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Achieving Aliphatic Amine Addition to Arylalkynes via the Lewis Acid Assisted Triazole-Gold (TA-Au) Catalyst System

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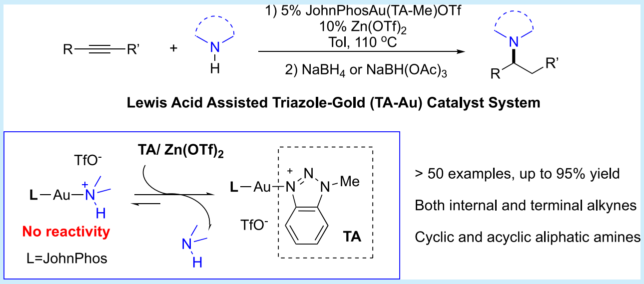
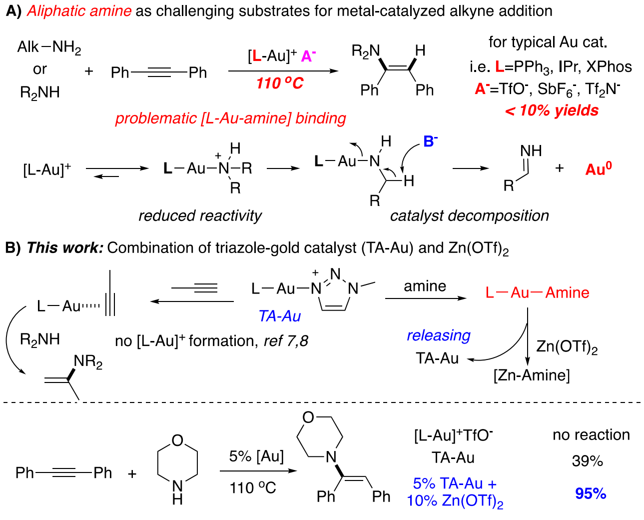
ABSTRACT: Transition metal catalyzed intermolecular hydroamination of the arylalkynes with aliphatic amine is generally problematic due to the good coordination between amine and metal cation. With the combination of 1,2,3-triazole coordinated gold(I) catalyst (TA-Au) and Zn(OTf)$_2$ cocatalyst, this challenging transformation was achieved with good to excellent yields and regioselectivity. Compared to previously reported methods, this approach offered an alternative catalyst system to achieve this fundamental chemical transformation with high efficiency and practical conditions.



Hydroamination of alkene and alkyne is one of the critical transformations in chemical synthesis since it offers the atom economic approach through direct C−N bond construction.[1] Compared with the alkene, alkyne activation is more challenging due to the high reaction kinetic barrier, especially for nonactivated (by EWG or EDG) internal alkynes.[2] With the combined efforts from researchers worldwide, various catalytic systems have been developed to achieve effective alkyne activation under mild conditions.[3] The choice of amine is also one important concern, which has been often overlooked. Compared to commonly used stabilized amine (such as aniline and amide), aliphatic amines are more basic with a better coordination ability toward metal cations. Therefore, aliphatic amines are usually problematic substrates in hydroamination reactions as the N-metal coordination significantly reduces both amine nucleophilicity and metal catalyst π-activation capability.[4] As a result, alkyne hydroamination with aliphatic amine is one extremely challenging task, and new methods to achieve this transformation under mild conditions are highly desirable.

Scheme 1. TA-Au Catalyzed Hydroamination of Alkynes



Over the past two decades, homogeneous gold catalysis has been considered one of the most effective strategies for alkyne activation due to its superior π-acid reactivity.[5] Both Au(I) and Au(III) catalytic systems have been applied for alkyne hydroamination.[6] However, while reactions with stabilized amine work well, most reported systems gave a poor performance with the aliphatic amine. This is mainly due to the amine coordination, which quenched gold catalyst reactivity (Scheme 1A). A high reaction temperature is generally demanded, facilitating the needed alkyne activation by releasing gold cation from dynamic Au−N binding. However, gold cation decomposition at an elevated temperature significantly reduced the overall efficiency of the transformation with a low gold catalyst turnover number (TON). To overcome the stability and reactivity dilemma, some special ligands have been developed and applied in this challenging aliphatic amine addition to the alkyne. Two representative recent examples are the cyclic(alkyl)(amino)carbene (CAAC) ligand[7] and P,N-ligand MorDalPhos ligand.[8] In both cases, a special bulky counterion such as B(C$_6$F$_5$)$_4^-$ was required to achieve satisfying results by minimizing potential base-mediated elimination. The require-

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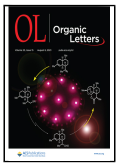

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ment of special primary ligand and counteranion not only reduced the practicality of these gold catalytic systems but also highlighted the challenges associated with this transformation.

To overcome gold cation stability issue, our group developed the 1,2,3-triazole gold complexes (TA-Au) as effective catalyst with enhanced stability, especially at elevated temperatures.[9] The general idea of TA-Au catalysis was to have 1,2,3-triazole serving as the dynamic L-ligand (DLL), forming stable [L-Au-(DLL)]$^+$ precatalyst as the off-cycle resting state. Our initial assumption was that triazole could dissociate from [L-Au-(DLL)]$^+$, giving the active [L-Au]$^+$ catalysts to react with alkyne substrates. On the basis of this assumption, several new transformations with the TA-Au system have been discovered. However, the different reactivity of TA-Au catalyst (even with the same primary ligand) raised our concern on whether this simple TA-releasing hypothesis was accurate as different reactivity was observed between TA-Au and [L-Au]$^+$.[10] Through detailed mechanistic investigation using react IR and in-suit NMR, we successfully confirmed the dissociation mechanism with alkyne direct addition to TA-Au, forming alkyne-TA-Au π-complex without going through the formation of [L-Au]$^+$.[11] This study not only explains the significantly improved gold catalyst stability observed with TA-Au but also offers new mechanistic insight into achieve new reactivity with TA-Au over the [L-Au]$^+$ even bearing same primary ligand. Taking advantage of TA-Au catalytic system, we reported the alkyne hydroamination with stabilized amine (aniline) at a high temperature. However, the reaction did work well with aliphatic amines using only TA-Au, giving poor yields (<20%).[9] Herein, we report a combination of TA-Au and Zn(OTf)$_2$ as a practical system for aliphatic amine addition to both internal and terminal alkynes, giving corresponding hydroamination products in good to excellent yields (up to 95%) with a large scope of amine choices (>50 examples).

Our interest in tackling this challenging problem was initiated by the counteranion effect associated with [(CAAC)-Au]$^+$ system for the aliphatic amine addition to the alkyne, where $B(C_6F_5)_4^-$ produced the optimal result while other anions gave significantly worse results. Although it makes sense that the electron-rich CAAC ligand helps keep [L-Au]$^+$ stable from decomposition, it is not apparent that why noncoordinated anion $B(C_6F_5)_4^-$ is also critical for improved performance. After carefully considering the plausible reaction pathway, we postulated that Lewis base-assisted gold reduction might cause trouble in gold catalyzed reaction involving aliphatic amines. As shown in Scheme 1A, aliphatic amine could easily coordinate with [L-Au]$^+$, forming [L-Au-NHR$_2$]$^+$ as the dominated gold species in the reaction mixture. Therefore, a high temperature is required to break this coordination (releasing [L-Au]$^+$ catalyst). Aliphatic amine usually contains α-proton, which might cause gold reduction (decomposition) through a potential elimination pathway, especially in the presence of coordination anions as base at a high temperature. Therefore, the key to facilitating effective aliphatic amine hydroamination is to avoid the formation of this gold-amine complexes.

On the basis of this analysis and previously reported TA-Au catalytic reaction mechanism, one solution to prevent the intrinsic aliphatic amine reduction pathway is to develop a practical system adopting TA-Au as the resting state instead of the [L-Au-amine]$^+$. With this proposed solution in mind, we first monitored the DLL ligand exchange between TA-Au and morpholine **2a** using ^{31}P NMR. As shown in Figure 1A, mixing **2a** with TA-Au **Cat-1** gives the formation of [L-Au-**2a**]$^+$ instantly even at room temperature, suggesting the good binding ability of aliphatic amine toward gold cations even over 1,2,3-triazole. After screening various amine-scavengers,[12] Zn(OTf)$_2$ was identified as the optimal choice, recovering the formation of TA-Au in almost 80% with the addition of 1eq of Zn^{2+} salt. This result suggested that the addition of Zn(OTf)$_2$ will help to break the equilibrium between TA-Au and [L-Au-amine]$^+$, avoiding the formation of the undesired [L-Au-amine]$^+$ intermediates. As the result, the combination of TA-Au and Zn(OTf)$_2$ could be the potential solution for the challenging alkyne hydroamination with the aliphatic amine (see SI for details). To testify to this hypothesis, reactions between internal alkyne **1a** and amine **2a** were performed under various gold-catalyzed conditions. The results are summarized in Figure 1B. First, simple [L-Au]$^+$ gave almost no conversion due to a rapid gold decomposition at high temperatures. In addition, only a trace amount of hydroamination product **3a** was observed while using TA-Au alone, indicating the stabilization effect of triazole at a high temperature. Notably, the low yield with TA-Au suggested that [L-Au-amine]$^+$ is the dominant gold-complexes in the catalytic cycle, which is subjected to decomposition. Finally, the combination of TA-Au (5 mol %) and Zn(OTf)$_2$ (10 mol %) gave the desired product **3** in 20% yield. This result was promising and proved the feasibility of Lewis Acid as an amine-scavenger to promote the TA-Au alkyne activation. Further condition optimization was performed. Therefore, 5 mol % JohnsPhosAu(TA-Me)OTf, 10 mol % Zn(OTf)$_2$ in toluene (1 M) at 110 °C was identified as the optimal conditions, giving **3a** in 95% yield. Reaction results with some representative alternative conditions are summarized in Table 1.

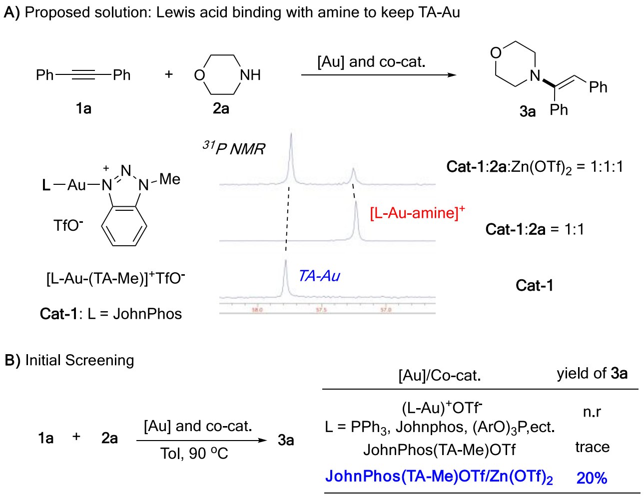
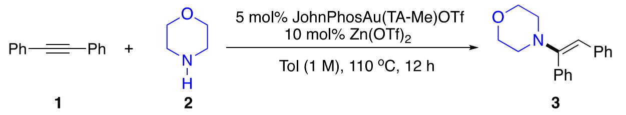


Figure 1. Prevent gold decomposition with TA-Au.

Similar to other literature reported hydroamination of internal alkynes, *cis*-addition was observed as the only product due to the enamine equilibrium to the formation of more stable isomers under this condition.[7,8] The primary ligands were crucial for good reaction performance. In general, electron-deficient phosphine ligands, such as PPh$_3$ and (ArO)$_3$P, gave poor results due to the quick catalyst decomposition, even with triazole as a stabilization factor (entries 2 and 3). Electron-rich phosphine ligands, such as XPhos, can promote this reaction due to a more stabilized gold cation (entry 4). JohnsPhosAuNTf$_2$ was tested as an alternative silver-free catalyst. As expected, a lower yield was observed (30%, entry 5). Screening of Lewis acids (Ga^{3+}, Yb^{3+}, In^{3+}, Cu^{2+} etc.) revealed Zn(OTf)$_2$ as the optimal choice. A

Table 1. Reaction Conditions Screening[a,b]



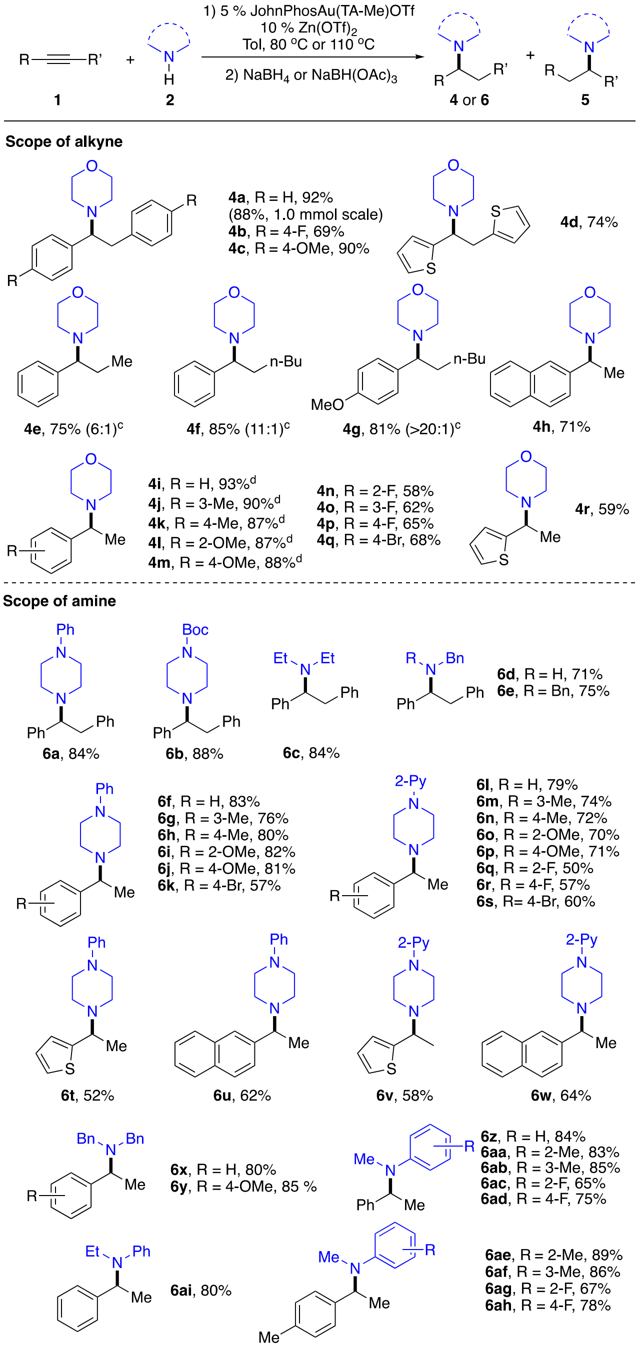
entry	reaction conditions vary from standard	yield of 3
1	none	95%
2	$PPh_3Au(TA\text{-}Me)OTf$	6%
3	$(ArO)_3PAu(TA\text{-}Me)OTf$	n.r.
4	XPhosAu(TA-Me)OTf	85%
5	$JohnPhosAuNTf_2$, no $Zn(OTf)_2$	30%
6	$JohnPhosAuNTf_2$ instead	60%
7	JohnPhosAuCl instead	40%
8	no $Zn(OTf)_2$	39%
9	$Cu(OTf)_2$ as Lewis acid	60%
10	$Ga(OTf)_3$, $Yb(OTf)_3$, or $In(OTf)_3$ as Lewis acid	40−42%
11	$Zn(NTf_2)_2$ instead of $Zn(OTf)_2$	70%
12	$Zn(OAc)_2$ instead of $Zn(OTf)_2$	45%
13	dioxane as solvent	85%
14	0.5 M	85%
15	at 100 °C	87%
16	no gold	n.r

[a] General reaction conditions: **1** (0.2 mmol, 1.0 equiv), **2** (0.4 mmol, 2.0 equiv), [Au] catal. (0.01 mmol, 5 mol %), Lewis acid (0.02 mmol, 10 mol %) in dry solvent (0.2 mL) under Ar at 110 °C. [b] Yield was determined by ^1H NMR using 1,3,5-trimethoxybenzene as an internal standard.

similar LA-assisted effect was also observed with $Cu(OTf)_2$ as cocatalyst, though less effective than $Zn(OTf)_2$ (entry 9). Other commonly used Lewis acids, such as Ga^{2+}, Yb^{3+}, and In^{3+}, could not increase the yield of desired hydroamination product **3a** (entry 10) compared to the reaction without Lewis acid (entry 8). This result suggested that these Lewis acids were not valid amine-scavengers. With $JohnPhosAuNTf_2$ in the presence of $Zn(OTf)_2$, the desired product was obtained in 60% yield (entry 6). The yield was increased compared to the one without $Zn(OTf)_2$ (entry 5). Although significant gold decomposition was observed (by formation of gold mirror), this experiment offered an additional evidence for our hypothesis on the role of $Zn(OTf)_2$ to assist morpholine releasing as the key influence. The coordination counterions, NTf_2 and OAc, led to decreased yields (entries 11 and 12), which further supported our hypothesis on the Lewis base induced gold decomposition pathway. Dioxane was also suitable solvent with a slightly decreased yield (entry 13). This reaction required a relatively harsh condition (high temperature at 110 °C and concentration 1 M) to reach the complete conversion, in which the most gold catalyst suffered from decomposition. No gold decomposition (by forming the gold mirror) was observed using our TAAu/LA system, highlighting the advantage of enhancing thermal stability while remaining high catalyst efficiency (entries 14 and 15). A control experiment showed that early transition metal $Zn(OTf)_2$ alone could not catalyze the reaction, ruling out the possible Zn catalyzed alkyne activation pathway[13] (entry 16).

With the optimal condition in hand, the reaction scope was explored.[14] The results are summarized in Scheme 2. We first evaluated the scope of alkynes. For diaryl alkyne (**4a**−**4c**), the reaction works well for both electro-deficient and electron-rich aromatic rings. Alkynes with electron-rich aromatic ring afforded desired hydroamination product with good to excellent yields. In comparison, electron-deficient aromatic alkynes gave moderate yields (i.e., **6k**). Unsymmetric alkynes (**4e**−**4g**) were also evaluated, affording good to excellent regioselectivity. Interestingly, the regioselectivity could be improved by employing the electron-rich aromatic rings, leading to **4g** as the only product. This result is consistent with previously

Scheme 2. Reaction Scope for Alkyne and Aliphatic Amine[a,b]



[a] Conditions: For internal alkyne: **1** (0.2 mmol, 1.0 equiv), [Au] cat. (5.0 mol %), $Zn(OTf)_2$ (10.0 mol %), and **2** (0.4 mmol, 2.0 eq) were added into dry toluene (1 M) under Ar. The reaction mixture was stirred at 110 °C for 12 h. For terminal alkyne: **1** (0.2 mmol, 1.0 equiv), [Au] cat. (5.0 mol %), $Zn(OTf)_2$ (10.0 mol %), and **2** (0.3 mmol, 1.5 equiv) were added into dry toluene (0.05 M) under Ar. The reaction mixture was stirred at 110 °C for 6 h. [b] Isolated yield. [c] Ratio of **4** and **5** was determined by crude ^1H NMR spectra of reaction mixture. [d] 80 °C.

reported examples using Mor-DalPhos-Au. Besides internal alkynes, the scope of terminal alkynes (**4i**−**4r**) was also explored. Similarly, both electron-deficient and electron-rich aromatic alkynes worked well, giving the desired products in good to excellent yields. Aromatic rings with electron-donation groups gave high yields due to the better coordination capability. Notably, electron-rich heterocyclic thiophene alkyne (**4r**) was suitable substrate for this transformation, though with modest yields. No reaction was observed with 1-Hexyne or 3-Hexyne, indicating a higher activation barrier for aliphatic alkynes.

Various aliphatic amines were applied to this transformation. To our great satisfaction, many of these substrates are suitable for this transformation. Both 1-phenylpiperazine (**6a**, **6f**−**6k**) and 1-pyridylpiperaziene (**6l**−**6s**) were applied to react with either internal or terminal alkynes, giving the desired products in good to excellent yields. Interestingly, the 2-pyridine group on nitrogen (**6v**, **6w**) was tolerated under this condition, suggesting good coordination capability of triazole over pyridine and highlighting the good reactivity of TA-Au. Though under strong Lewis-acid conditions, the N-Boc carbamate (**6b**) was compatible, giving the desired product in excellent yield. This result highlighted the relative mild condition of gold catalyzed hydroamination, allowing further N-modification through simple Boc-deprotection and NH coupling. Both acyclic secondary amines (**6c**, **6e**, **6z**−**6ah**) and benzyl amine (**6d**) worked well in this transformation, giving the desired products in good yields in general.

Primary aliphatic amine, 1-butylamine, did not give any conversion, likely due to a stronger coordination toward gold cation. Nevertheless, this result revealed a new facile route to achieve 2-benzyl amine derivatives with high efficiency.

In summary, we disclosed a new protocol to achieve aliphatic amine addition to terminal and internal arylalkynes using the combination of TA-Au and $Zn(OTf)_2$. The amine binding with gold cation was the main challenge for the observed poor performance of aliphatic amine hydroamination. The key discovery here is the application of $Zn(OTf)_2$ as amine-scavengers to release TA-Au and reactivate the reaction path for the formation of gold-alkyne π-complexes. TA was crucial to enhance the stability of gold catalyst, especially at elevated temperatures. The process was proved by NMR study, and challenging aliphatic amine hydroamination was achieved with broad substrate scope and good overall yields. This new catalytic system not only revealed an effective and practical strategy to construction synthetic challenge aliphatic amine derivatives but also suggested the great advantage of triazole as dynamic-L-Ligand in tuning metal center reactivity. The appreciation of TA-Au and Lewis acid catalytic systems in other challenging transformations is expected and under investigation.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.1c02098.

Experiment procedures, conditions optimization, characterization for all products (PDF)

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Notes

The authors declare no competing financial interest.

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