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Gold-Catalyzed Oxidative Cycloadditions to Activate a Quinoline Framework

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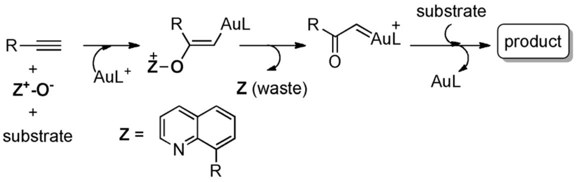
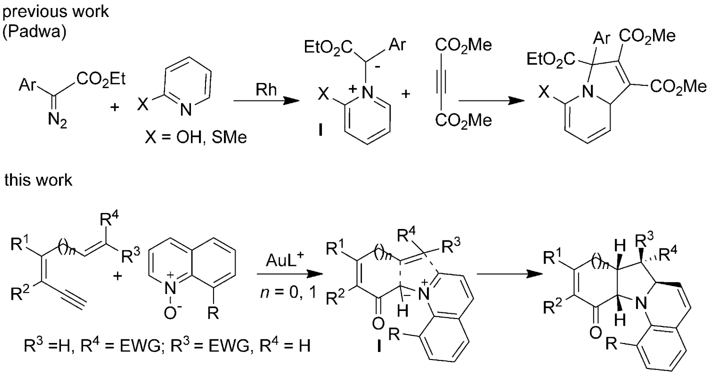
One advent in gold catalysis is to generate α-oxo gold carbenes[1] by an intermolecular oxidation of terminal alkynes by using pyridine-based oxide derivatives[2,3] with 8-alkylquinoline oxide ($Z^+{-}O^-$) being the most effective.[3] Besides easy and safe operation, gold carbenes generated in this method might exhibit chemoselectivity[3e,i] distinct from other metal carbenes produced from hazardous α-diazo carbonyl reagents.[4] Importantly, this alkyne oxidation enables one-pot synthesis of α-functionalized carbonyl products by the trapping of this carbene with a suitable substrate, as depicted in Equation (1). In all reports,[2,3] the side products **Z** (8-alkylquinolines) are considered to be useless waste. Catalytic activation of a pyridine-based framework is a challenging issue in synthetic chemistry, but very few examples have been reported for the pyridine cycloaddition reaction.[5] We report herein a new and stereocontrolled catalytic cycloaddition[6] using an α-oxo gold carbene, a tethered electron-deficient alkene, and 8-alkylquinoline, as depicted by α-carbonyl pyridinium ylides **I** (Scheme 1). The importance of this synthetic method is an easy access to indolizine frameworks that are common substructures for many bioactive alkaloids including the families of solanidine,[7e–k] demissidine,[7e,g,i] and solanidane[7l] (**A**–**C**), as depicted in Scheme 2.[7]

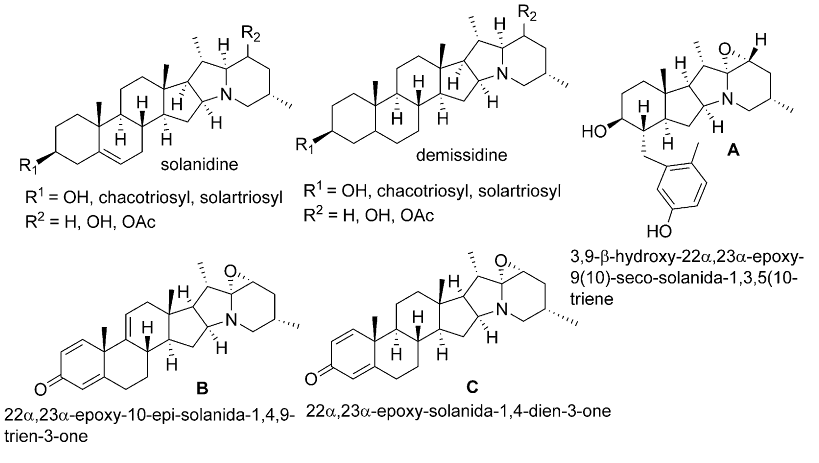


(1)



Scheme 1. Catalytic generation and cycloaddition of pyridinium ylides.

Although [3+2]-cycloadditions of α-carbonyl pyridinium ylides with alkenes or alkynes have been well documented, their operations commonly involve initial depropoanation of 2-oxomethyl pyridinium salts with strong bases in excess proportions (>1.0 equiv).[8,9] The generation of reactive pyridinium ylides by a base-free catalytic process is important in this field. Although Padwa[5b] reported the generation of α-carbonyl pyridinium ylides from rhodium carbenes and special pyridines (X=OH, SMe, Scheme 1), the resulting ylides **I′** reacted only with dimethyl acetylenedicarboxylate (DMAD). We sought a new catalytic generation of pyridini-



Scheme 2. Representative naturally occurring alkaloids.

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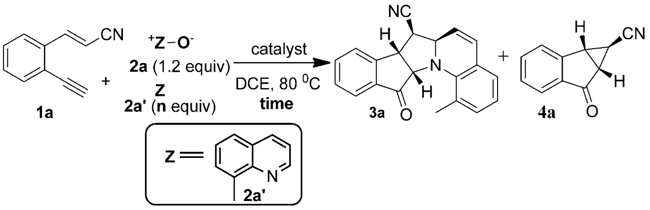
Table 1. Reactions over various gold catalysts.



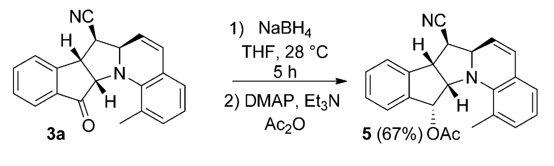
Entry	Cat.[a] (mol %)	**2a'** [*n* equiv]	*t* [h]	Compound yields [%][b]		
				1a	**3a**	**4a**
1	[AuCl(IPr)] (5)/AgNTf$_2$ (5)	0	9	–	37	42
2	[AuCl(IPr)] (5)/AgNTf$_2$ (10)	0	9	–	46	41
3	[AuCl(IPr)] (5)/AgNTf$_2$ (10)	1.5	9	–	78	–
4	[AuCl(IPr)] (5)/AgSbF$_6$ (10)	1.5	9	–	71	11
5	[AuCl(L)] (5)/AgNTf$_2$ (10)	1.5	9	–	35	45
6	[AuCl(PPh$_3$)] (5)/AgNTf$_2$ (10)	1.5	16	55	15	25
7	AgNTf$_2$ (10)	1.5	16	85	–	–

[a] [**1a**] = 0.04 M, IPr = 1,3-bis(diisopropylphenyl)imidazol-2-yliden, L = P(*t*Bu)$_2$(*o*-biphenyl). [b] Product yields are given after separation from a silica column.

um ylide intermediates that can react with alkenes by using cheap and readily available alkynes.

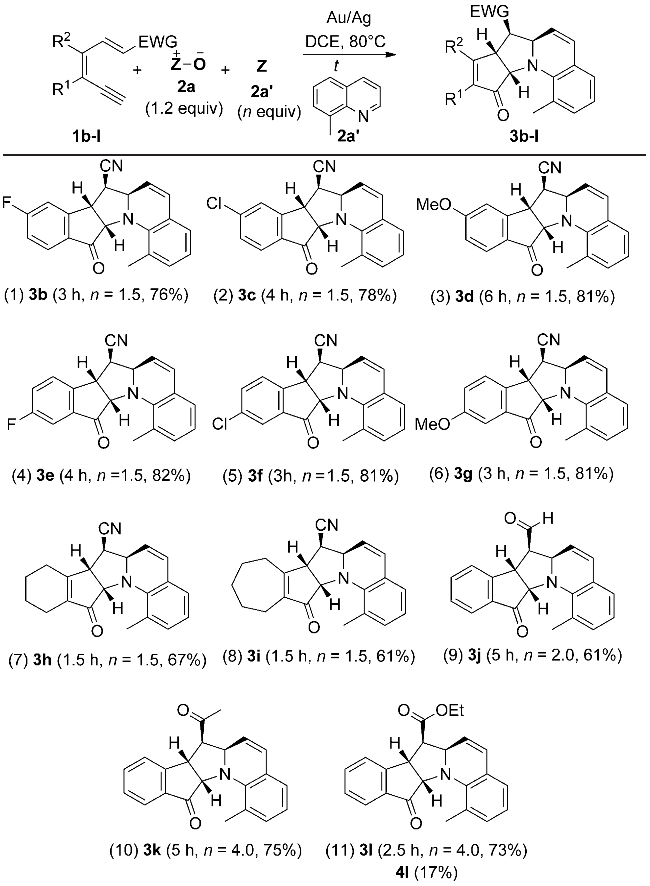
As shown in Table 1, [AuCl(IPr)]/AgNTf$_2$ (IPr = 1,3-bis-(diisopropylphenyl)imidazol-2-ylidene, 5 mol %) was tested first because of its high activity in several alkyne oxidations;[3d–g] the treatment of 3,5-dien-1-yne **1a** and 8-methylquinoline oxide **2a** (1.2 equiv) in hot 1,2-dichloroethane (DCE, 80 °C, 9 h) gave an oxidative [2+2+1]-cycloadduct **3a** and cyclopropyl indanone **4a**[3f] in 37 and 42 % yields respectively (Table 1, entry 1); only one diastereomeric form was produced for desired **3a** despite its four stereogenic centers. Notably, a change of catalyst composition, Au/Ag = 1:2, gave compounds **3a** and **4a** in 46 and 41 % yields, respectively (entry 2). The presence of external 8-methylquinoline (1.5 equiv) greatly improved the chemoselectivity to give only **3a** in 78 % yield (entry 3). Under the same conditions, [AuCl(IPr)]/AgSbF$_6$ (Au/Ag = 5:10 mol %, entry 4) gave mainly cycloadduct **3a** in 71 % yield, together with cyclopropyl indanone **4a** in a minor proportion (11 %). [AuCl{P(*t*Bu)$_2$(*o*-biphenyl)}]/AgNTf$_2$ (Au/Ag = 5:10 mol %) gave a mixture of **3a** and **4a** in comparable yields (entry 5). In contrast, [AuCl(PPh$_3$)]/AgNTf$_2$ or AgNTf$_2$ with the same Au/Ag ratio were either less active or inactive (Table 1, entries 6–7).

The structural configuration of cycloadduct **3a** was determined by X-ray diffraction of its acyl derivative **5**,[10] which was obtained by NaBH$_4$-reduction in THF, followed by a standard acetylation procedure [Eq. (2)].



(2)

Table 2. Oxidative cycloadditions with 3,5-dien-1-ynes.[a]



(1) **3b** (3 h, *n* = 1.5, 76%) (2) **3c** (4 h, *n* = 1.5, 78%) (3) **3d** (6 h, *n* = 1.5, 81%)

(4) **3e** (4 h, *n* = 1.5, 82%) (5) **3f** (3h, *n* = 1.5, 81%) (6) **3g** (3 h, *n* = 1.5, 81%)

(7) **3h** (1.5 h, *n* = 1.5, 67%) (8) **3i** (1.5 h, *n* = 1.5, 61%) (9) **3j** (5 h, *n* = 2.0, 61%)

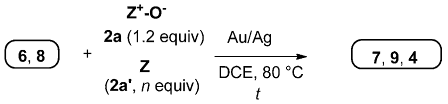
(10) **3k** (5 h, *n* = 4.0, 75%) (11) **3l** (2.5 h, *n* = 4.0, 73%) **4l** (17%)

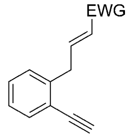
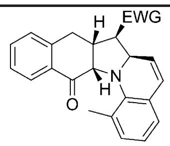
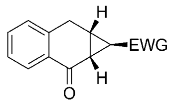
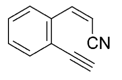
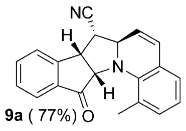
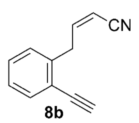
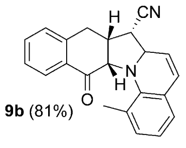
[a] [substrate] = 0.04 M, Au/Ag = [AuCl(IPr)] (5 mol %):AgNTf$_2$ (10 mol %). Product yields are reported after separation from a silica column.

Table 2 shows the substrate scope involving various 3,5-dien-1-ynes **1b–l** bearing an *E*-configured electron-deficient alkene; the competitive cyclopropanation product[3f] **4a** was completely suppressed with added 8-methylquinoline (1.5–2.0 equiv) in most instances. As shown in entries 1–6 (Table 2), the reactions were applicable to various benzenoid substrates **1b–g** bearing a fluoro, chloro, and methoxy substituent at their phenyl C(4) or C(5)-carbon atoms, giving desired cycloadducts **3b–g** with yields exceeding 76 %. To our pleasure, the substrate scope was further expanded through its compatibility with nonbenzenoid substrates **1h–i** to give desired products **3h–i** in 61–67 % yields (entries 7–8). We examined the reactions on distinct alkene substrates **1j–l** bearing an enal, enone, and ethyl enoate group; their resulting products **3j–l** were obtained in 61–73 % yields (entries 9–11) in the presence of 8- methylquinoline (2–4 equiv). Herein, cyclopropyl indanone **4l**, an analogue of **4a**, was isolated in 17 % yield in the ester case (entry 11). The compatibility with varied electron-withdrawing groups (EWG) demonstrated the broad substrate scope.

Table 3 shows the reactions on distinct 3,6-dien-1-ynes **6a–c** bearing *E*-configured electron-deficient alkenes (EWG = CN, COMe, and CO$_2$Et); their corresponding prod-

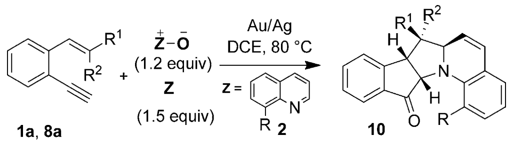
Table 3. Reactions of additional dienynes.



	Substrates[a]	[n equiv]	t [h]	Compound, yield [%][b]	
					
1	EWG = CN (**6a**)	2	4.0	**7a**, 83	–
2	EWG = COMe (**6b**)	2	6.5	**7b**, 74	–
3	EWG = CO_2Et (**6c**)	2	6.0	**7c**, 70	**4c**, 17
4	 **8a**	1.5	4.5	 **9a** (77%)	–
5	 **8b**	4	6.0	 **9b** (81%)	–

[a] [substrate] = 0.04 M, Au/Ag = [AuCl(IPr)] (5 mol %):$AgNTf_2$ (10 mol %). [b] Product yields are reported after separation from a silica column.

Table 4. Reactions with various quinolines.



1a, **8a** **2** **10**

Entry	Dienyenes[a]	Z	t [h]	Compound, yield [%][b]
1	**1a** (R^1 = CN,R^2 = H)	**2b'** (R = H)	12	**1a**, 56
2	**1a**	**2c'** (R = Et)	2.5	**10a**, 96
3	**1a**	**2d'** (R = *i*Pr)	2.5	**10b**, 96
4	**1a**	**2e'** (R = Bn)	2.5	**10c**, 74
5	**8a** (R^1 = H,R^2 = CN)	**2c'**	2.5	**10d**, 84
6	**8a**	**2d'**	2.5	**10e**, 82
7	**8a**	**2e'**	2.5	**10f**, 67

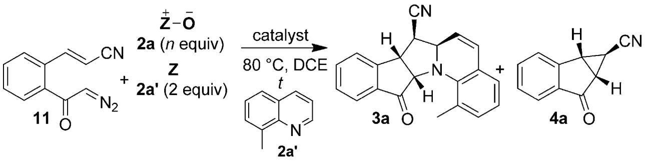
[a] [substrate] = 0.04 M, Au/Ag = [AuCl(IPr)] (5 mol %):$AgNTf_2$ (10 mol %). [b] Product yields are reported after separation from a silica column.

ucts **7a–c** were produced with excellent stereoselectivity and satisfactory yields (70–85 %; Table 3, entries 1–3). The accessible azacycles of expanded size, such as **7a–c**, again highlight the utility of this cycloaddition. We prepared *Z*-configured 3,5-dien-1-yne **8a** and 3,6-dien-1-yne **8b** to assess the stereospecificity (entries 4–5); their resulting products **9a** (77 %) and **9b** (81 %) have the cyano group *trans* to the two bridgehead protons, reflecting the retention of the *Z*-alkene geometry. The structural configuration of compound **9a** was confirmed by ^1H NOE spectroscopy and X-ray diffraction studies.[10]

Cycloadditions using various quinolines **2b'–e'** (**Z**) and their oxides **2b–e** ($\mathbf{Z^+-O^-}$) are shown in Table 4; electron-deficient pyridines ($\mathbf{Z^+-O^-}$), such as 2-chloro- and bromopyridine were unsuccessful because they tended to deactivate the alkyne oxidations unless Brønsted acids were present.[2] Nevertheless, key pyridinium ylides **I** in our system are intolerant to Brønsted acids. With *E*-configured 3,5-dien-1-yne **1a** (Table 4, entry 1) a mixture of unsubstituted quinoline **2b'** (1.2 equiv) and its oxide **2b** (1.5 equiv) gave mainly unreacted **1a** under standard conditions, but, for 8-ethyl-, isopropyl-, and benzyl-substituted quinolines (**2c'–e'**, entries 2–4) and their oxides, their corresponding cycloadducts **10a–c** were obtained in satisfactory yields (74–96 %, entries 2–4). The use of these quinolines **2c'–d'** and their oxides **2c–d** on *Z*-configured 3,5-dien-1-yne **8a** gave distinct diastereomeric cycloadducts **10d–f** in 67–84 % yields (entries 5–7), again showing the stereospecificity. We postulate that unsubstituted quinoline **2b'** greatly reduced gold acidity because of its strong coordination with the gold catalyst.

Table 5 presents experimental data to assess the role of α-oxo gold carbene **I** by using diazo carbonyl species **11** as a probe. The treatment of diazo carbonyl species **11** with 8-methylquinoline (**2a'**, 2.0 equiv) and [AuCl(IPr)]/$AgNTf_2$ (2 equiv) in hot DCE (80 °C, 12 h) led to a complicated mixture of products (Table 5, entry 1); this procedure failed to generate α-oxo gold carbene **I**. In the presence of 8-methylquinoline oxide (**2a**, 0.5 equiv), compounds **3a** and **4a** were obtained in 43 and 12 % yields, respectively (entry 2); oxide **2a** clearly assists the carbene formation, possibly through its stabilization effect. We postulate that the oxide acts as a base to coordinate with the electrophilic carbon atom of gold carbenes. With an increased $AgNTf_2$ loading (Au/Ag = 5:10 mol %), the yield of desired **3a** was increased to 51 % (entry 3). $AgNTf_2$ and $Rh_2(OAc)_4$ (1 mol %) were either inactive or ineffective to produce cycloadduct **3a** even though oxide **2a** was present (entries 4–5). Although gold carbene **I**

Table 5. Reactions of additional dienynes.



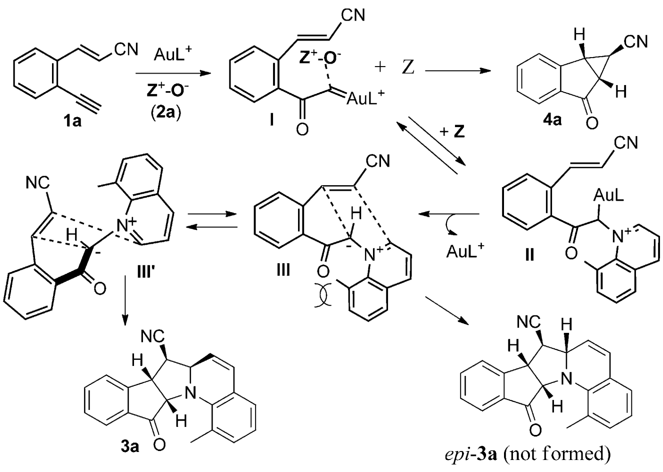
11 **2a'** **3a** **4a**

Entry	Cat. (mol %)[a]	**2a** [n equiv]	t [h]	Compound yields [%][b]		
				11	**3a**	**4a**
1	[AuCl(IPr)] (5)/$AgNTf_2$ (5)	0	12	–	–	–
2	[AuCl(IPr)] (5)/$AgNTf_2$ (5)	0.5	9	–	43	12
3	[AuCl(IPr)] (5)/$AgNTf_2$ (10)	0.5	9	–	51	2
4	$AgNTf_2$ (10)	0.5	18	–	–	–
5	$Rh_2(OAc)_4$ (1.0)	0.5	18	–	18	51

[a] [**11**] = 0.04 M. [b] Product yields are reported after separation from a silica column.

proved to be a viable intermediate, the use of α-oxo diazo species **11** appears to be an inferior method.

The high stereospecificity of this cycloaddition, as manifested by *E*- and *Z*-configured 3,5-dien-1-ynes **1a** and **8a**, is reminiscent of a dipolar [3+2]-cycloaddition, on a α-carbonyl pyridinium ylide **III** (or **III′**)[11,12] Many dipolar [3+2]-cycloadditions proceed through a concerted route to exhibit high stereoselectivity;[12] some α-carbonyl pyridinium ylides have such behavior in stoichiometric reactions.[9c] We envisage that an initial alkyne oxidation of species **1a** with 8-methylquinoline oxide **2a** (Z^+-O^-) generates an α-oxo gold carbene **I** that is shown to be a viable intermediate (see Table 3). This gold carbene reacts reversibly with 8-methylquinoline to generate adduct **II**, as depicted in Scheme 3. To address the stereospecificity, we envisage that species **II** undergoes a dissociation of AuL^+ to give an α-carbonyl pyridinium ylide **III** that was shown to be a detectable species.[11] This process is favored by bulky 8-methylquinoline oxides (alkyl = Et and isopropyl), thus resulting in the high yields of their cycloadducts **10a**–**b** and **10d**–**e** (Table 4, entries 2–3 and 5–6). The ylide intermediate **III** likely reacts with its tethered alkene through two possible conformations **III** and **III′**. Conformation **III′** is sterically less hindered than state **III**, in which the carbonyl group is too near to its methyl substituent; its corresponding product *epi*-**3a** was not produced at all. The concerted-type [3+2]-cycloaddition, as in conformation **III′**, delivers the observed cycloadduct **3a**.



Scheme 3. A plausible mechanism to rationalize the stereospecificity.

As external 8-methylquinoline **2a′** (**Z**) suppressed the yield of side-product **4a** from starting **1a**, its formation arose mainly from α-oxo gold carbene **I**, rather than from the pyridine ylide **III** (or **III′**). This hypothesis was actually inferred from a separate experiment that chiral gold catalyst can induce asymmetric induction on cyclopropane product **4a**, but no induction effect on desired **3a**.[13] In our preferable catalyst composition $Au^I/Ag^I = 1{:}2$, we speculate that free Ag^+ tends to stabilize the ylide species **III** to improve the cycloaddition selectivity.

This postulated mechanism provides insight into the newly generated "α-oxo gold carbenes **I**" in the alkyne oxidation. Not only does the use of 8-methylquinoline oxide facilitate carbene formation through stabilization, as depicted in a control experiment (Table 5, entry 2), but also the carbene forms a reversible adduct with 8-methylquinoline to retain a carbene reactivity, as postulated in current reports.[1–3] Among various *N*-oxides, 8-methylquinoline oxide is actually a poor oxidant to oxidize α-oxo gold carbene because of its large steric size.[14]

In summary, we report a gold-catalyzed oxidative cycloaddition between 3,*n*-dien-1-ynes ($n = 5$, 6) and 8-alkylquinoline oxides in the presence of 8-alkylquinolines. This reaction is applicable to a broad range of 3,5- and 3,6-dien-1-ynes to afford different-sized azacyclic products with high stereospecificity. The use of α-carbonyl diazo reagents is accessible to desired products, but with less efficiency. We postulate a reaction mechanism in which the cycloaddition begins with an alkyne oxidation to give an α-oxo gold carbene that then reacts with 8-methylquinoline to generate a an α-carbonyl pyridinium ylide to enable a concerted [3+2]-cycloaddition with a tethered alkene. The generation of a reactive pyridinium ylide from cheap alkyne highlights the value of this gold catalysis.

Acknowledgements

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Keywords: catalysis · cycloaddition · gold · oxidative cyclization · stereoselectivity

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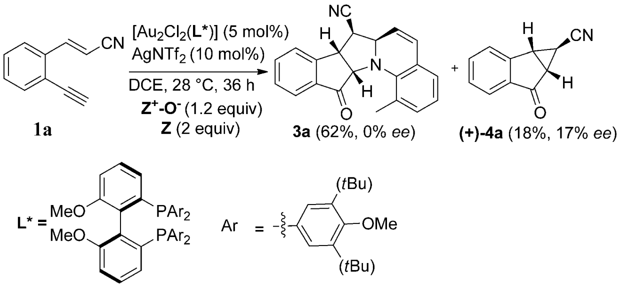
[13] We employed chiral [Au_2Cl_2(**L**)]/$AgNTf_2$ (5/10 mol%, **L**=(*R*)-DTBM-MeO-Biphep) to perform the following cycloaddition in DCE (28°C, 36 h), giving a mixture of desired **3a** and cyclopropyl indanone (+)-**4a** in 62 and 18% yield, respectively. Notably, no asymmetric induction was obtained for compound **3a**, whereas cyclopropyl indanone (+)-**4a** was obtained with 17% *ee*.



[14] We have been able to compare the oxidation properties of 8-methylquinoline oxide and 3,5-dichloropyridine oxide toward α-oxo gold carbene species **I**; their results are shown in the Supporting Information (Scheme S1).

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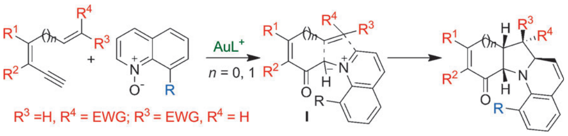
Gold-Catalyzed Oxidative Cycloadditions to Activate a Quinoline Framework



R^3 =H, R^4 = EWG; R^3 = EWG, R^4 = H

Going for gold! Gold-catalyzed reactions of 3,5- and 3,6-dienynes with 8-alkylquinoline oxides results in an oxidative cycloaddition with high stereospecificity (see scheme); this process involves a catalytic activation of a quinoline framework. The reaction mechanism involves the intermediacy of α-carbonyl pyridinium ylides in a concerted [3+2]-cycloaddition with a tethered alkene.