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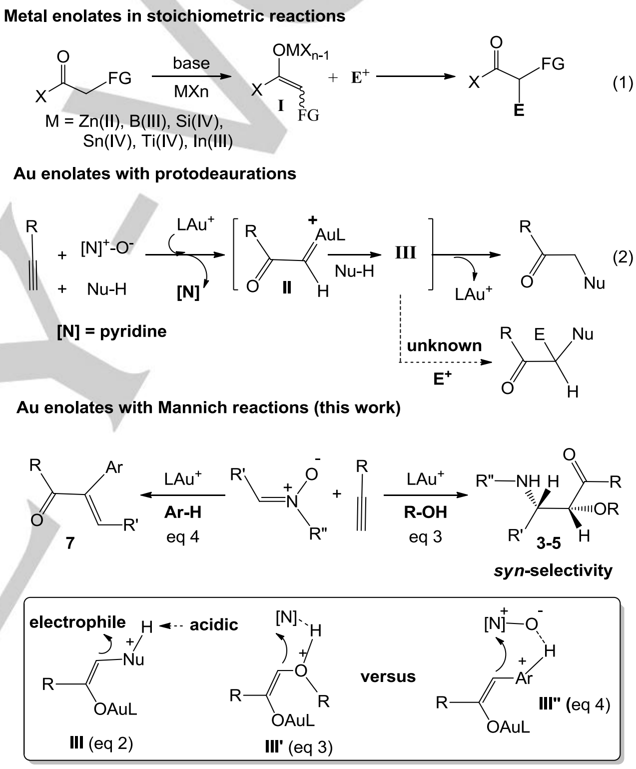
Catalytic Transformations of Alkynes into α-Alkoxy or α-Aryl Enolates to Enable Mannich Reactions via Cooperative Catalysis. Evidence for Nucleophile-Directed Chemoselectivity

Rajkumar Lalji Sahani, Manoj D. Patil, Sachin Bhausaheb Wagh, and Rai-Shung Liu*

Abstract: Catalytic formation of gold enolates from alkynes, nitrones and nucleophiles is described; their Mannich reactions manifest nucleophile-directed chemoselectivity to indicate cooperative catalysis. For 1-alkyn-4-ols and 2-ethynylphenols, their gold-catalyzed nitrone oxidations afforded *N*-containing dihydrofuran-3(2*H*)-ones with *syn*-selectivity; the mechanism involves the Mannich reactions of gold enolates with imines *via* an O-H--N bonding. For aryloxyethynes, their gold enolates react selectively with nitrones to deliver 3-alkylidenebenzofuran-2-ones, as controlled by a C-H--O hydrogen bonding.

Metal enolates (**I**) are versatile carbanions to implement many C-C bond formations including the well-known Aldol[1] and Mannich[2] reactions, Robinson annulations[3] and Claisen rearrangement.[4] Despite their widespread applications, metal enolates (**I**) were typically prepared from organic carbonyls, bases and metal salts in excessive proportions (> 1.0 equiv, eq 1).[5] Catalytic formation of metal enolates from a convenient source is highly desirable in organic synthesis. Our interest in alkynes as the enolate source began with Zn(II)-catalyzed alkyne hydrations, but their Zn(II) enolates reacted only with reactive aldehydes.[6] One notable advance in gold catalysis is to generate α-oxo gold carbenes (**II**) from the alkyne oxidations with pyridine-based oxides.[7] These gold carbenes (**II**) react with suitable organic functionalities to manifest typical carbene reactions.[8-10] In the context of intermolecular X-H insertions (X = N, O, C, S), gold carbenes (**II**) could be trapped with nucleophiles (Nu-H) to form gold enolates (**III**), but inevitably leading to protodeauration reactions (eq 2).[9] Protodemetallations are known to be very feasible for those metal carbenes generated from diazo precursors.[11] We envisage that gold enolates (**III**) comprise a Brønsted acid that might trap a suitable carbon-based electrophile via cooperative catalysis (eq 2). To realize this hypothesis, we report gold-catalyzed oxidations of 4-substituted 1-ynes with nitrones[12] to achieve their 1,2,2-trifunctionalizations via gold enolates (**III**). A notable feature of these gold enolates (**III**) is the remarkable nucleophile-directed chemoselectivity due to a change of hydrogen bonding. In the case of alcohol nucleophiles, their gold enolates (**III'**) react with imine intermediates, to afford 2-α-aminobenzyldihydrofuran-3(2*H*)-ones with *syn*-selectivity, showing novel oxidative Mannich reactions (eq 3). In the case of arene nucleophiles, their enolates (**III"**) react with nitrones to furnish 3-alkylidenebenzofuran-2-ones, manifesting new oxidative cycloalkenations (eq 4). The development of alkynes as the surrogates of α-alkoxy and α-aryl enolates in a catalytic process highlights the significance of this work.



We examined the oxidations of 2-ethynylphenol **1a** with nitrone **2a** in a 1:1 ratio over gold catalysts L'AuCl/AgNTf$_2$ (L' = PPh$_3$, IPr and P(*t*-Bu)$_2$(*o*-biphenyl) in dichloroethane (DCE, 28 °C), yielding 2-α-aminobenzyldihydrofuran-3(2*H*)-one **3a** in a *syn*/*anti* mixture according to the NMR analysis of their crude products. Herein, P(*t*-Bu)$_2$(*o*-biphenyl)Au/NTf$_2$ gave the best yield, up to 95%. Flash chromatography of this mixture on a silica bed afforded **3a** in pure *syn*-isomer; the molecular structure was confirmed with X-ray diffraction.[13] Altering the silver salt to AgSbF$_6$ maintained the same efficiency (entry 4), but the *syn*/*anti* = 3.5:1 selectivity was slightly improved with dichloromethane (entry 5), and further improved to a ratio of 7:1 in cold DCM (0 °C, entry 6). Other solvents such as toluene, nitromethane and 1,4-dioxane became ineffective for P(*t*-Bu)$_2$(*o*-biphenyl)Au/NTf$_2$ (entries 7-9). AgNTf$_2$ alone was entirely catalytically inactive (entry 10).

We examined the substrate scope with various 2-ethynylphenol **1** with nitrones **2**; the results appear in Table 2. A typical operation was performed in DCM (0 °C, 9-12 h); the

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[a] Dr. R. L. Sahani, M. D. Patil, Dr. S. B. Wagh, Prof. Dr. R.-S. Liu
Frontier Research Center for Matter Science and Technology
Department of Chemistry, National Tsing-Hua University
Hsinchu (Taiwan, ROC)
E-mail: rsliu@mx.nthu.edu.tw

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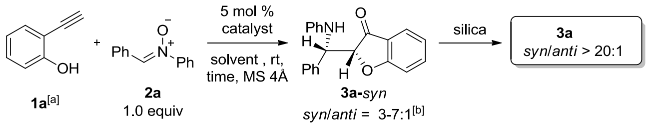
crude products were subjected to flash chromatography to yield *syn*-configured 2-α-aminobenzyldihydrofuran-3(2*H*)-ones predominantly. For 4-substituted 2-ethynylphenol **1b** and **1c** (R^1 = Cl and Me), their nitrone oxidations afforded *syn*-configured **3b** and **3c** in 88-90% yields (entries 1-2). This *syn*-selectivity is observed also for their 5-substituted analogue **3d** in 90% yield (entry 3). We tested the reactions on nitrones **2b**-**2e** bearing different imine moieties X = Br, Cl, Me and OMe), which delivered the desired *syn*-configured products **3e**-**3h** with yields exceeding 95% (entries 4-7). For nitrones **2f**-**2g** bearing alterable anilines (Y = Cl and OMe), their corresponding reactions afforded expected products **3i**-**3j** in favor of *syn*-selectivity (entries 8-9)**.** We prepared thiophene-containing nitrones **2h** and **2i** that delivered compounds **3k** and **3l** with high *syn*-selectivity (entries 10-11).

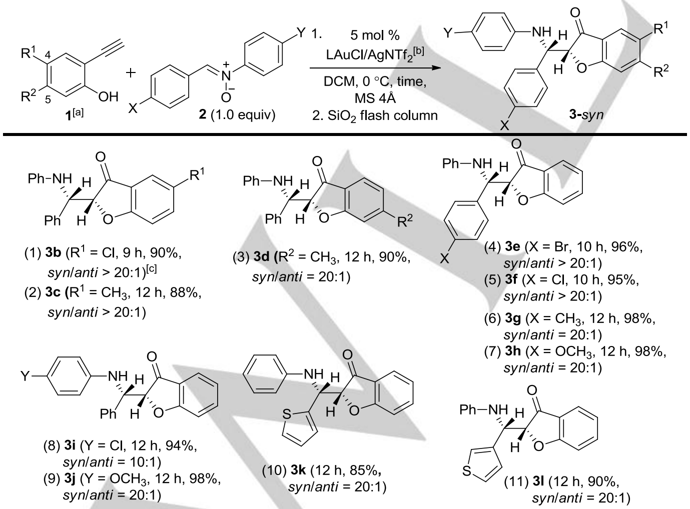
Table 1. Reactions of 2-ethynylphenol **1a** with nitrone over gold catalysts



entry	catalyst	Solvent/ temp °C	time (h)	yields %	
				1a	**3a** (*syn*/*anti*)
1	PPh$_3$AuCl/AgNTf$_2$	DCE / 28	12	20	65 (3:1)
2	IPrAuCl/AgNTf$_2$	DCE / 28	3	0	88 (2.4:1)
3	LAuCl/AgNTf$_2$	DCE / 28	3	0	95 (3:1)
4	LAuCl/AgSbF$_6$	DCE / 28	3	0	92 (3:1)
5	LAuCl/AgNTf$_2$	DCM / 28	3	0	95 (3.5:1)
6	LAuCl/AgNTf$_2$	DCM / 0	12	0	88 (7:1)
7	LAuCl/AgNTf$_2$	toluene / 28	12	38	45 (2.4:1)
8	LAuCl/AgNTf$_2$	MeNO$_2$ / 28	12	55	28 (1.7:1)
9	LAuCl/AgNTf$_2$	dioxane / 28	12	92	0
10	AgNTf$_2$	DCE / 28	12	96	0

[a] **1a** = 0.15M, **2a** = 1.0 equiv. L = P(*t*-Bu)$_2$(*o*-biphenyl), [b] = *syn*/*anti* ratios and percentage yields were estimated on crude products.

Table 2. Synthesis of 2-α-aminobenzyldihydrofuran-3(2*H*)-ones

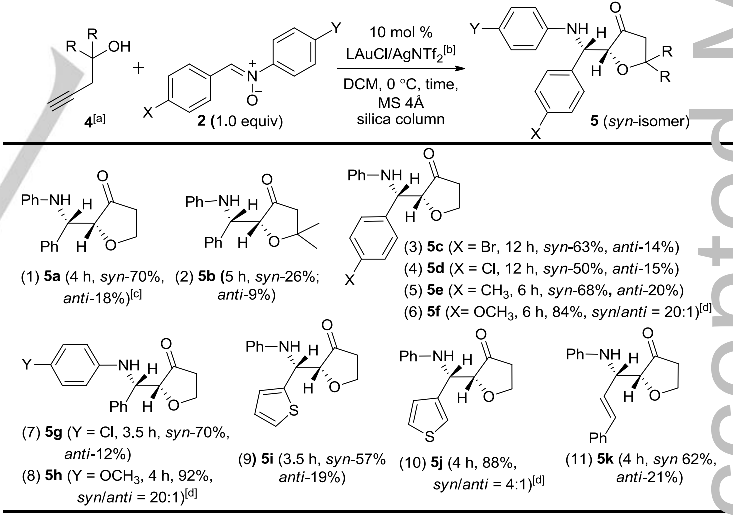


(1) **3b** (R^1 = Cl, 9 h, 90%, *syn*/*anti* > 20:1)[c]
(2) **3c** (R^1 = CH$_3$, 12 h, 88%, *syn*/*anti* > 20:1)
(3) **3d** (R^2 = CH$_3$, 12 h, 90%, *syn*/*anti* = 20:1)
(4) **3e** (X = Br, 10 h, 96%, *syn*/*anti* > 20:1)
(5) **3f** (X = Cl, 10 h, 95%, *syn*/*anti* > 20:1)
(6) **3g** (X = CH$_3$, 12 h, 98%, *syn*/*anti* = 20:1)
(7) **3h** (X = OCH$_3$, 12 h, 98%, *syn*/*anti* = 20:1)
(8) **3i** (Y = Cl, 12 h, 94%, *syn*/*anti* = 10:1)
(9) **3j** (Y = OCH$_3$, 12 h, 98%, *syn*/*anti* = 20:1)
(10) **3k** (12 h, 85%, *syn*/*anti* = 20:1)
(11) **3l** (12 h, 90%, *syn*/*anti* = 20:1)

[a] **1a** = 0.15M, **2a** = 1.0 equiv. [b] = P(*t*-Bu)$_2$(*o*-biphenyl). [c] = *syn*/*anti*-ratios and percentage yields are calculated after a flash column on silica gel.

These nitrone oxidations worked well for acyclic 4-yn-1-ols, further expanding the substrate scope (Table 3). Treatment of 4-yn-1-ol **4a** with nitrone **2a** in DCM yielded 2-(α-aminobenzyl)dihydrofuran-3(2*H*)-one **5a** with respective yields 70% and 18% of *syn*- and *anti*-isomers (entry 1). The molecular structure of **5a**-*syn* was confirmed with X-ray diffraction.[13] In the case of 2-methylpent-4-yn-2-ol **4b**, its corresponding product **5b** was obtained in a small yield with *syn*/*anti* = 3:1 (entry 2); the Ingold-Thorpe effect was unfavorable for the overall reactions because the nitrone attack at alkyne is the initial step. These reactions were compatible with nitrones **2b**-**2e** bearing various imine moieties (X = Br, Cl, Me and OMe), yielding desired **5c**-**5f** with *syn*/*anti* = 3.3-20:1, (entries 3-6). The reactions were amenable to other nitrones **2f** and **2g**, further affording Mannich products **5g** and **5h** with *syn*-selectivity (entries 7-8)**.** Thiophene-derived nitrones **2h** and **2i** were also applicable substrates to deliver **5i** and **5j** in satisfactory yields with *syn*/*anti* ratios 3-4:1 (entries 9-10). Styrene-containing nitrone **2j** was also suitable for this gold catalysis to afford **5k** efficiently (entry 11).

Table 3. Catalytic Reactions on 4-Hydroxy-1-ynes



(1) **5a** (4 h, *syn*-70%, *anti*-18%)[c]
(2) **5b** (5 h, *syn*-26%; *anti*-9%)
(3) **5c** (X = Br, 12 h, *syn*-63%, *anti*-14%)
(4) **5d** (X = Cl, 12 h, *syn*-50%, *anti*-15%)
(5) **5e** (X = CH$_3$, 6 h, *syn*-68%**,** *anti*-20%)
(6) **5f** (X= OCH$_3$, 6 h, 84%, *syn*/*anti* = 20:1)[d]
(7) **5g** (Y = Cl, 3.5 h, *syn*-70%, *anti*-12%)
(8) **5h** (Y = OCH$_3$, 4 h, 92%, *syn*/*anti* = 20:1)[d]
(9) **5i** (3.5 h, *syn*-57% *anti*-19%)
(10) **5j** (4 h, 88%, *syn*/*anti* = 4:1)[d]
(11) **5k** (4 h, *syn* 62%, *anti*-21%)

[a] **1a** = 0.24M,. [b] L = P(*t*-Bu)$_2$(*o*-biphenyl). [c] The yields are calculated after purification on a silica column. [d] *Syn* and *anti*-isomers are not separable.

We examined the oxidations of phenoxyethyne **6a** with nitrones; gratifyingly, the chemoselectivity is influenced by an aryl nucleophile. In the reaction of phenoxyethyne **6a** with nitrone **2a** in ratio 1:2.1, 3-benzylidenebenzofuran-2-one **7a** and 1,2-diphenyldiazene oxide **8** were isolated in 67% and 31% yields respectively (eq 5); diazene oxide **8** was not observed in preceding nitrone oxidations. The *E*-configuration of compound **7a** was verified with X-ray diffraction of its relative **7i** (see Table

4, entry 8).[13] In the case of a 1:1 ratio of **6a**/**2a**, the yields of compounds **7a** and **8** were decreased to 37% and 16%. We performed deuterium-labeling experiments (eq 6) that confirmed that the benzylidene moiety of compound **7a** arose entirely from the nitrone, instead of the imine. Accordingly, this reaction requires phenoxyethyne **6a** and nitrones **2a** in a 1:2 molar proportion**.**

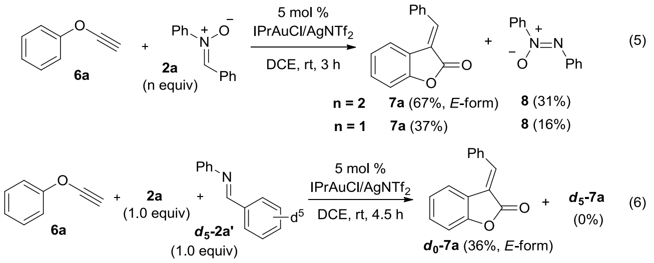
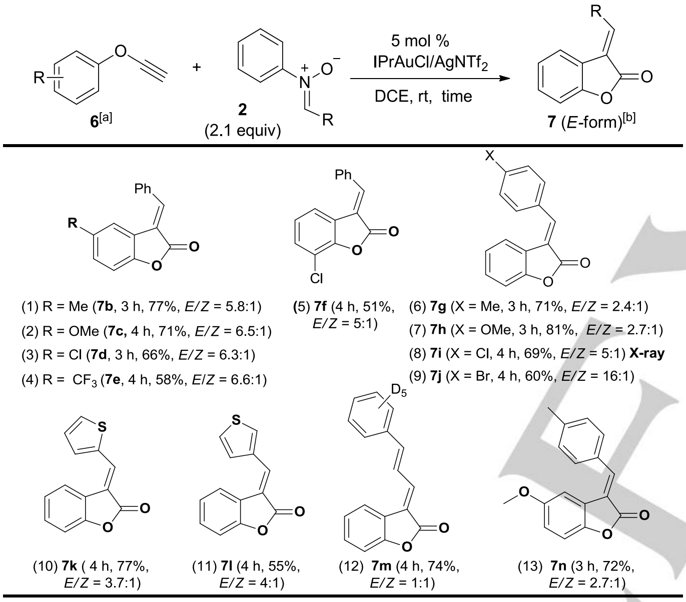


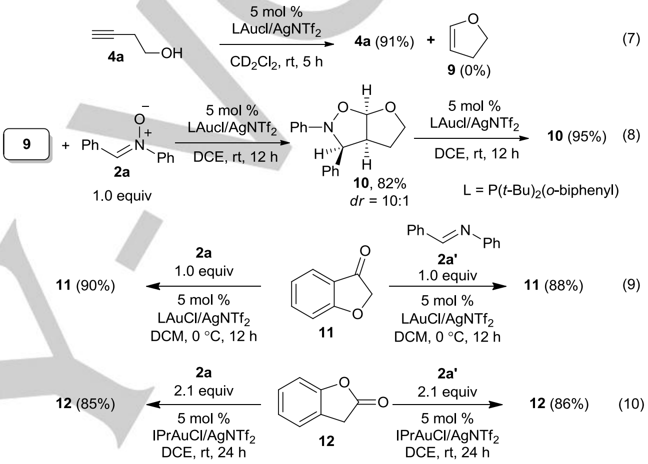
Table 4. Gold-catalyzed reactions of various nitrones



[a] **6a** = 0.20M, [b] Product yields are reported after purification from a silica column

We assessed the generality of these oxidative cycloalkenations using nitrones bearing various imine (RCH=N) moieties because the aniline parts became diazene oxides. The oxidations of various 4-phenoxyethynes **6b**-**6e** (R = Me, OMe, Cl and CF_3) with model nitrone **2a** (2.1 equiv) delivered **7b**-**7e** in 58-77% yields in favor of *E*-isomers (*E*/*Z* = 5.8-6.6:1, entries 1-4). We prepared also ortho-chloro derivative **6f**, delivering compound **7f** in 51% yield (*E*/*Z* = 5:1, entry 5). These oxidative cycloalkenations were compatible with nitrones bearing electron-deficient and -rich imine moieties (X = Me, OMe, Cl and Br), affording products **7g**-**7j** in reasonable yields (entries 6-9). The molecular structure of chloro derivative **7i** was confirmed with X-ray diffraction.[13] Synthesis of 2- and 3-thienylidene derivatives **7k** and **7l** proceeded smoothly with 77% and 55% yields respectively (entries 10-11). In the case of d_5-containing dienylidene derivative **7m**, its deuterated sample allowed us to determine its ratio *E*/*Z* = 1:1. Two variants of alkynes and nitrones were also feasible with the reaction, as manifested by benzofuran-2-one **7n** with 72% yield (entry 13).

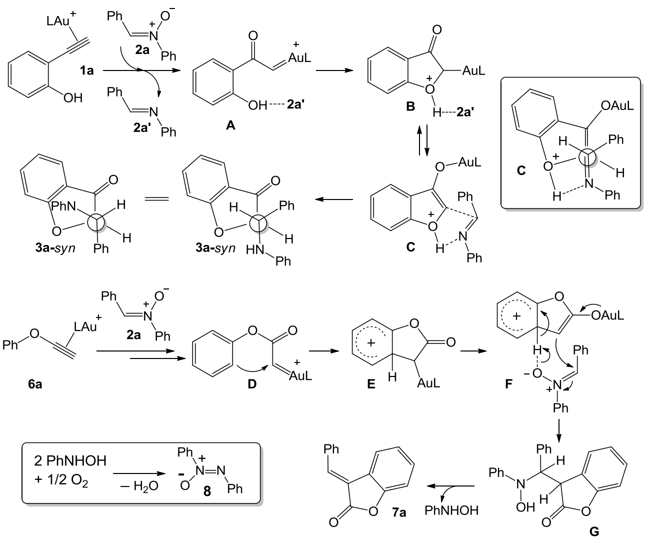
We performed control experiments to elucidate the reaction mechanism. Treatment of butyn-1-ol **4a** with gold catalyst in CD_2Cl_2 showed no sign of the cycloisomerization (eq 7). In consistent with literature report[14a], the reaction of 2,3-hydrofuran **9** with nitrone **2a** led to [3+2]-cycloaddition product **10** (eq 8), which was very stable in the presence of gold catalyst. Accordingly, compound **10** cannot be a precursor for our oxidative mannich product **5a**. We prepared benzofuran-3(2*H*)-one **11** and benzofuran-2(3*H*)-one **12,** which did not react with either nitrone **2a** or imine **2a'** in the presence of gold catalyst (eqs 9-10). Protodeauration products such as **11** and **12** were unlikely to occur in our reaction system.[14b]



We postulate a mechanism, involving gold carbenes **A** that are subsequently attacked by their tethered phenols to yield oxonium-type gold enolates **B**.[15] Imine **2a',** released in the nitrone oxidation of species **1a**, was trapped by these oxonium species **B** via a hydrogen bonding O-H---N, subsequently forming a complex **C**. This assessment rationalizes well an observation (see Scheme s-1, SI) that the amino part of compound **3a** arises entirely from nitrone **2a** even if external deuterated imine **2a'** is present. A preferable open-transition state of species **C** involves *anti*-orientations between the C=N/C=C and C-O/phenyl pairs, ultimately yielding the observed product **3a** with *syn*-selectivity.

The nitrone oxidation of phenoxyethyne **6a** to form 3-benzylidenebenzofuran-2-one **7a** and 1,2-diphenyldiazene oxide **8** is rationalized in a mechanism involving gold carbene **D**. After an aryl attack at gold carbenes **D,** the resulting gold enolates **E** reacted with a second nitrone to form a complex pair **F**. We postulate that the cyclohexadienyl C-H moiety of gold enolate **E** is highly congested, rendering its hydrogen bonding with an imine less feasible. The complex pair induces the formation of a C-C bond to afford Mannich product **G**. The *N*-hydroxyaniline group of species **G** is better than aniline as a leaving group, readily forming benzofuran-2-one **7a** and *N*-hydroxyaniline. In solution, *N*-hydroxyaniline is readily convertible to 1,2-diphenyldiazene oxide **8** in an auto-oxidation process.[16]

This work reports catalytic formations of α-alkoxy and α-aryl gold enolates from 4-substituted alkynes and nitrones to enable Mannich reactions. In the cases of 2-ethynylphenols **1** and 4-



Scheme 1. Plausible mechanism for gold-enolate enabled mannich reaction

hydroxy-1-ynes **4,** their nitrone oxidations delivered α-alkoxy enolates that reacted preferably with imines with *syn*-selectivity. In the case of aryloxyethynes, their resulting α-aryl enolates reacted selectively with a second nitrone to afford 3-benzylidenebenzofuran-2-one derivatives**.** Herein, a change of the chemoselectivity of the Mannich reactions is attributed to two distinct hydrogen bonds,[17] O-H--N versus C-H--O; cooperative catalysis is thus ascertained. The use of alkynes as the surrogates of α-alkoxy and α-aryl enolates highlights the significance of this work.

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Keywords: alkynes • nitrones • oxidative Mannich reactions • oxidative cycloalkenations • enolates

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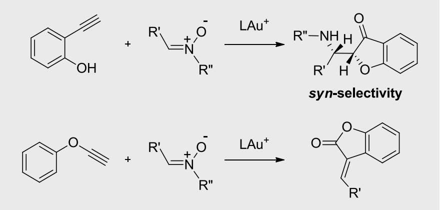

We report catalytic formation of gold enolates from alkynes, nitrones and nucleophiles; their Mannich reactions manifest nucleophile-directed chemoselectivity to indicate a cooperative catalysis.

*Rajkumar Lalji Sahani, Manoj D. Patil, Sachin Bhausaheb Wagh, and Rai-Shung Liu**

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Catalytic Transformations of Alkynes into α-Alkoxy or α-Aryl Enolates to Enable Mannich Reactions via Cooperative Catalysis. Evidence for Nucleophile- Directed Chemoselectivity