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Au(I)-Catalyzed Enantioselective 1,3-Dipolar Cycloadditions of Münchnones with Electron-Deficient Alkenes

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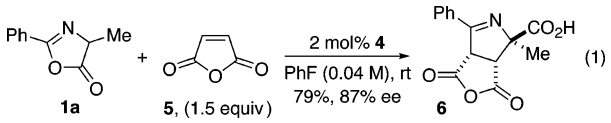
Synthetic methods relying on gold complexes as catalysts have recently been the focus of intense development.[1] Despite numerous advances, relatively few enantioselective gold-catalyzed transformations have been described. The earliest example of an enantioselective gold(I)-catalyzed transformation, the Hayashi−Ito aldol reaction, was proposed to rely on activation of the nucleophile as a chiral monophosphineAu(I) enolate.[2] In contrast, the majority of recently reported methods rely on the electrophilic nature of cationic bisphosphinegold(I) complexes to activate π-bonds toward addition of nucleophiles.[3] Therefore, the utility of chiral bisphosphinegold(I) complexes would be signficantly extended if they could be employed as catalysts for enantioselective transformations that are not predicated on π-bond activation. To this end, herein we describe the development of a bisphosphinegold(I)-catalyzed enantioselective 1,3-dipolar cycloaddition[4] reaction of mesoionic azomethine ylides (münchnones) with alkenes.

We were inspired by Tepe's recent report of silver(I)acetate-catalyzed münchnone/alkene 1,3-dipolar cycloadditions,[5,6] to consider the use of our recently developed bisphosphinegold(I) carboxylate complexes as catalysts for this transformation.[3c] Gratifyingly, treatment of a THF solution of azlactone **1a** and 1.5 equiv of *N*-phenylmaleimide (**3**) with 2 mol % triphenylphosphinegold(I) benzoate at room temperature, followed by in situ esterification, afforded the desired Δ^1-pyrroline (±)-**2a** in 85% yield with excellent diastereoselectivity (Table 1, entry 1).

Having established an achiral phosphinegold(I) benzoate as a catalyst for the formation for **2a**, we next focused on the enantioselective reaction of **1a** and **3** (Table 1). In general, the diphenyl-substituted biarylphosphinegold(I) benzoate complexes successfully employed in the hydroamination gave modest selectivity for the reaction of **1a** and **3** (entries 2−5). While substitution on the phosphine aryl ring resulted in improved selectivity (entry 8), we were pleased to find the (*S*)-Cy-SEGPHOS(AuOBz)$_2$ (**4**)[7]-catalyzed cycloaddition gave **2a** with a notable increase in enantioselectivity (88% ee) (entry 9). Further optimization of reaction conditions revealed that the reaction performed similarly in various solvents;[8] however, employing fluorobenzene (PhF) as the solvent produced a further improvement and provided **2a** in 76% yield and 95% ee (entry 10).[9] Notably, in all cases only the *exo*-adduct was observed.

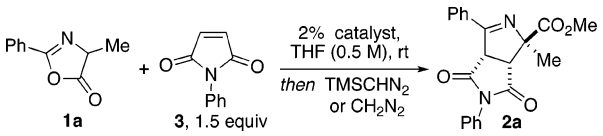


(1)

A variety of electron-deficient alkenes were found to be viable dipolarophiles in the gold(I)-catalyzed münchnone cycloaddition. For example, 2 mol % gold(I) benzoate **4**-catalyzed the reaction of **1a** with maleic anhydride (**5**), under conditions similar to those used with *N*-phenylmaleimide to afford acid **6** in 79% yield and 87% ee (eq 1).[10] Acyclic alkenes could also be employed as partners in the gold(I)-catalyzed cycloaddition (Table 2). Generally, the reactions performed best using a 3:1 mixture of THF and PhF and slightly higher catalyst loading (3.5%). Notably, in all cases the reactions proceeded with excellent diastereo- and regioselectivity.

Various azlactones (**1b**−**j**) were prepared, and the results of their gold(I) benzoate-catalyzed enantioselective cycloaddition with *N*-phenylmaleimide are shown in Table 3. Substitution at the para position of the azlactone aromatic ring was well tolerated (entries 1−4). While increasing the steric demand at the azlactone C2 or C4 position resulted in decreased reactivity in PhF, switching the solvent to a mixture of THF and PhF permitted isolation of the cycloadducts in good yields (entries 5, and 7−9). The use of this solvent mixture allowed for smooth reaction of azlactone **1f**, bearing

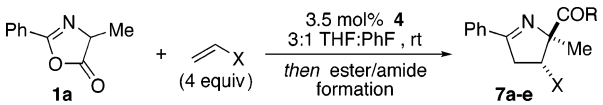
Table 1. Development of the Au(I)-Catalyzed Cycloaddition[a]



entry	catalyst	time (h)	yield (%)[b]	ee (%)[c]
1	PPh_3AuOBz	0.5	85	−
2	(*R*)-BINAP(AuOBz)$_2$	2	78	−8
3	(*R*)-SEGPHOS(AuOBz)$_2$	3	81	−40
4	(*R*)-DIFLUOROPHOS(AuOBz)$_2$	3	56	−44
5	(*R*)-Cl−MeO-BiPHEP(AuOBz)$_2$	3	80	−5
6	(*R*)-SYNPHOS(AuOBz)$_2$	3	62	−55
7	(*R*)-3,5-xylyl-BINAP(AuOBz)$_2$	3	63	−24
8	(*R*)-DTBM-SEGPHOS(AuOBz)$_2$	7	81	−83
9	(*S*)-Cy-SEGPHOS(AuOBz)$_2$, (**4**)	2	70	88
10	**4**	5	76	95[d]

[a] Reactions run with 0.33 mmol **1a**; for conditions concerning in situ ester formation see Supporting Information (SI). [b] Isolated yield. [c] Absolute configuration determined by X-ray crystallography on the corresponding α-methylbenzylamide (see SI). [d] Reaction performed at 0.5 M in PhF.

Table 2. Reaction of **1a** with Various Acyclic Alkenes[a]



entry	product		time (h)	yield (%)[b]	ee (%)
1	**7a**, X = $CO_2{}^t$Bu	R = OMe	24	56	99[c]
2	**7b**, X = $CO_2{}^t$Bu	R = $NHCH_2Ph$	14	74	95
3	**7c**, X = CO_2Et	R = OMe	14	66	90
4	**7d**, X = CO_2Me	R = OMe	14	89[d]	93
5	**7e,** *X* = CN	R = $NHCH_2Ph$	14	68	76

[a] Reactions run with 0.33 mmol **1a** at 0.5 M; for conditions concerning in situ ester/amide formation see SI. [b] Isolated yield unless otherwise noted. [c] Reaction run with 10 equiv of alkene and 2% mol **4**. [d] Yield determined by ^{1}H NMR.

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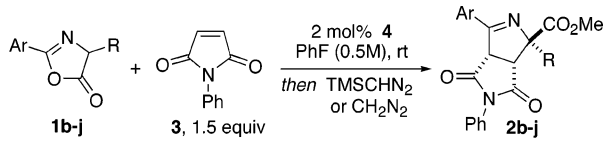
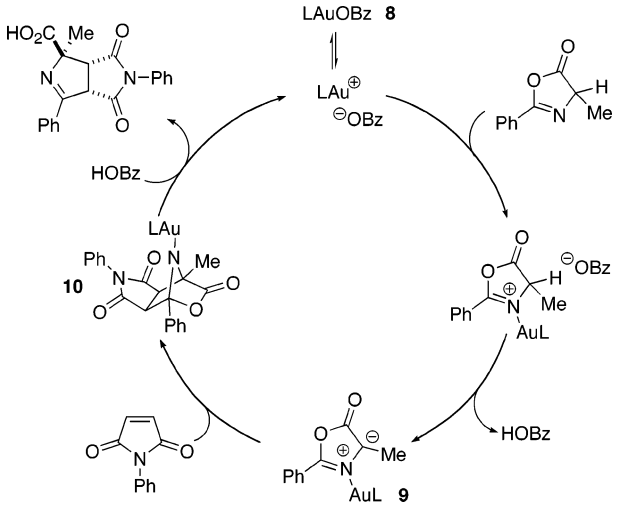
Table 3. Reaction of *N*-Phenylmaleimide (**3**) with Azlactones[a]



entry		product	time (h)	yield (%)[b]	ee (%)
1	**b**, R = Me	Ar = *p*-MeO−C_6H_4−	18	77	95
2	**c**, R = Me	Ar = *p*-Br−C_6H_4−	15	75	93
3	**d**, R = Me	Ar = *p*-Cl−C_6H_4−	15	72	92
4	**e**, R = Me	Ar = *p*-$NO_2C_6H_4$−	1.5	98	91
5	**f**, R = Me	Ar = *o*-Me−C_6H_4−	4	73	86[c]
6	**g**, R = H	Ar = Ph	24	84	−98[d]
7	**h**, R = allyl	Ar = Ph	8	86	87[c]
8	**i**, R = Ph	Ar = Ph	1.5	35	78[e]
9	**j**, R = Bn	Ar = Ph	36	71	68[c]

[a] Reactions run with 0.33 mmol azlactone; for conditions concerning in situ ester formation see SI. [b] Isolated yield. [c] Run at 0.5 M in 3:1 THF/PhF. [d] At 0.5 M in aceteone, using (*R*)-DTBM-SEGPHOS(AuOBz)$_2$; note also the change in the sense of ligand chirality. [e] Run at 0.25 M in 3:1 THF/PhF at 0 °C with 5% mol **4**.

Scheme 1. Proposed Mechanism of Au(I)-Catalyzed 1,3-DCR



a 2-methylphenyl C2 substituent, providing product **2f** in good yield with 86% ee.[11] Similarly, C4 allyl-substituted azlactone **1h** underwent gold(I)-catalyzed cycloaddition to furnish **2h** in 86% yield and 87% ee; however, a decrease in enantioselectivity was observed with a further increase in the size of the C4 substituent to benzyl (entry 9). The reaction of **3** with glycine-derived azlactone **1g** catalyzed by **4** produced **2g** with only 81% ee. Fortunately, switching the catalyst to (*R*)-DTBM-SEGPHOS(AuOBz)$_2$ allowed for the isolation of cycloadduct **2g** in 84% yield and 98% ee (entry 6).

A proposed catalytic mechanism, paralleling those postulated for reactions of acyclic azomethine ylides, is shown in Scheme 1.[6] Dissociation of a carboxylate counterion from **8** provides an open coordination site for azlactone binding. Deprotonation of the activated substrate, presumably by benzoate, generates *N*-aurated-dipole **9**. Reaction of **9** with the dipolarophile produces initial cycloadduct **10**. Subsequent C−O bond cleavage and protonation followed by dissociation of the Δ^1-pyrroline regenerates the catalyst.[12]

In summary, we have developed the first catalytic enantioselective reaction of azlactones with alkenes to provide Δ^1-pyrrolines.[13,14] Notably, the gold-catalyzed cycloadditions proceed with excellent diastereo- and regioselectivity. The reaction is proposed to proceed through a 1,3-dipole[15] generated by deprotonation of a gold(I)-activated azlactone and therefore represents an important departure from the mechanistic paradigm of π-activation most commonly proposed in contemporary asymmetric catalysis with gold complexes. The development of enantioselective reactions relying on gold(I)-catalyzed generation of nucleophiles is ongoing and will be reported in due course.

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Supporting Information Available: Experimental procedures and compound characterization data; X-ray crystallgraphic data. This material is available free of charge via the Internet at http://pubs.acs.org.

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(7) See Supporting Information (SI) for an X-ray structure of (*S*)-Cy-SEGPHOS(AuCl)$_2$.

(8) THF (2 h, 70%, 88% ee), acetone (2 h, 82%, 85% ee), DME (3 h, 79%, 87% ee), CH_2Cl_2 (5 h, 59%, 88% ee), benzene (5 h, 64%, 88% ee), toluene (5 h, 62%, 87% ee).

(9) Under these conditions, the choice of carboxylate counterion had no notable effect on the reaction. (benzoate, 5 h, 76%, 95% ee; *p*-nitrobenzoate, 5 h, 70%, 95% ee; acetate, 5 h, 71%, 95% ee).

(10) Cycloadduct **6** was not isolated; yield determined by ^{1}H NMR (see SI).

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