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Gold(I)-Catalyzed Diastereo- and Enantioselective 1,3-Dipolar Cycloaddition and Mannich Reactions of Azlactones

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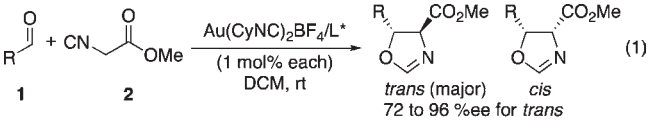
Supporting Information

ABSTRACT: Azlactones participate in stereoselective reactions with electron-deficient alkenes and *N*-sulfonyl aldimines to give products of 1,3-dipolar cycloaddition and Mannich addition reactions, respectively. Both of these reactions proceed with good to excellent diastereo- and enantioselectivity using a single class of gold catalysts, namely C_2-symmetric bis(phosphinegold(I) carboxylate) complexes. The development of the azlactone Mannich reaction to provide fully protected anti-α,β-diamino acid derivatives is described. 1,3-Dipolar cycloaddition reactions of several acyclic 1,2-disubstituted alkenes and the chemistry of the resultant cycloadducts are examined to probe the stereochemical course of this reaction. Reaction kinetics and tandem mass spectrometry studies of both the cycloaddition and Mannich reactions are reported. These studies support a mechanism in which the gold complexes catalyze addition reactions through nucleophile activation rather than the more typical activation of the electrophilic reaction component.

1. INTRODUCTION

In their seminal contribution to enantioselective Lewis acid catalysis, Hayashi and Ito reported an aldol-type reaction between aldehydes **1** and isocyanate **2** using a bifunctional catalyst containing both a phosphinegold(I) moiety and an amine (eq 1).[1] The authors proposed transition state **A**, wherein both the electrophile and nucleophile simultaneously interact with the catalyst. This early precedent not withstanding activation of nucleophilic species is not commonly invoked in gold catalysis. The majority of recent developments in homogeneous gold catalysis involve reactions which are proposed to be initiated by coordination of a cationic gold species with C−C π-bonds to form an activated electrophile.[2,3] Therefore the utility of gold complexes would be significantly extended if they could be employed as catalysts for transformations that are not predicated on π-bond activation.



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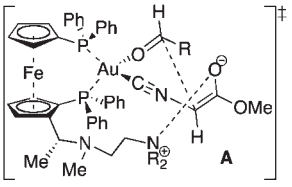
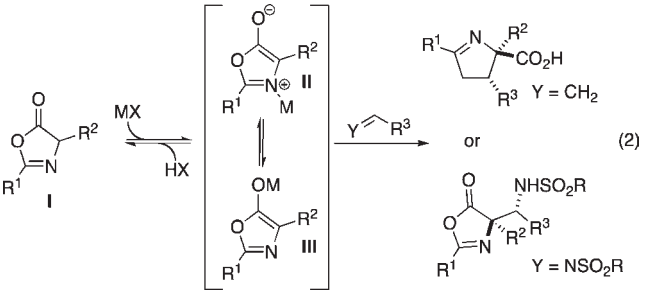
1 **2**



We recently developed chiral bis(phosphinegold(I) carboxylate) complexes as catalysts for the intramolecular hydroamination of allenes; exploiting the soft, carbophilic nature of cationic gold(I) as a means of effecting π-bond electrophile activation.[4] These carboxylate complexes are reminiscent of the catalyst used by Hayashi and Ito in that both types of catalyst combine a phosphinegold(I) moiety with a weak organic base. Thus we were interested to explore whether phosphinegold(I) carboxylate could be employed as catalysts for generating nucleophilic reactive intermediates similar to those proposed by Hayashi and Ito.

In this context, we were attracted to the potential of our gold carboxylate complexes to activate azlactones as nucleophiles. Azlactones participate in a wide variety of transformations allowing ready access not only to structurally complex amino acid derivatives but also to highly substituted heterocycles.[5] Recent efforts have focused on the use of azlactones as substrates in catalytic, often stereoselective, reactions.[6] Reactive intermediates derived from azlactones have recently been employed as nucleophiles in a number of transformations including Pd-catalyzed arylation[7a] and allylation[7c−j] and organocatalytic conjugate addition[6b−d,f,l,k] and Mannich reactions.[8]



(2)

Additionally, Tepe reported the silver(I) acetate-catalyzed reaction of azlactones with electron-deficient alkenes to afford Δ^1-pyrrolines and proposed the reaction to be a [3 + 2] dipolar cycloaddition proceeding via a metalated münchnone intermediate (eq 2).[9] We viewed this as an attractive opportunity to test our hypothesis that gold carboxylates could activate azlactones as nucleophiles that would participate in enantioselective addition

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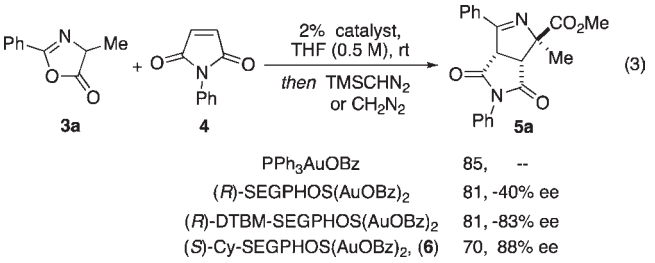
reactions. Herein we provide a full account of our studies that resulted in the development of gold-catalyzed enantioselective [3 + 2] dipolar cycloaddition[10] and Mannich reactions of azlactones. Furthermore, we also demonstrate kinetic, labeling and electrospray ionization mass spectrometry (ESI-MS) experiments concerning the reaction mechanisms of both the gold-catalyzed Mannich and 1,3-dipolar cycloaddition reactions.

2. RESULTS AND DISCUSSION

2.1. Development of the Enantioselective Dipolar Cycloaddition Reaction (DCR) of Azlactones with Electron-Deficient Alkenes. We initially explored the triphenylphosphinegold(I) benzoate-catalyzed cycloaddition of azlactone **3a** with maleimide **4** and were pleased to find that cycloadduct **5a** was formed in 86% yield after only 0.5 h (eq 3). Optimization of the enantioselective reaction revealed two major factors impacting the enantioselectivity. First, the use of phosphine ligands substituted with sterically bulky groups was essential to obtaining high enantioselectivities.[11] The improvement from 40% to 83% ee, when the parent (*R*)-SEGPHOS(AuOBz)$_2$ and was replaced with (*R*)-DTBM-SEGPHOS(AuOBz)$_2$ as a catalyst, is illustrative (eq 3). Ultimately, (*S*)-Cy-SEGPHOS(AuOBz)$_2$, (*S*)-(**6**), proved to be the most general catalyst for the enantioselective cycloaddition.

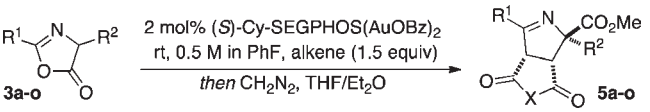


(3)

A second notable improvement was achieved by changing the solvent from THF to fluorobenzene. In this solvent, (*S*)-(**6**) catalyzed the formation of **5a** in 95% ee (Table 1, entry 1). The scope of the gold(I)-catalyzed enantioselective 1,3-dipolar cycloaddition reaction of azlactones with electron-deficient alkenes is summarized in Tables 1 and 2 in order to facilitate the overall discussion.

The reaction shows excellent scope in terms of the azlactone substituents (Table 1) and the alkene dipolarophile (Table 2). In one case where the standard conditions did not afford the cycloadduct with the desired enantioselectivity, we found that the selectivity could be improved by either using DTBM-SEGPHOS(AuOBz)$_2$ as a catalyst (Table 1, entries 7 vs 8). Additionally, while sterically demanding azlactone substituents resulted in notably decreased reaction rates in fluorobenzene, running the reaction in a 3:1 mixture of fluorobenzene:THF restored the reaction rate without significant impact on the enantioselectivity. The exception was the dialkylsubstituted substituted substrate, 2,4-dimethyloxazolin-5-one (**3o**), which underwent the desired cycloaddition with *N*-phenylmaleimide (**4**) under the standard conditions with poor enantioselectivity (Table 1, entry 16). Subsequently, we found that the selectivity of this reaction could be significantly improved by lowering the reaction temperature. We obtained cycloadduct **5o** in 64% ee by carrying out the reaction at 0 °C and in 78% ee at −20 °C (Table 1, entries 17 and 18). The scope of the reaction was successfully extended to include acrylate esters and acrylonitrile under very similar conditions; catalyst (*S*)-**6** enabled the formation of cycloadducts **8a**−**e** with generally high levels of regio-, diastereo-, and enantioselectivity (Table 2).

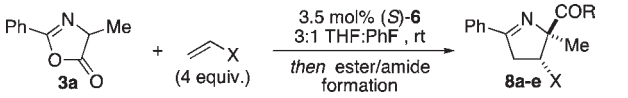
Table 1. Enantioselective Gold(I)-Catalyzed 1,3-DCR of Azlactones with Maleimides/Maleic Anhydride



entry	product	R^1	R^2	X	time (h)	yield (%)[a]	ee (%)[b]
1	**5a**	Ph	Me	NPh	2	76	95
2	**5b**	*p*-$O_2NC_6H_4$	Me		1.5	98	95
3	**5c**	*p*-BrC_6H_4	Me		15	75	93
4	**5d**	*p*-ClC_6H_4	Me		15	72	92
5	**5e**	*p*-$MeOC_6H_4$	Me		18	65	95
6	**5f**	*o*-MeC_6H_4	Me		4	73	86[c]
7	**5h**	Ph	H		24	41	81
8	**5h**	Ph	H		24	84	-98[d]
9	**5i**	Ph	Bn		36	71	68[c]
10	**5j**	Ph	allyl		8	86	87[c]
11	**5k**	Ph	Ph		1.5	41	51[e]
12	**5k**	Ph	Ph		1.5	81	78[f]
13	**5l**	Ph	Me	O	12	79	87[g]
14	**5m**	Ph	Me	NMe	24	89	-96[h]
15	**5n**	Ph	Me	NEt	24	92	-98[h]
16	**5o**	Me	Me	NPh	1.5	85	39
17	**5o**	Me	Me		1.5	81	64[f]
18	**5o**	Me	Me		3.5	65	-78[i]

[a] Isolated yield unless otherwise noted. [b] Determined by enantiodiscriminating HPLC. [c] Run at 0.5 M in 3/1 PhF/THF. [d] Run at 0.5 M in acetone, using (*R*)-DTBM-SEGPHOS(AuOBz)$_2$. [e] Run at 0.25 M in 3/1 PhF/THF at rt, with 5 mol % (*S*)-**6**. [f] Run at 0.25 M in 3/1 PhF/THF, at 0 °C with 5 mol % (*S*)-**6**. [g] Run at 0.04 M in PhF, yield by ^{1}H NMR against internal standard. [h] Using (*R*)-**6**. [i] Run at 0.25 M in 3/1 PhF/THF at −20 °C using (*R*)-**6**.

Table 2. Enantioselective Gold(I)-Catalyzed Reactions of Azlactones and Monosubstituted Alkenes[a]



entry	product		time (h)	yield (%)[b]	ee (%)
1	**8a**, X = $CO_2{}^tBu$	R = OMe	24	56	99[c]
2	**8b**, X = $CO_2{}^tBu$	R = $NHCH_2Ph$	14	74	95
3	**8c**, X = CO_2Et	R = OMe	14	66	90
4	**8d**, X = CO_2Me	R = OMe	14	89[d]	93
5	**8e**, X = CN	R = $NHCH_2Ph$	14	68	76

[a] Reactions run at 0.5 M in **3a**. [b] Isolated yield unless otherwise noted. [c] Ten equiv. of *tert*-butyl acrylate used. [d] Yield determined by ^{1}H NMR analysis of crude product against an internal standard.

Since 2003, a variety of catalytic systems have been described for the enantioselective synthesis of substituted pyrrolidines through the 1,3-dipolar cycloaddition of acyclic α-iminoesters; generally these methods provide *endo*-cycloadducts.[12,13] In contrast, the cycloaddition of azlactone derived dipoles gives rise to Δ^1-pyrrolines and therefore offer the potential for manipulation of the endocyclic imine.[14] For example, palladium-catalyzed hydrogenation of the imine gave pyrrolidine *exo*-**9** (eq 4).

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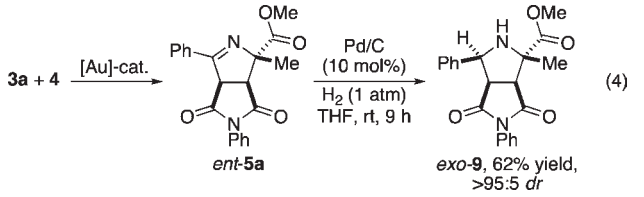
This is complementary to the result generally obtained from the acyclic dipole precursor.



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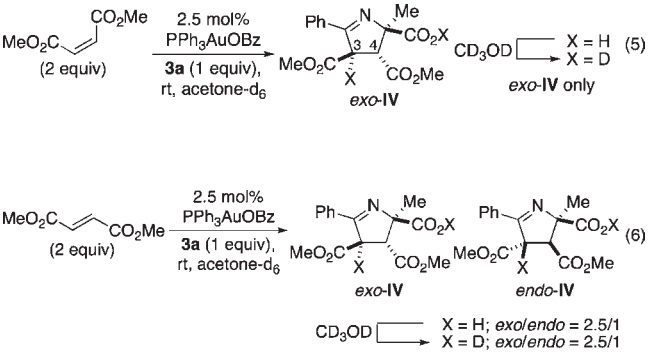
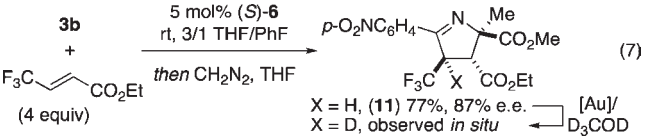
2.3. Stereospecificity of the Gold(I)-Catalyzed Cycloaddition Reaction. In the context of cycloaddition chemistry, the stereospecific conversion of alkene geometry to central chirality is commonly taken as an indication of a concerted reaction mechanism, while a nonstereospecific conversion is regarded as evidence of a stepwise mechanism. Indeed, the initial impetus for extending the scope of the gold(I)-catalyzed 1,3-DCR to acyclic 1,2-disubstituted alkenes was to assess whether the reaction is stereospecific. To this end, reaction of **3a** with dimethyl maleate, catalyzed by $Ph_3PAuOBz$ and monitored by ^1H NMR, gave rise to a single cycloadduct (*exo*-**IV**) (eq 5). In contrast, the reaction of **3a** with dimethyl fumarate, similarly monitored, gave rise a 2.5:1 mixture of *exo*- and *endo*-**IV** (eq 6).[15] In order to assess whether the *trans*-relationship of the diesters arose from a nonconcerted cycloaddition or a postcycloaddition epimerization, excess methanol-d_4 was added to the reaction mixture after the gold-catalyzed reaction was complete. This addition led to the rapid and nearly complete disappearance of the diagnostic doublets due to the C3 methine proton; therefore, the stereochemical course of these reactions could not be ascertained.

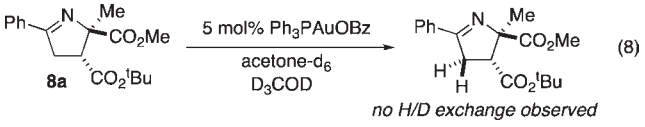


Initial attempts at derivatization and isolation of the products of these reactions were complicated by the presence excess maleate and fumarate esters as well as the presence of byproduct from the cycloaddition and (primarily) derivatization reactions. The initial cycloadducts are carboxylic acids; a fact we sought to exploit in developing a protocol for product isolation. This lead to the serendipitous discovery that treatment of the crude product obtained from reaction of **3a** and dimethyl maleate with 10% aqueous K_2CO_3 followed by reacidification, extraction into organic medium, and finally by esterification with diazomethane afforded compound *rac*-**8d**. This compound had been previously established as the product obtained from the gold(I)-catalyzed reaction of **3a** and methyl acrylate followed by treatment with diazomethane (Table 2, entry 4). The ester hydrolysis/decarboxylation sequence is consistent with the facile nature of the H/D exchange discussed above; however, an attempt to exploit the carbon acid nature of this system via alkylation (NaH/THF, followed by addition of allyl bromide) did not proceed smoothly.

When dimethyl fumarate was reacted with **3a** and subjected to the same sequence described above, diastereomers **8d** (major) and *epi*-**8d** (minor) were obtained as an inseparable mixture. The fumarate and maleate diesters were (separately) reacted with **3a** under our standard conditions developed for enantioselective reactions of acrylate esters. The crude products were then subjected to the ester hydrolysis/decarboxylation sequence and finally esterification (or amidation) to allow assessment of the enantioselectivity of these reactions (Table 3). The products were obtained with good enantioselectivity, but the *endo*-/*exo*-diastereoselectivity of the reaction with the fumarate ester was essentially unchanged as compared to that observed with the achiral catalyst.

In order to avoid the complication of potential C3 epimerization, we sought to use alkenes would not produce cycloadducts with a C3 ester group; however, attempts to react **3a** with *cis*- and (separately) *trans*-ethyl crotonate esters suffered from attenuated reactivity and eventually complex mixtures resulting from decomposition. While reaction of the *p*-nitrophenyl substituted azlactone (**3b**) with ethyl 4,4,4-trifluoro-2-butenoate afforded **11** in good yield and stereoselectivity, H/D exchange at the indicated position was readily observed upon subjection of **11** to methanol-d_4 and the achiral catalyst in acetone-d_6 (eq 7).





Ultimately, we decided to evaluate the possibility that appropriately deuterated acrylate ester would allow the desired investigation to proceed. Indeed, we noted that no H/D exchange was observed when **8a** (derived from **3a** and *tert*-butyl acrylate) was treated with catalytic $Ph_3PAuOBz$ and methanol-d_4 (eq 8). Thus, acrylate **12** and its *trans*-monodeutero analogue (*trans*-**12-d$_1$**) were prepared (see Supporting Information for preparation of these materials). Monitoring the reaction of **3a** with alkene **12** by ^1H NMR spectroscopy showed the formation of a single cycloadduct exhibiting two well-resolved signals (δ = 3.52 ppm: dd, J^2 = 17.5 J^3 = 8.0 Hz, 1H) and (δ = 3.46 ppm: dd, J^2 = 17.5, J^3 = 8.5 Hz, 1H) due to the C3 methylene group (eq 9). This compound was isolated and characterized as the *N*,*N*-dimethyl amide. The reaction of **3a** and *trans*-**12-d$_1$**, similarly monitored, indicated the formation of a single cycloadduct with deuterium substitution at only one position (eq 9). Specifically only a simple doublet was observed in this region of the spectrum (δ = 3.50 ppm: d, J = 7.5 Hz, 1H). With the alkene as the limiting reactant,

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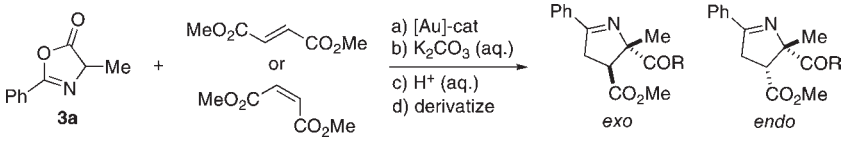
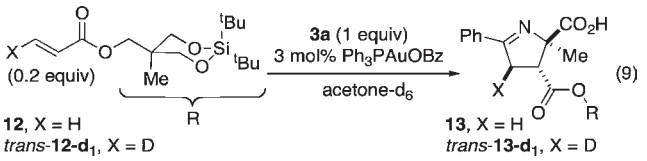
Table 3. Gold(I)-Catalyzed DCR/Hydrolysis/Decarboxylation Sequence



entry	alkene (equiv)	solvent	catalyst	product[a] (*exo*/*endo*)	d.r. (*exo*/*endo*)	yield (%)	e.e. (*exo*/*endo*)
1	maleate (2)	acetone-d_6	2.5 mol% PPh_3AuOBz	**8d** only	n.a.	69	n.a.
2	maleate (4)	3/1 PhF/THF	3.5 mol% (*R*)-**6**	**8d** only	n.a.	55	82/n.a.
3	fumarate (2)	acetone-d_6	2.5 mol% PPh_3AuOBz	**8d**/*epi*-**8d**	3:1[b]	59	n.a.
4	fumarate (2)	acetone-d_6	2.5 mol% PPh_3AuOBz	**10d**/*epi*-**10d**	2:1[c]	63	n.a.
5	fumarate (4)	3/1 PhF/THF	3.5 mol% (*R*)-**6**	**10d**/*epi*-**10d**	2:1[c]	60	94/84

[a] **8d**/*epi*-**8d** *R* = OMe; **10d**/*epi*-**10d** *R* = *p*-$O_2NC_6H_4CH_2NH$. [b] Isolated d.r., inseparable diastereomers. [c] Isolated d.r., all four stereolsomers separated by analytical enantiodiscriminating HPLC.

the cycloaddition reaction was complete before any significant H/D exchange was observed.



(9)

Thus it was determined that the gold(I)-catalyzed reaction of **3a** with an acrylate ester is stereospecific; this observation is most consistent with a concerted process. In all cases, the gold(I)-catalyzed 1,3-DCR of azlactones with monosubstituted alkenes has proceeded with excellent regioselectivity. Moreover that selectivity serves to form a bond between what had been C4 of the azlactone and the α-position of the α,*β*-unsaturated ester (or nitrile); that is to say the observed regioselectivity is exactly opposite that which might reasonably be expected from a stepwise process. This same regioselectivity was also observed in the reaction of **3b** with a nonsymmetric 1,2-disubstituted alkene (eq 7). Taken together with the stereospecific nature of the reaction, these observations on regioselectivity are also suggestive of a concerted process.[16]

2.3. Development of the Enantioselective Mannich Reaction of Azlactones with *N*-Sulfonyl Aldimines. Investigation into the mechanism of the gold(I)-catalyzed 1,3-DCR suggested that the reaction proceeds via a concerted process. In the context of a normal electron demand cycloaddition, an intermediate such as **II** or **III** (eq 2) could be considered as the nucleophilic component. However we sought to develop a reaction, predicated on gold(I)-activation of the nucleophile, which could be more clearly viewed as proceeding through a traditional nucleophile/electrophile pair of reactants. We thus posited that such bis(phosphinegold(I) carboxylate) complexes might be competent catalysts for stereoselective reactions of azlactones with electrophiles other than electron-deficient alkenes, such as imines and/or aldehydes.

In contrast to the high enantioselectivities obtained in the Hayashi–Ito aldol reaction,[1] the sole previous report of gold(I)-catalyzed reaction of isocyantes **2** with imines was not enantioselective.[17,18] Moreover, Ooi[8a] and Wang[8b] have recently reported organocatalytic approaches to the enantioselective azlactone Mannich reaction; however, both examples demonstrated high levels of stereoselectivity, providing the *syn*-Mannich addition products with good ee, but each method was limited to a single class of imines derived from either aliphatic[8a] or aromatic[8b] aldehydes, respectively. Thus, the development of a general, functional group tolerant method for the enantioselective (and *anti*-diastereoselective) Mannich reaction of azlactones would complement these organocatalytic methods and extend the realm of gold-catalyzed addition reactions beyond the aldol reaction.

Toward this goal, we examined a variety of dinuclear gold(I) benzoate catalysts for the Mannich reaction. Under our previously developed reaction conditions (fluorobenzene, rt), the (SEGPHOS)gold(I)-catalyzed reaction of azlactone **3a** and *N*-sulfonylimine **14a** provided the desired product in excellent diastereoselectivity but modest enantioselectivity (Table 4, entry 1). The use of SEGPHOS ligands with bulky aryl groups at phosphorus afforded **15a** with a modest improvement in the enantioselectivity (entries 2, 3). On the other hand, changing the phosphine group from aryl to cyclohexyl provided a substantial increase in enantioselectivity (entries 4, 5). The most notable increases in enantioselectivity occurred when the ligand class was changed from the biaryl to spirocyclic (entries 6 – 8). For example, (*R*)-xylyl-SDP$(AuOBz)_2$, (*R*)-**16**,[19] (see Figure 1 for X-ray structure of the corresponding dichloride) catalyzed the formation of **15a** with 89% ee at room temperature. Finally, a bulkier group on the imine enabled the highest level of both enantio- and diastereocontrol (entries 9 and 10). Further optimization of the reaction conditions revealed that use of fluorobenzene as solvent was essential to obtaining the Mannich adducts with high diastereo- and enantioselectivity.[20]

Having determined reaction conditions for the highly selective formation of **15b**, we conducted experiments to explore the scope of the gold(I)-catalyzed enantioselective Mannich reaction of azlactones with aldimines (Table 5). Addition to both aromatic and aliphatic imines was achieved with our optimized catalyst system to give the Mannich products in good yield and selectivities. Notably, both electron-poor and electron-rich aromatic imines, including the furyl-substituted imine (entry 4), were well tolerated in the reaction. Additionally, both acyclic and cyclic aliphatic imines were competent electrophiles and

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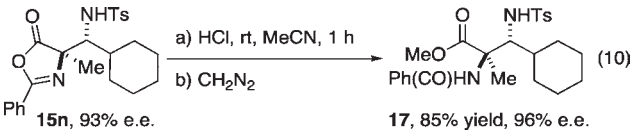
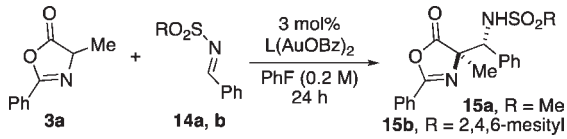
provided the desired products in excellent diastereoselectivity. For example, the imine derived from 3-benzyloxypropanal afforded **15l** in 96% yield and >20:1 dr (94% ee of the major diastereomer, entry 11). Furthermore, both electron-poor and electron-rich azlactones could be used (entries 6−8).

To the best of our knowledge this constitutes the first reported enantioselective Mannich reaction catalyzed by gold. The Mannich adducts were obtained in high diastereo- and enantioselectivities with up to >20:1 dr and 94% ee. Notably, the gold-catalyzed reaction provides the *anti*-diastereomer as the major product, in contrast to previously reported methods which are highly *syn*-selective.[8a,8b] Moreover, ring opening of an initial Mannich addition product under the action of mineral acid, followed by esterification with diazomethane provided the fully and differentially protected α,β-diamino acid[22] methyl ester (**17**) without loss of enantioenrichment of the material (eq 10).



Up to this point the gold-catalyzed Mannich reaction has been optimized for alanine derived azlactones and the reactivity of substrates bearing larger substituents at C4 is attenuated, particularly at low temperature. However, appreciable levels of selectivity may be achieved at room temperature. For example, allyl substituted substrate **3j** was reacted with imine **14b** to afford addition product **15o** with 80% ee and 6.7:1 d.r. using catalyst (*R*)-**6**, albeit in modest yield (Table 6, entry 3). Using the more reactive *p*-nosyl imine and THF as cosolvent, the corresponding products (**15p**/**15p**′) were obtained in excellent yield but with poor diastereoselectivity (entry 5). The results in Table 6, which show the variation of selectivity with respect to reaction conditions including ligand structure, suggest the reaction could be optimized for other substrates.

Table 4. Optimization of Reaction Conditions for the Enantioselective Mannich Reaction



entry	ligand	R	(°C)	yield[a] (%)	d.r.[b] (*anti*/*syn*)	ee[c] (%)
1	(*R*)-SEGPHOS	Me	rt	64	>20:1	40
2	(*R*)-DM-SEGPHOS	Me	rt	61	14:1	−42
3	(*R*)-DTBM-SEGPHOS	Me	rt	20	4.3:1	−57
4	(*S*)-Cy-SEGPHOS	Me	rt	51	4.6:1	−82
5	(*S*)-Cy-SEGPHOS	Me	−10	43	3.8:1	−82
6	(*R*)-xylyl-SDP, (*R*)-**16**	Me	rt	62	4.6:1	89
7	(*R*)-**16**	Me	5	52	3.5:1	88
8	(*R*)-**16**	Me	−10	42	3.8:1	90
9	(*R*)-**16**	Mes	rt	61	4.0:1	90
10	(*R*)-**16**	Mes	−20	76[d]	6.6:1	94

[a] Isolated yield. [b] Determined by ^{1}H NMR analysis of crude reaction mixture. [c] Determined by enantiodiscriminating HPLC. [d] Used 5 mol % of (*R*)-**16**.

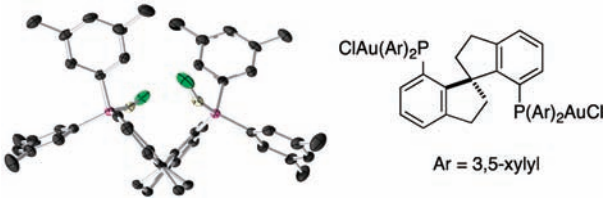
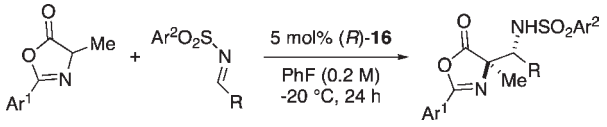


Figure 1. Solid-state structure of (*R*)-xylyl-SDP(AuCl)$_2$ (50% probability ellipsoids). Hydrogen atoms omitted for clarity.[21]

Table 5. Enantioselective Gold(I)-Catalyzed Azlactone Mannich Reaction[a]



entry	product	Ar^1	Ar^2	R	yield[b] (%)	d.r.[c] (*anti*/*syn*)	ee[d] (%)
1	**15b**	Ph	Mes	Ph	76	6.6:1	94
2	**15c**	Ph	Mes	*p*-ClC_6H_4	70	6.9:1	86
3	**15d**	Ph	Mes	*p*-$MeOC_6H_4$	58	6.9:1	82
4	**15e**	Ph	Mes	3-furyl	50[e]	6:1	92
5	**15f**	Ph	*p*-Tol	Me	91	17.2:1	94
6	**15g**	*p*-$MeOC_6H_4$	p-Tol	Me	98	>20:1	93
7	**15h**	*p*-BrC_6H_4	*p*-Tol	Me	89	>20:1	87
8	**15i**	*p*-$O_2NC_6H_4$	*p*-Tol	Me	96	>20:1	83
9	**15j**	Ph	*p*-Tol	pent-1-en-5-yl	87	11:1	92
10	**15k**	Ph	*p*-Tol	$PhCH_2CH_2$	88	8:1	93
11	**15l**	Ph	*p*-Tol	$BnOCH_2CH_2$	96	>20:1	94
12	**15m**	Ph	*p*-Tol	^{i}Pr	69[f]	>20:1	91
13	**15n**	Ph	*p*-Tol	cyclohexyl	73	>20:1	93

[a] Reactions carried out on 0.15 mmol scale, 1.05 equiv of aromatic imine or 1.2 equiv of aliphatic imine; Mes = 2,4,6-mesityl. [b] Isolated yield. [c] Determined by ^{1}H NMR analysis of crude product mixtures. [d] Determined for major diastereomer by enantiodiscriminating HPLC, absolute stereochemistry of **15b** and **15f** were established by X-ray crystallography, and other products assigned by analogy. [e] Reaction run in 3/2 PhF/$CHCl_3$ at 0.2 M in azlactone. [f] Reaction run at rt.

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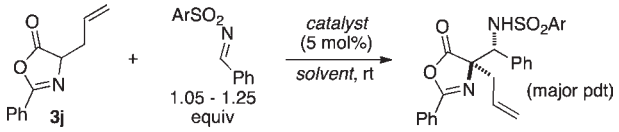
Table 6. Gold-Catalyzed Mannich Reactions of Azlactone 3j[a]



entry	catalyst	solvent	product (*anti*/*syn*)	Ar	yield (%)	d.r.[b] (*anti*/*syn*)	ee[c] (%)
1	PPh_3AuOBz[d]	THF	**15o**/**15o′**	Mes	70/23	2.9:1	−/−
2	(*R*)-**16**[d]	PhF	**15o**[e]	Mes	49	4:1	30
3	(*R*)-**6**	PhF	**15o**[e]	Mes	41	6.7:1	−80
4	PPh_3AuOBz	THF	**15p**/**15p′**	*p*-$NO_2C_6H_4$-	83[f]	5:1	−/−
5	(*R*)-**6**	PhF/THF 3/1	**15p**/**15p′**	*p*-$NO_2C_6H_4$-	97[f]	1.7:1	−72/−15

[a] Reactions carried out on 0.1 mmol scale; Mes = 2,4,6-mesityl. [b] Determined by ^{1}H NMR analysis of crude product mixture. [c] Determined by enantiodiscriminating HPLC. [d] Using 3 mol % catalyst. [e] Only the major diastereomer was isolated. [f] Mixture of diastereomers.

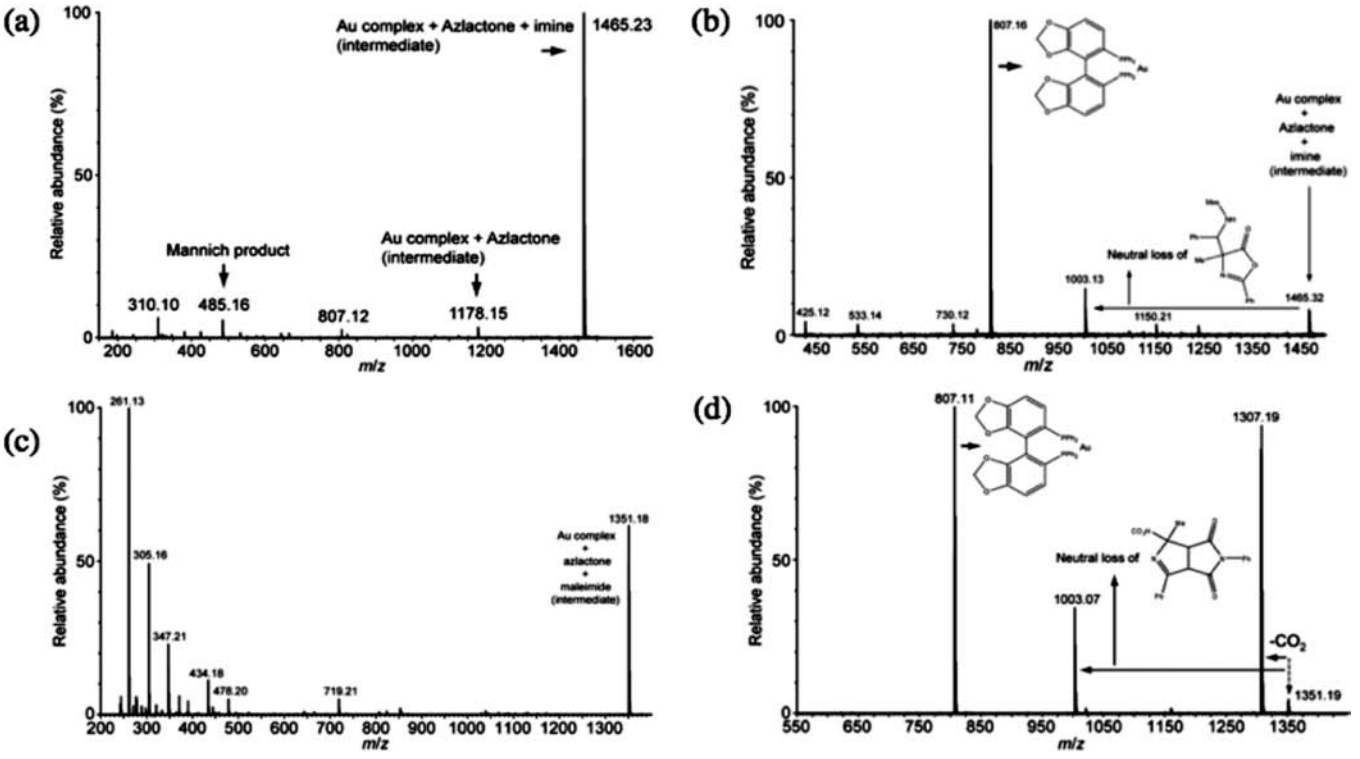


Figure 2. (a) ESI-MS spectrum of the Mannich reaction of azlactone **3a** with imine **14b** catalyzed by (*R*)-SEGPHOS$(AuOBz)_2$ at t = 10 min. (b) MS/MS spectrum resulting from collisionally activated dissociation (CAD) of the singly charged positive ion at m/z = 1465. (c) ESI-MS spectrum of the 1,3-DCR of azlactone **3a** with maleimide **4** catalyzed by (*R*)-SEGPHOS$(AuOBz)_2$ at time = 40 min. (d) MS/MS spectrum resulting from collisionally activated dissociation (CAD) of the singly charged positive ion at m/z = 1351.

2.4. Tandem MS Studies. We sought to gain further insight into the reaction mechanisms of both the gold-catalyzed 1,3-DCR and Mannich reaction and to obtain experimental data that would allow some measure of direct comparison to be drawn between the two reactions. To this end, we investigated the kinetic behavior of both reactions as well as subjecting both types of reaction mixture to analysis by ESI-MS(/MS). Tandem mass spectrometry experiments have previously been used to determine the nature of reaction intermediates, and we hypothesized such an experiment would shed some light on the identity of relevant gold-containing species in solution.[23]

We began our mechanistic investigations by studying the gold-catalyzed Mannich reaction. When the reaction of **3a** with **14b** catalyzed by (*R*)-SEGPHOS$(AuOBz)_2$ was monitored by ESI-MS, after 10 min we were able to detect two ions, each corresponding to a critical intermediate (Figure 2a): a signal at m/z 1178.2, which we attribute to the cationic azlactone-gold(I) complex, and a second signal at m/z 1465.2, consistent with the cationic intermediate azlactone-gold(I)-imine complex. No signal corresponding to a gold(I)-imine complex was observed. Both species were characterized by tandem mass spectrometry experiments. The ESI-MS(/MS) spectrum of

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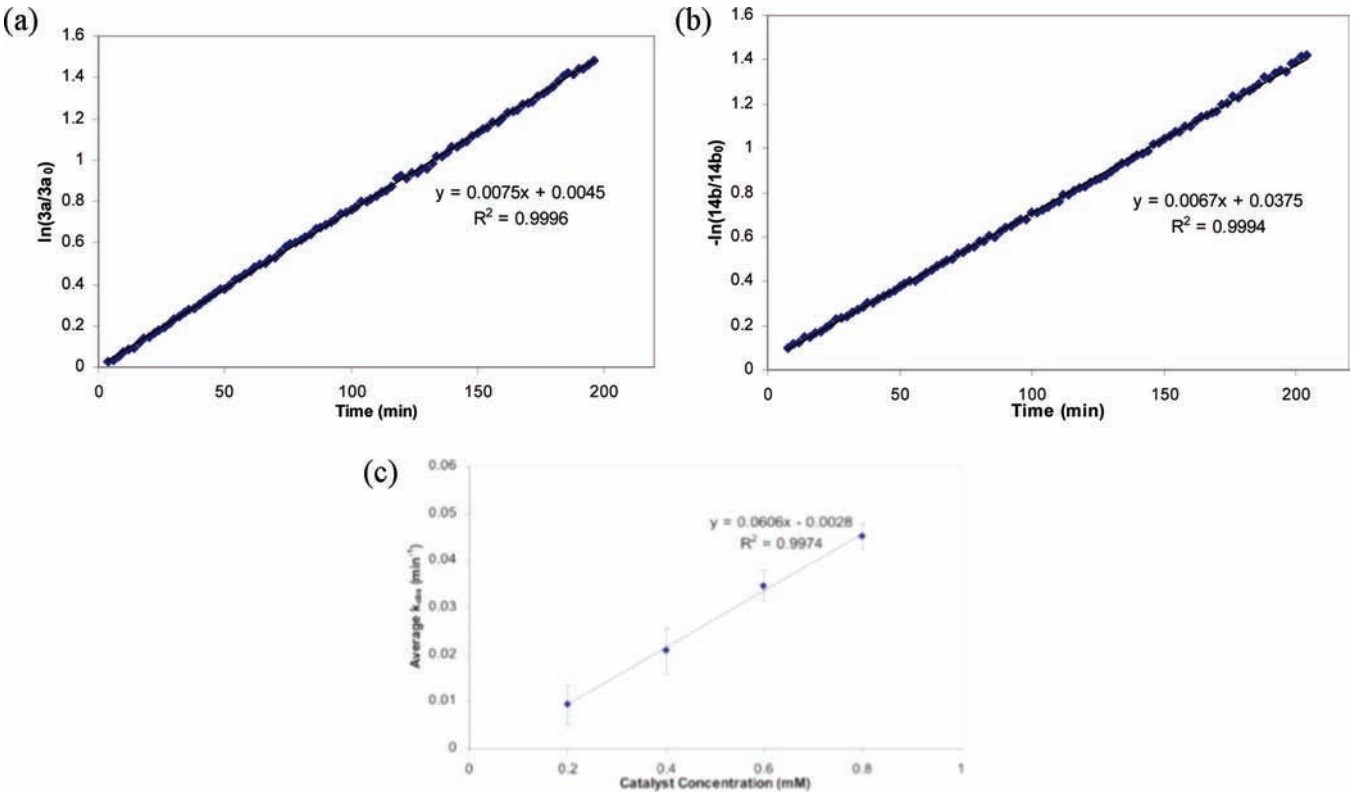
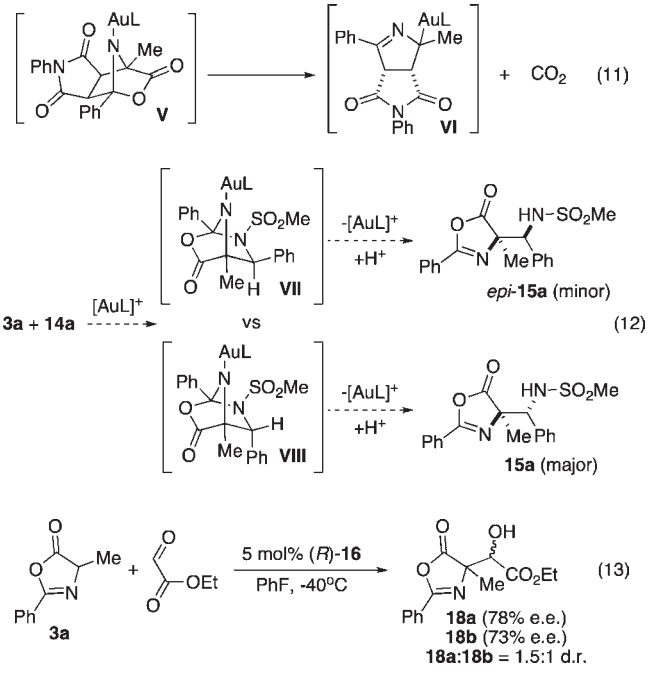


Figure 3. Kinetic data for (*R*)-SEGPHOS(AuOBz)$_2$-catalyzed reaction of **3a** with imine **14b** to form **15b**. (a) Pseudofirst-order kinetics in azlactone **3a** (33.3 nM) was observed when a large excess (10 equiv) of imine **14b** (335 nM) was used. (b) Pseudofirst-order behavior in imine **14b** (28.5 nM) was observed when a large excess (10 equiv) of azlactone (290 nM) was used. (c) Average measured k_{obs} at various (*R*)-SEGPHOS(AuOBz)$_2$ concentrations (0.33−1.33 nM) for the reaction of **3a** (33.3 nM) with **14b** (267 nM).

the ion of *m*/*z* 1465.2 showed predominantly neutral loss of the Mannich product (Figure 2b). These data are consistent with a nucleophile-activation mechanism where the gold is coordinated to the azlactone.

When the same studies were performed for the cycloaddition reaction between **3a** and *N*-phenylmaleimide (**4**), after 40 min we were able to intercept one ion corresponding to the cationic azlactone-gold(I)-maleimide intermediate at *m*/*z* 1351.2 (Figure 2c). The ESI-MS(/MS) data for this reaction mixture showed that loss of neutral CO_2 was the primary mode of fragmentation for this intermediate. This observation supports the notion of initial formation of a bridged, bicyclic cycloadduct followed by extrusion of CO_2 (Figure 2d and eq 11).[24,25]

A cycloaddition/fragmentation mechanism could also be operative for the Mannich reaction; however, we did not observe any signals suggesting loss of CO_2 when analyzing these reaction mixtures by ESI-MS(/MS). Analogous intermediates, along this pathway from which fragmentation or expulsion of CO_2 might occur, appear unlikely to produce the observed stereochemical outcome (cf. eqs 11 and 12). While **VII** presumably suffers less severe nonbonding steric interaction between the methyl and phenyl groups as compared to **VIII**, it is **VIII** that would lead to the (experimentally observed) predominant diastereomer **15a**. Additionally in the gold(I)-catalyzed aldol reaction of **3a** with ethyl glyoxalate, fragmentation of an initial cycloadduct would likely favor formation of an oxazoline, but this was not observed; instead the reaction afforded the highly substituted azlactone diastereomers **18a** and **18b** (eq 13).[26] Reasoning along these lines there is not a compelling case for such a cycloaddition/fragmentation mechanism for the Mannich reaction.[27]



2.5. Kinetic Studies. Kinetic studies performed on the Mannich reaction showed that the reaction exhibited a first-order dependence on azlactone, imine, and gold(I). Standard solutions of

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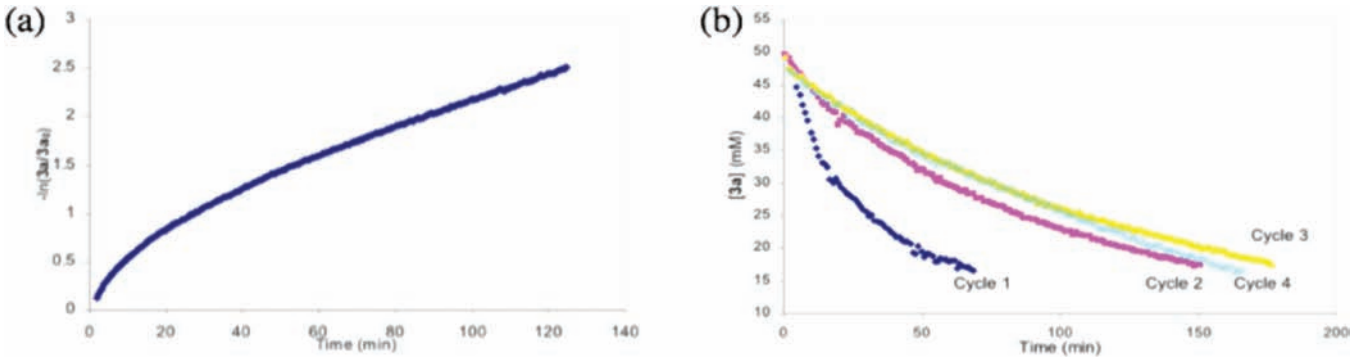


Figure 4. Kinetic data for the $Ph_3PAuOBz$-catalyzed 1,3-DCR of **3a** and **4** (a) A plot of $-\ln(\mathbf{3a}/\mathbf{3a}_0)$ vs time in the 1,3-DCR of **3a** (47.6 nmM) and **4** (476 nM) is nonlinear. (b) Overlays of kinetic data for consecutive additions of azlactone **3a** (50.0 nM x 3) to solution of **4** (523 nM) catalyzed and $Ph_3PAuOBz$ (0.57 nM). Time $t = 0$ corresponds to the beginning of each cycle, and the left axis represents the concentration of **3a** at the beginning of each cycle.

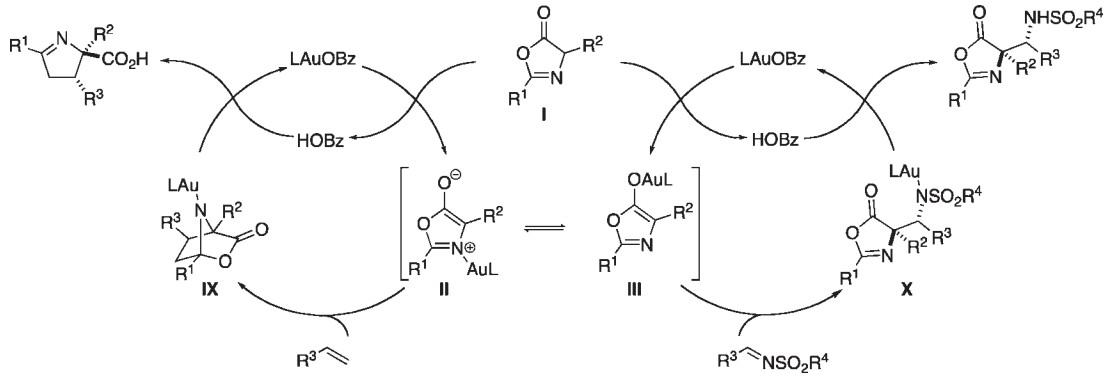


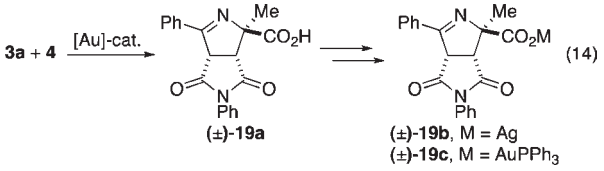
Figure 5. Mechanistic proposals for gold(I)-catalyzed 1,3-DCR and Mannich reactions.

azlactone **3a**, *N*-(mesitylsulfonyl)benzaldimine (**14b**), and relevant gold catalysts were prepared individually in deuterated solvent, and 1,3,5-trimethoxybenzene was used as an internal standard.[28a] A plot of $-\ln(\mathbf{3a}/\mathbf{3a}_0)$ vs time showed that the reaction exhibited pseudo-first-order behavior in azlactone when a large excess of imine was used (Figure 3a). When an excess of azlactone was used, the reaction also showed pseudofirst-order kinetics in imine (Figure 3b).

To determine the kinetic order in gold(I), the reaction was conducted at 1−4 mol % catalyst loading, under pseudofirst-order conditions. The pseudofirst-order constants (k_{obs}) are tabulated in Table S18 (Supporting Information). A plot of the averaged k_{obs} at each catalyst loading can be subjected to a linear regression with $R^2 = 0.997$ (Figure 3c), suggesting that the reaction is first order in (*R*)-SEGPHOS(AuOBz)$_2$. Furthermore, when the same experiments are conducted with a mononuclear catalyst, $Ph_3PAuOBz$, the same first-order dependence in gold(I) catalyst is observed. These experiments suggest that only one gold center is active in the rate-limiting transition state.

Interestingly, the kinetic profiles observed for the reaction of azlactone **3a** with *N*-phenylmaleimide (**4**) were much more complicated. In particular, the logarithmic first-order plot of $-\ln(\mathbf{3a}/\mathbf{3a}_0)$ vs time under flooding conditions was nonlinear at lower conversions (Figure 4a). However, the reaction exhibited pseudofirst-order behavior in **3a** at higher conversion and longer reaction times. The same curvature was observed when we flooded in **3a** and monitored the conversion of **4** to product.[28b] Furthermore, this behavior was not sensitive to the relative order of addition of the reagents or prestirring **3a** in the presence of catalyst prior to the addition of **4**.

We hypothesized that curvature in the plot could be due to a less than first-order dependence on azlactone, catalyst deactivation, or product inhibition. Given that the product is a free carboxylic acid and the catalyst bears a carboxylate counterion, product inhibition seemed to be a likely explanation. To test for product inhibition, 0.5 equiv of product (or of AcOH) was combined with **3a**, **4**, and $Ph_3PAuOBz$ at the start of the reaction. However the kinetic profile with either additive present was effectively unchanged.[28c] Furthermore, complex (±)-**19c**, composed of $[PPh_3Au]^+$ and the conjugate base of cycloadduct (±)-**19a**, was prepared, isolated, and used to catalyze the reaction of **3a** and **4**, again the kinetic profile remained unchanged (eq 14).[28d]



To test for catalyst deactivation,[29] the reaction of **3a** and **4** was monitored, and an additional 0.67 equiv of **3a** was added each time the concentration of **3a** fell below 15.8 mM (corresponding to ~67% conversion). The reaction was "cycled" in this manner four times, and data for each cycle is presented as a set of overlaid traces (Figure 4b), where t=0 corresponds to the addition of each aliquot of starting material. The rate of the reaction in cycle 1 is clearly faster than that in cycles 2−4, supporting a process in

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which the concentration of active catalyst decreases at the beginning of the reaction but stabilizes at longer reaction times. This observation is consistent with catalyst deactivation at the early stages of the reaction and explains our earlier observations of curvature in the pseudofirst-order rate plot. In fact, a plot of $-\ln(\mathbf{3a}/\mathbf{3a_0})$ vs time generated from cycle 4, (i.e., after the concentration of catalyst has become constant), shows first-order dependence in **3a**.[28e] Because the precise concentration of active catalyst in solution cannot be determined, we were unable to perform a detailed kinetic analysis of the reaction of **3a** with **4**. However, based on the kinetic profiles of the reactions after the concentration of catalyst has stabilized, we believe that the overall reaction is positive order in both reactants.

3. CONCLUSIONS

The majority of recently reported gold-catalyzed transformations fall into the reactivity manifold in which gold serves to activate carbon−carbon π-bonds as electrophiles toward nucleophilic additions. In this report we provide evidence that phosphinegold(I)-carboxylate complexes can serve to activate pro-nucleophiles toward deprotonation by the counterion. On the basis of the data presented in the preceding sections, we propose two related catalytic cycles for the 1,3-DCR and Mannich reactions. In both cases initial activation of the azlactone as a nucleophile is followed by C−C bond forming reaction with the electrophile (Figure 5).

We have proposed a divergent set of intermediates for the 1,3-DCR (**II**/**III** → **IX**) and Mannich reactions (**II**/**III** → **X**). With electron-deficient alkenes, the activated azlactones react through a concerted 1,3-dipolar cycloaddition process.[30] In the presence of chiral biarylphosphine ligands, the chemistry provides a highly diastereo- and enantioselective entry into complex Δ^1-pyrrolines. In contrast, the gold-catalyzed reaction of azlactones with activated imines proceeds through an addition mechanism. Employing *spiro*-bisphosphines as ligands, the first gold(I)-catalyzed enantioselective Mannich reaction was developed. Thus, the bisphosphinegold(I)-catalyzed Mannich reaction provides direct access to a variety of aliphatic and aromatic α,β-diamino acid derivatives in high diastereo- and enantioselectivities. Moreover, these studies introduce *spiro*-bisphosphines[19] as an alternative class of ligands to the biaryl-derived bisphosphine[11] ligands typically applied in enantioselective catalysis with gold.[31] Further studies regarding this mode of gold(I) activation are ongoing in our laboratories and will be reported in due course.

■ ASSOCIATED CONTENT

Supporting Information. Experimental procedures, analytic and spectroscopic data for new compounds, mass spectrometric, kinetic, and X-ray crystallographic data. This material is available free of charge via the Internet at http://pubs.acs.org.

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