Gold Catalysis

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Copper Salts as Additives in Gold(I)-Catalyzed Reactions**

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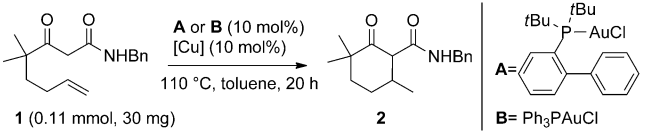
Over the past 15 years, gold catalysis has become an essential tool in organic chemistry.[1] In particular, spectacular transformations have been reported in the field of homogeneous gold(I)-catalysis,[2] the usefulness of which has been demonstrated through various total syntheses of natural products.[3] The overwhelming majority of gold(I)-catalyzed reactions involve [LAu][Y] as active species, where Y is a weakly coordinating anion, L = phosphine, phosphite, phosphoramidite, carbene, or other species, and Y = TfO^-, $(RO)_2PO_2^-$, Tf_2N^-, BF_4^-, PF_6^-, SbF_6^-, or other species (Tf = trifluoromethanesulfonyl). These electrophilic compounds are usually generated by anion metathesis between LAuX (X = Cl, Br) and a silver salt (AgY), and are not necessarily isolated.[4] In spite of the possible interference of silver with the catalytic process,[5] such two-component systems are widely used, because both gold halide precursors and silver salts are readily available and quite easy to handle. Although the vein of gold-catalyzed synthesis seems inexhaustible, some problems associated with the use of fragile cationic complexes remain to be solved. For example, the classical $[Ph_3PAu]^+$ (or other phosphine–gold cationic intermediates) may rapidly decay to give gold(0) (as mirror, precipitate, or nanoparticles) and inactive $[(Ph_3P)_2Au]^+$.[6] Although gold nanoparticles can sometimes be extremely active,[7] in most cases, the reduction of $[LAu]^+$ means deactivation. As $[LAu]^+$ is normally stable in solution, the decomposition process is attributed to the interaction between the cationic complex and a reductive substrate such as an alkyne, allene, or alkene.[6–8] Thus, some Au^I-catalyzed reactions remain limited in terms of scalability, catalyst loading, and temperature range. Most of them have been carried out with a few milligrams of starting material and attempts to work at larger scale have resulted in significant erosion of the yields.[9] To ensure a sufficient concentration of active species, a proportion of catalyst that exceeds 1 mol% is usually necessary. Lastly, high temperatures accelerate the decomposition process, especially above 80°C, which is detrimental to the development of energetically demanding transformations. To circumvent these problems, work has been focused on the ligands used in Au^I catalysis.[6,10] On our side, we envisaged to play on the anion metathesis itself. We reasoned that a gradual (possibly reversible) delivery of $[LAu]^+$ from a reservoir of stable [LAuX] should prevent rapid decomposition of all of the gold. This does not seem to be possible with silver salts, as the precipitation of AgX makes this step very fast and irreversible. We herein report that copper salts address these issues.

During the course of our studies on gold-catalyzed hydroalkylations of unactivated alkenes,[11] we decided to evaluate the influence of some additives. Surprisingly, we observed that a catalytic mixture of [(JohnPhos)AuCl] (**A**; 10 mol%) and $Cu(OTf)\cdot 0.5\,C_6H_6$ (10 mol%) was able to catalyze the transformation of the ene-β-ketoamide **1** into the cyclized product **2** (Table 1, entry 1). No silver salt was added in the reaction mixture. To the best of our knowledge, no report mentions the joint use of a neutral Au^I complex and a copper salt.[12,13] Intrigued by this finding, we decided to test various catalytic systems. At first, all the experiments were carried out at 110°C in toluene for 20 h on a 0.11 mmol scale (30 mg). After checking that **A** alone was not able to catalyze the cyclization, various Cu^I and Cu^{II} complexes were eval-

Table 1: Screening of the Au/Cu catalytic system in intramolecular hydroalkylation of ene-β-ketoamide **1**.



1 (0.11 mmol, 30 mg) **2** **B**= Ph_3PAuCl

Entry	[Au]	[Cu]	Conv. [%][a]	d.r.[b]
1	**A**	$CuOTf\cdot 0.5\,C_6H_6$	100	80:20
2	none	$CuOTf\cdot 0.5\,C_6H_6$	15	n.d.
3	none	$(MeCN)_4CuPF_6$	0	–
4	none	$(MeCN)_4CuBF_4$	20	n.d.
5	none	$Cu(OTf)_2$	15[c]	n.d.
6	none	$(MeCN)_5Cu(SbF_6)_2$	–[d]	–
7	none	$CuCl_2$	0	–
8	none	$Cu(OAc)_2$	0	–
9	**A**	$(MeCN)_4CuPF_6$	100	85:15
10	**B**	$(MeCN)_4CuPF_6$	76	87:13
11	**A**	$(MeCN)_4CuBF_4$	100	82:18
12	**A**	$Cu(OTf)_2$	100	95:5
13	**B**	$Cu(OTf)_2$	100	88:12
14	**A**	$(MeCN)_5Cu(SbF_6)_2$	–[d]	–
15	**A**	$CuCl_2$	0	–
16	**A**	$Cu(OAc)_2$	0	–

[a] Estimated by ^1H NMR spectroscopy; 100% Conversion corresponds to an 80% yield of isolated product in all cases. [b] Estimated by ^1H NMR spectroscopy, ratios shown are *trans/cis*. [c] No reaction if JohnPhos is added. [d] Decomposition. Ac = acetyl, n.d. = not determined, OTf = trifluoromethanesulfonate.

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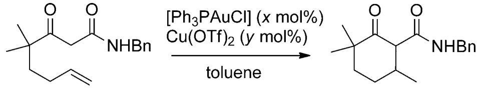
uated. Without gold, no or low conversions were observed (entries 2–8).[14,15] In contrast, when 10 mol% of gold complex **A** or [Ph_3PAuCl] (**B**) was used, the transformation worked well in most cases (entries 9–13), except with $(MeCN)_5Cu(SbF_6)_2$, which promoted decomposition (entry 14), and with $CuCl_2$ and $Cu(OAc)_2$, which proved inactive (entries 15 and 16). In terms of diastereomeric ratio, the best result was obtained with the **A**/$Cu(OTf)_2$ system (entry 12).[16] The gold-free JohnPhos/$Cu(OTf)_2$ catalytic mixture does not promote any reaction.

Focusing next on the [Ph_3PAuCl]/$Cu(OTf)_2$ catalytic system, we noticed that, with the same catalytic loading, full conversion of **1** could be reached in 1 h at 110°C in toluene (Table 2, entry 1). When using 1 mol% of [Ph_3PAuCl] and 10 mol% of $Cu(OTf)_2$, 95% conversion was obtained after 1 h (entry 2). Reduction of the loading of the copper complex to 5 mol% affected the rate of the transformation (entry 3). The proportion of [Ph_3PAuCl] could be reduced to 0.1 mol%, with full conversion being reached in 3 h (entry 4). In this case the diastereomeric ratio was greater than 95:5, which is due to an equilibration between the *trans* and the *cis* isomers (see below). The reaction still proceeded at 80°C but was slower (entries 5 and 6), and it virtually did not work at 50°C (entry 7).

Table 2: Effects of complex loading, temperature, and reaction time.



1 (0.11 mmol, 30 mg) **2**

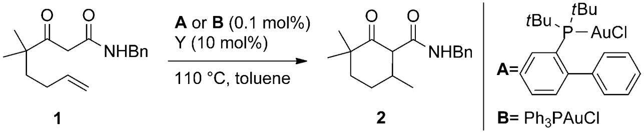
Entry	*x*	*y*	*T* [°C]	Time [h]	Conv. [%][a]	d.r.[b]
1	10	10	110	1	100	86:14
2	1	10	110	1	95	80:20
3	1	5	110	1	63	80:20
4	0.1	10	110	3	100	95:5
5	1	10	80	2	92	80:20
6	1	10	80	4	95	>95:5[c]
7	1	10	50	3	<5	n.d.

[a] Estimated by ^1H NMR spectroscopy. [b] Estimated by ^1H NMR spectroscopy, ratios shown are *trans/cis*. [c] Minor diastereomer not detected in the ^1H NMR spectrum.

Reduction of the loading of [(JohnPhos)AuCl] (**A**) was also tested. With 0.1 mol%, complete conversion required 2 h at 110°C (Table 3, entry 1). Again, decreasing the proportion of $Cu(OTf)_2$ to 5 mol% resulted in prolonged reaction time (20 h). Interestingly, the transformation could be carried out on a 2 g scale (entry 2). In this case, the concentration of **1** was higher than that in the 30 mg scale experiment (0.1 M vs. 0.5 M), resulting in a higher reaction rate.[17] Even with [Ph_3PAuCl] (**B**) and $Cu(OTf)_2$, full conversion was reached after 1.5 h (1 g scale, entry 3).

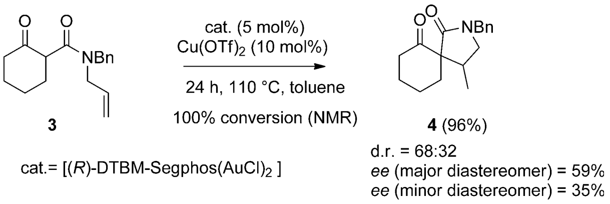
The transformations catalyzed by the Au/Cu system reported in Table 3 could be carried in an open vessel using undistilled toluene without affecting the yields or the diastereoselectivities. When AgOTf was used instead of $Cu(OTf)_2$, low or no conversions were measured with **A** (entries 4 and 5) or **B** (entry 6), respectively. Of particular interest, the Au/Cu method is also compatible with the chiral biarylphosphine digold complex [(*R*)-DTBM-Segphos-$(AuCl)_2$] (Scheme 1). A catalytic 1:2 mixture of this complex and $Cu(OTf)_2$ transformed ene-β-ketoamide **3** into the diastereomeric mixture **4**.[18] An enantiomeric excess of 59% was measured for the major diastereomer. To the best of our knowledge, this unoptimized reaction represents the first example of a catalytic asymmetric hydroalkylation of an unactivated olefin.

Table 3: Comparison of Au/Cu and Au/Ag catalytic systems.



Entry	L	Y	Amount of **1** [g]	Time [h]	Conv. [%]	d.r.[a]
1	**A**	$Cu(OTf)_2$	0.030[b]	2	100	95:5
2	**A**	$Cu(OTf)_2$	2[c]	1	100[d]	88:12
3	**B**	$Cu(OTf)_2$	1[e]	1.5	100[f]	95:5
4	**A**	AgOTf	0.030[b]	2	28	n.d.
5	**A**	AgOTf	2[c]	1	20[g,h]	n.d.
6	**B**	AgOTf	1[e]	1.5	0[d]	–

[a] Estimated by ^1H NMR spectroscopy, ratios shown are *trans/cis*. [b] 0.11 mmol. [c] 7.25 mmol. [d] 78% yield of isolated product (1.56 g). [e] 3.63 mmol. [f] 70% yield of isolated product (0.70 g). [g] 25%, 28%, 32% after 4, 7, and 24 h, respectively. [h] Same conditions, but protected from light.



Scheme 1. Enantioselective hydroalkylation of an unactivated olefin. DTBM-Segphos = (4,4'-bi-1,3-benzodioxole)-5,5-diylbis(di(3,5-di-*tert*-butyl-4-methoxyphenyl)phosphine).

How gold and copper activate the substrate is a puzzling question. The formation of active nanoparticles is unlikely, because neither the purple color that often occurs with the [Ph_3PAuCl]/AgX systems nor a precipitate were observed when using Au/Cu mixtures. Also, as discussed below, the presence of inactive $[(Ph_3P)_2Au]^+$ could hardly be detected by ^{31}P NMR. Besides, the formation of the enantioenriched product **4** rules out the sole intervention of $(Au)_n$ nanoparticles. To gain some insight, the reaction of **1** under the experimental conditions of Table 1 (toluene, 110°C, [Ph_3PAuCl]/$Cu(OTf)_2$ 10 mol% each), was monitored by NMR spectroscopy (Figure 1). After 2 h, although full conversion of **1** was reached, [Ph_3PAuCl] remained the major gold species ($\delta^{31}P = 33$ ppm). Only a very small peak at $\delta = 44$ ppm could also be observed. After 5 days at 110°C, the two peaks showed similar integration. The chemical shift of $\delta = 44$ ppm actually corresponds to the inactive $[(Ph_3P)_2Au][OTf]$.[7,19] Pertaining to the absence of reactivity shown in Table 3, entry 6, this complex forms quickly and quantita-

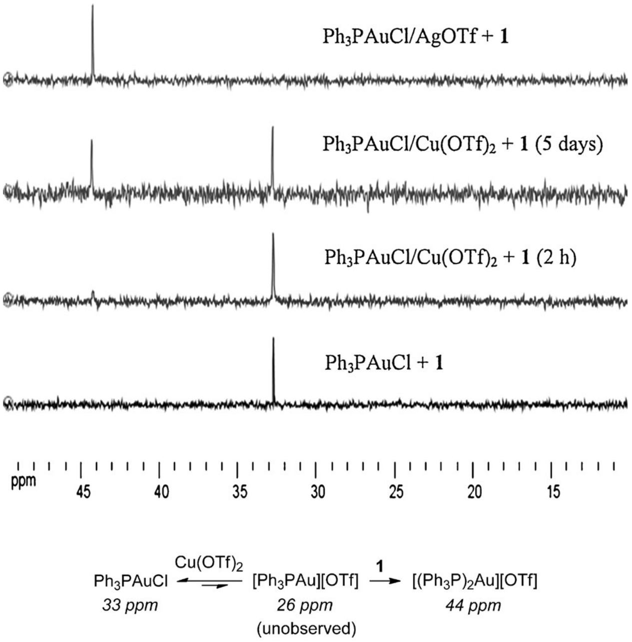
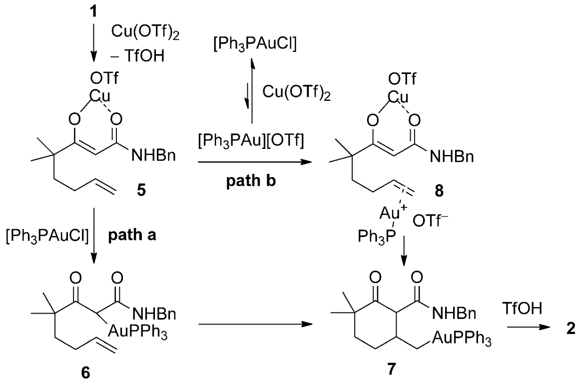


Figure 1. ^{31}P NMR spectra of the reaction of **1** catalyzed by [Ph$_3$PAuCl]/Cu(OTf)$_2$ in toluene after 2 h and 5 days at 110 °C, and reference spectra of [Ph$_3$PAuCl]/AgOTf and [Ph$_3$PAuCl] in toluene recorded in the presence of **1** after 1 h at 110 °C.



Scheme 2. Neutral and cationic pathways to rationalize the Au/Cu-catalyzed enantioselective hydroalkylation of **1**.

tively when mixing [Ph$_3$PAuCl], AgOTf, and **1**. No other gold complex, such as [Ph$_3$PAu][OTf] (expected at δ = 26 ppm),[19,20] could be detected.[21,22]

From this set of data, two mechanistic scenarios can be proposed (Scheme 2), both starting from the copper *O*-enolate **5**.[23] Following the neutral path a, nucleophilic attack on [Ph$_3$PAuCl] gives rise to the gold *C*-enolate **6**.[24] Insertion of the alkene into the C–Au bond furnishes **7** (6-*exo*-trig cyclization) and then **2** after protodemetallation.[25] Alternatively, **7** could be formed following the cationic path b, which consists of the coordination of Ph$_3$PAu$^+$ to the alkene to give **8**, which triggers the nucleophilic attack of the copper enolate.

As **6** could not be observed, we envisaged that its cyclization and subsequent protodemetallation were fast processes. To verify this hypothesis, **6** was prepared independently by treating **1** with NaH and [Ph$_3$PAuCl] (Figure 2).

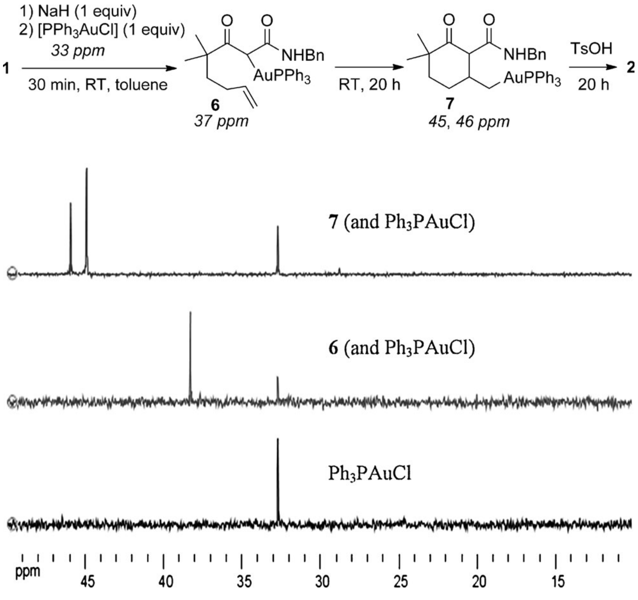
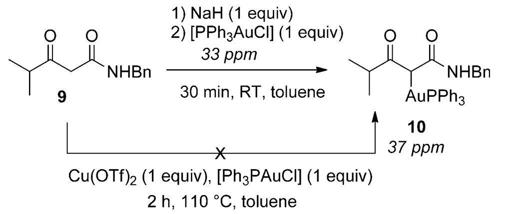


Figure 2. Formation and reactivity of the gold *C*-enolate **6**. Chemical shifts shown are for ^{31}P NMR spectroscopy.

The ^{31}P spectrum recorded after 30 min showed some remaining [Ph$_3$PAuCl] and a new peak at $\delta = 37$ ppm. A ^{13}C DEPT 135 experiment confirmed the disappearance of a CH$_2$ signal and showed a new CH doublet ($^2J_{CP} = 53$ Hz). The ^{31}P NMR peak of **6** disappeared after 20 h at room temperature, replaced by two new peaks at $\delta = 45$ and 46 ppm, which were attributed to the two diastereomers of the alkylgold complex **7**.[26] As protodeauration did not occur spontaneously, PTSA·H$_2$O (PTSA = *para*-toluenesulfonic acid) was added to the mixture, leading to **2** in poor yield (28 %).[27]

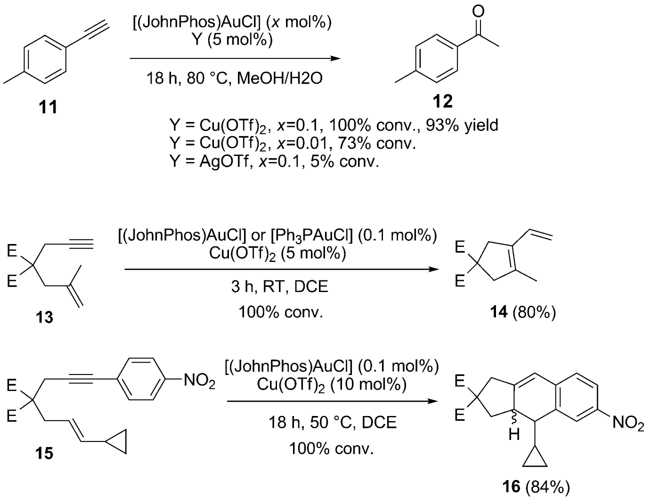
Next, we questioned the formation of **6** under the reaction conditions. For this purpose, we used β-ketoamide **9**, which cannot cyclize (Scheme 3). To obtain the NMR data for the



Scheme 3. Unlikely formation of a gold *C*-enolate under the reaction conditions. Chemical shifts shown are for ^{31}P NMR spectroscopy.

corresponding *C*-enolate **10**, compound **9** was treated with NaH and [Ph$_3$PAuCl]. The ^{31}P NMR spectrum showed a peak at $\delta = 37$ ppm, and the ^{13}C DEPT 135 experiment clearly indicated the disappearance of one CH$_2$ and the appearance of a CH doublet, as before. In a second experiment, **9** was treated with one equivalent of Cu(OTf)$_2$ (1 equiv) and then [Ph$_3$PAuCl] (1 equiv). After two hours at 110 °C, only the peak corresponding to [Ph$_3$PAuCl] and [(Ph$_3$P)$_2$Au][OTf] were observed, the latter species being a minor component of the mixture.

These results indicate that path b is more likely. We have seen that with the Au/Ag system, the quantitative instant production of catalytically active $[Ph_3PAu][OTf]$ is rapidly followed by its deactivation, which is caused by the organic substrate in the form of $[(Ph_3P)_2Au][OTf]$ and $(Au)_n$. This is probably the reason why the conversion of **1** is low and the active species not even visible in the ^{31}P spectrum. With the Au/Cu catalytic mixture, we assume that the concentration of $[Ph_3PAu][OTf]$ remains very low, actually too low to allow this complex to be detected (Figure 1). If anion metathesis eventually occurs as we suppose, reactions that involve activation of a single chemical function should also be possible with the Au/Cu system. Thus, a few other typical gold-catalyzed transformations of alkynes were studied (Scheme 4). We first turned our attention to hydration:[28] *p*-tolylacetylene **11** was treated with [(JohnPhos)AuCl] (0.1 mol%) and $Cu(OTf)_2$ (5 mol%) for 18 h at 80°C in a 2:1 $MeOH/H_2O$ mixture. Gratifyingly, the desired methylketone **12** was obtained in a 93% yield. No reaction took place with the copper salt alone. As TfOH could also be formed in appreciable amount under these experimental conditions,[29] it was tested as a catalyst (10 mol%), but only 14% of the alkyne was converted in this case. Thus, the two metals are needed for the effective formation of the hydration product. When the proportion of [(JohnPhos)AuCl] was decreased to 0.01 mol%, a good conversion (73%) was measured after 18 h.[30] On the other hand, a poor conversion (5%) was observed when using AgOTf instead of $Cu(OTf)_2$. We next evaluated the Au/Cu system in enyne cycloisomerization.[31] Compound **13** was treated with [(JohnPhos)AuCl] (0.1 mol%) or $[Ph_3PAuCl]$ (0.1 mol%) and $Cu(OTf)_2$ (5 mol%), giving rise to the five-membered ring product **14** in 80% yield after 3 h in 1,2-dichloroethane.[32] Although this reaction takes place at room temperature, ^{19}F NMR studies support the anion metathesis scenario (see the Supporting Information for details). No reaction occurred in the sole presence of $Cu(OTf)_2$ or TfOH. [(JohnPhos)AuCl] could be used jointly with $(MeCN)_4CuPF_6$, but full conversion required a longer reaction time of 18 h. When $(MeCN)_4CuPF_6$ was used alone, only 10% conversion was monitored after 18 h. Lastly, enyne **15** was transformed into the formal [4+2] cycloadduct **16** using [(JohnPhos)AuCl] (0.1 mol%) and $Cu(OTf)_2$ (10 mol%) at 50°C in 1,2-dichloroethane. Yield and diastereoselectivity are comparable to those reported for the same reaction using $[(JohnPhos)Au(MeCN)][SbF_6]$ (2 mol%).[33]



Scheme 4. Au/Cu-catalyzed transformations of alkynes. DCE = 1,2-dichloroethane, E = CO_2Me.

In conclusion, the Au/Cu system allows the use of standard gold complexes such as $[Ph_3PAuCl]$ and avoids fast decay of the active species. On the basis of NMR studies, we suggest that the replacement of the strongly coordinating chlorine anion for a weakly coordinating one (OTf^-, BF_4^-, PF_6^-) is possible with copper salts, yet it is slow and thus the production of active gold species is gradual. Therefore, scalable reactions at high temperature with low loading of the gold complex become possible. Although we do not pretend that the Au/Cu catalytic system is systematically the best choice, we have shown that it can outperform the Au/Ag system in some cases and that various solvents can be used (toluene, $MeOH/H_2O$, 1,2-dichloroethane). New opportunities now await, notably cascade reactions that would exploit the two metals. Also, the promise of enantioselective hydroalkylations of unactivated olefins, as shown in Scheme 1, represents an interesting new tool in asymmetric synthesis. Our findings in these areas will be reported in due course.

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[17] The diastereomeric mixture **2** was composed of *trans* and *cis* compounds in 88:12 ratio, instead of 95:5 for the 0.11 mmol scale reaction. This is actually not due to the amount of starting material engaged, but to the different reaction time between the two experiments. When **2** was treated once again with [(JohnPhos)AuCl] (0.1 mol%) and Cu(OTf)$_2$ (10 mol%), the ratio reached 95:5 after 2 h at 110 °C.

[18] Although **4** is also effectively formed with the [Ph$_3$PAuCl]/Cu(OTf)$_2$ catalytic system, no reaction takes place when **3** is treated with [Ph$_3$PAuCl] (5 mol%), Cu(OTf)$_2$ (10 mol%), and (*R*)-DTMB-Segphos (15 mol%). The gold-free Cu(OTf)$_2$/(*R*)-DTMB-Segphos promotes no reaction either.

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[21] Although oxidation by Cu^{II} could have occurred, no species corresponding to a Au^{III} complex could be detected.

[22] ^{31}P NMR study in the JohnPhos series was not informative because of the narrow range in the chemical shifts (see the Supporting Information).

[23] The presence of the paramagnetic Cu^{II} complex made studies by ^{1}H NMR spectroscopy difficult. However, directly after the addition of Cu(OTf)$_2$ and [Ph$_3$PAuCl], the formation of the copper enolate could be observed (see the Supporting Information). The NMR spectrum recorded after 15 min at 50 °C showed that no cyclized product was formed yet.

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[25] The protodeauration step can be promoted by D$_2$O (10 equiv). See the Supporting Information for details.

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