Au^I catalyst and the alkenyl β-keto esters allow them to partake in a process that is counterintuitive.[1c–1e,2] Further investigations to broaden the substrate scope and application of this enabling technology to construct cyclic motifs through Au^I catalysis are currently underway in our laboratory.

Experimental Section

General Procedure for the Au^I-Catalyzed Intramolecular Cyclization of Alkenyl β-Keto Esters 1: To a solution of 2-alkenyl β-keto esters **1** in $ClCH_2CH_2Cl$ (0.025 M) in a pressure tube was added Ph_3PAuCl (5–10 mol-%) and AgOTf (5–10 mol-%). The resulting mixture was stirred at 100 °C for the reported time. After the reaction was complete, the reaction mixture was poured into sat. NH_4Cl, and then the product was extracted with CH_2Cl_2 (3×), dried with $MgSO_4$, and concentrated in vacuo. The residue was purified by column chromatography on silica gel to afford corresponding product **2**.

General Procedure for the Au^I-Catalyzed Intramolecular Cyclization of 2-Alkenylbenzaldehydes 3 and 2-Alkenylaryl Ketones 5 & 7: To a solution of 2-alkenylbenzaldehydes **3** or 2-alkenylaryl ketones **5** and

7 in $ClCH_2CH_2Cl$ (0.025 M) in a pressure tube was added AuCl (5 mol-%), $P(C_6F_5)_3$ (5 mol-%) (or 5 mol-% Ph_3PAuCl), and AgOTf (5 mol-%). The resulting mixture was stirred at the reported temperature for the reported time. After the reaction was complete, the reaction mixture was poured into sat. NH_4Cl, and then the product was extracted with CH_2Cl_2 (3×), dried with $MgSO_4$, and concentrated in vacuo. The residue was purified by column chromatography on silica gel to afford corresponding product **4**, **6**, or **8**.

Supporting Information (see footnote on the first page of this article): Full experimental details and characterization data.

Acknowledgments

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[14] In the case of highly electron-rich substrates **1**, **3**, and **5** (R^1 = R^2 = OMe for **1** and **3**; R^1 = OMe, R^2 = H for **1** and **5**), serious decomposition occurred under all conditions examined,

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