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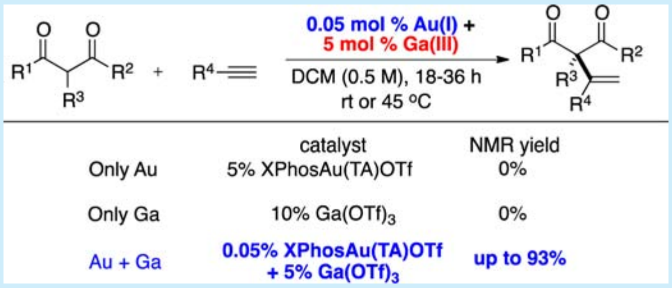
Synergistic Au/Ga Catalysis in Ambient Nakamura Reaction

Yumeng Xi, Dawei Wang, Xiaohan Ye, Novruz G. Akhmedov, Jeffrey L. Petersen, and Xiaodong Shi*

C. Eugene Bennett Department of Chemistry, West Virginia University, Morgantown, West Virginia 26506, United States

Supporting Information



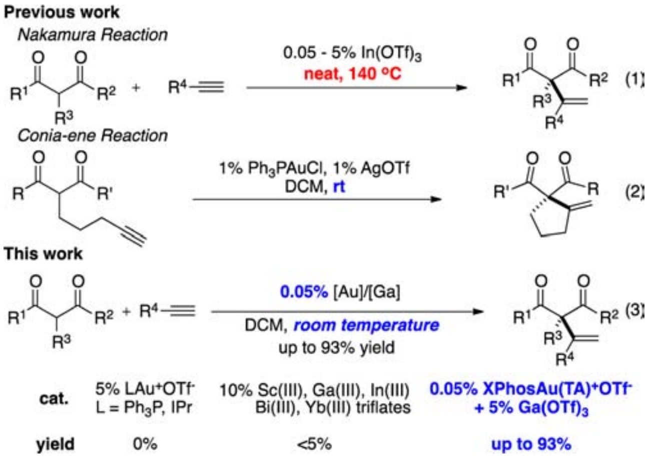
	catalyst	NMR yield
Only Au	5% XPhosAu(TA)OTf	0%
Only Ga	10% $Ga(OTf)_3$	0%
Au + Ga	0.05% XPhosAu(TA)OTf + 5% $Ga(OTf)_3$	up to 93%

ABSTRACT: The gold-catalyzed intermolecular addition of 1,3-dicarbonyl compounds to unactivated 1-alkynes (Nakamura reaction) is achieved at room temperature for the first time through synergistic gold/gallium catalysis. The developed system is highly efficient with a gold catalyst loading that can be as low as 500 ppm.

During the past decade, the cationic gold complex has emerged as one of the most effective catalysts for alkyne activation under mild conditions.[1] However, recent developments revealed a plausibly more complicated mechanism regarding the actual active catalysts in these processes.[2] The lack of mechanistic understanding hampered the developments for new transformations.[3] For example, the intermolecular addition of 1,3-dicarbonyl compounds to unactivated alkynes (Nakamura reaction)[4] is of fundamental interest due to the involvement of C–C bond formation from simple starting materials. However, the original In(III) catalyzed conditions required a high temperature (140 °C), which limited the applications. The gold(I) catalyzed intramolecular version (Conia-ene reaction) was reported back in 2004, where excellent yields were observed at room temperature.[5] In contrast, the gold(I) catalyzed Nakamura reaction has not been achieved to date. As indicated in Scheme 1, the $[L{-}Au]^+$ catalysts ($L = PPh_3$ or IPr) gave low yields of carbon-nucleophilic addition products even at an elevated temperature (<15% yield, 80 °C, 17 h). In addition, lowering the temperature significantly decreased the In(III) catalyst reactivity (<5% yield, 10% $In(OTf)_3$, rt, 17 h). Herein, we report the first successful gold-catalyzed Nakamura reaction assisted by $Ga(OTf)_3$. This new synergistic catalytic system[6] is highly efficient, promoting the reaction at room temperature with typical gold loading and at 45 °C with 0.05% loading (500 ppm, up to 93% yield).

In 2003, Nakamura reported an $In(OTf)_3$ catalyzed intermolecular addition of 1,3-dicarbonyl compounds to unactivated 1-alkynes (Nakamura reaction).[4] Several groups subsequently reported that this reaction could be achieved by other metal catalysts, such as Re, Ir, Ru, etc.[7] However, these transformations often required high temperatures to be successful. Although the gold(I) complexes have been reported as effective catalysts for alkyne activation under mild conditions, no desired products were observed for this transformation using the typical LAuCl/AgX catalyst combinations. Raising the reaction temperature to 80 °C caused significant gold complex decomposition. In 2009, we reported the application of 1,2,3-triazole gold complexes (TA-Au)[8] as the "thermal-stable" catalysts in promoting alkyne activation at higher temperature. Unfortunately, these TA-Au catalysts failed to promote the Nakamura reaction even at elevated temperature (<5% yield, 80 °C, 17h). In fact, the TA-Au catalysts were considered as a "less effective" catalyst for alkyne activation due to the good stability. This assumption was greatly challenged by the discovery

Scheme 1. Ambient Nakamura Reaction



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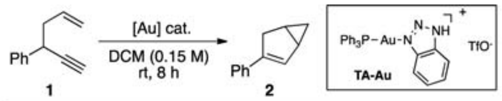
regarding the TA-Au catalyzed enyne cyclization–isomerization[9] shown in Scheme 2.

Scheme 2. $Ga(OTf)_3$-Assisted TA-Au Catalysis

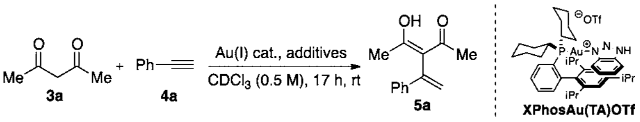


cat.	additive	time	yield
1% $PPh_3AuCl/AgOTf$	-	30 min	95%
2% TA-Au	-	8 h	5%
-	5% $Ga(OTf)_3$	8 h	0%
2% TA-Au	2% $Ga(OTf)_3$	8 h	80% (85% conv)

These results were surprising and encouraging since they suggested the application of a Au(I) and Ga(III) mixture as a new catalytic system for alkyne activation.[10] Thus, we decided to explore the reactivity of this bimetallic concept[11] in the Nakamura reaction. Our general hypothesis was that (A) as hard Lewis acid, the Ga(III) could activate the dicarbonyl compounds, making them better nucleophiles, and (B) potential formation of new active catalysts upon mixing Au(I) and Ga(III) might provide the needed reactivity to promote the challenging intermolecular carbon nucleophilic addition that simple gold systems could not achieve.

Diketone **3a** and alkyne **4a** were selected to evaluate the reaction conditions. As indicated in Table 1, the typical LAuCl/AgOTf conditions gave no reactions (entries 1–3) except when L = XPhos (entry 4), which gave the desired product in 28% NMR yield. Notably, no further conversion was obtained after 17 h. As expected, the combination of 5% $Ga(OTf)_3$ and 5% XPhosAu(TA)OTf gave a very clean reaction with the desired product observed in 90% yield (91% conversion, entry 5). Increasing the Au/Ga ratio to 1:2 led to the full conversion, and **5a** was obtained in excellent yield (98%, entry 6). This was likely due to the improved nucleophilicity of diketone through Ga(III) chelation (formation of gallium enolate). The combination of the Au/Ag system with $Ga(OTf)_3$ (instead of the TA-Au complex) gave a lower yield and slightly messier reaction (entries 7 and 8, unidentified side products), presumably due to the greater stability of triazole–gold complexes over the simple $[L–Au]^+$. Notably, $Ga(OTf)_3$ alone could not promote this reaction at all either at rt or at 45 °C (entry 10), which confirmed the important role of Au in this transformation.[12] Other acids, such as TfOH,[13] triflate salts of Zn(II), Ni(II), and Ag(I), were also tested as additives (entries 12–15). Much worse performances were observed, highlighting the special role of Ga(III) in this catalytic system.

Table 1. Optimization of Gold(I)-Catalyzed Nakamura Reaction[a]



entry	gold catalyst[b]	additive	yield (%)[c]
1	5% Ph_3PAuCl, 5% AgOTf	–	<5
2	5% IPrAuCl, 5% AgOTf	–	<5
3	5% XPhosAuCl, 5% AgOTf	–	28
4	5% XPhosAu(TA)OTf	–	<5
5	5% XPhosAu(TA)OTf	5% $Ga(OTf)_3$	90(91)[d]
6	**5% XPhosAu(TA)OTf**	**10% $Ga(OTf)_3$**	**98 (100)**[d]
7	5% XPhosAuCl, 5% AgOTf	10% $Ga(OTf)_3$	79 (88)[d]
8	5% Ph_3PAuCl, 5% AgOTf	10% $Ga(OTf)_3$	40
9	5% Ph_3PAu(TA)OTf	10% $Ga(OTf)_3$	38
10[e]	–	**10% $Ga(OTf)_3$**	**<5**
11	5% XPhosAuCl	10% $Ga(OTf)_3$	<5
12	5% XPhosAu(TA)OTf	10% $Ni(OTf)_2$	8
13	5% XPhosAu(TA)OTf	10% $Zn(OTf)_2$	6
14	5% XPhosAu(TA)OTf	10% AgOTf	<5
15	5% XPhosAu(TA)OTf	10% HOTf	35
16[e]	–	10% $M(OTf)_3$[f]	<6%

[a]Reaction conditions: **3a** (0.2 mmol), phenylacetylene (2.0 equiv), catalyst and additives in $CDCl_3$ (0.4 mL), rt, 17 h. [b]TA = 1*H*-benzotriazole. [c]Determined by ^1H NMR using 1,3,5-trimethoxybenzene as internal standard. [d]Conversion in parentheses. [e]Both rt and 45 °C, 17 h. [f]M = Sc, Yb, In, Bi.

With the optimal conditions in hand, we embarked on the evaluation of the substrate scope. As shown in Figure 1, a variety of aromatic alkynes were tested. Generally, over 90% yields were achieved. The electronic effect of substituent groups on the *para*-position of phenylacetylene was evaluated (**5a**–**5d**). Aromatic alkynes with substituents on *meta* and *ortho* positions (**5f**–**5h**) also gave very promising yields. Alkyne derivatives of the electron-rich heterocycle could proceed smoothly through this transformation (**5i**), as well as aliphatic alkynes, though with a lower yield (**5j**).[14] Unfortunately, internal alkynes, such as 1-phenylhexyne and diphenylacetylene, gave no reactions even at elevated temperature (45 °C).

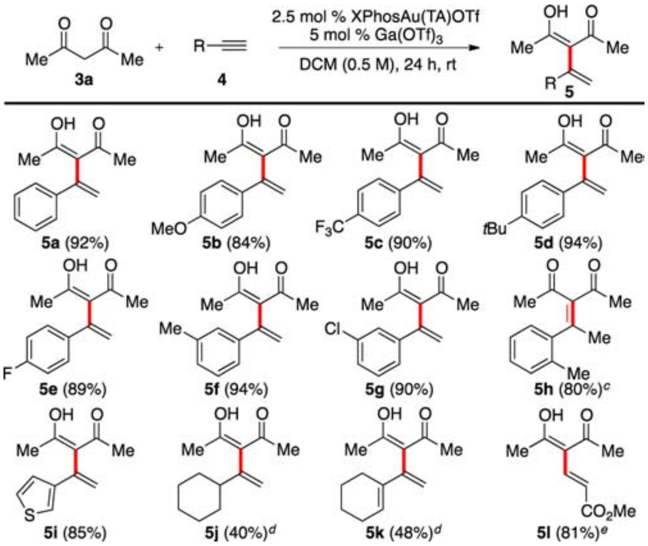


Figure 1. Scope of Alkynes[a,b] [a] General reaction conditions: **3a** (0.4 mmol), alkynes (2.0 equiv), 2.5 mol % XPhosAu(TA)OTf, and 5 mol % $Ga(OTf)_3$ in dry DCM (0.8 mL), rt. [b] Isolated yield. [c] Trace amount of direct adduct could be detected. [d] 4 equiv of alkyne, 5 mol % XPhosAu(TA)OTf, and 10 mol % $Ga(OTf)_3$ were used. [e] 1.2 equiv of alkyne was used.

To demonstrate the broad versatility of this transformation, the scope of 1,3-dicarbonyl nucleophiles was also evaluated as shown in Figure 2. Although, in some cases, slightly harsher conditions (condition B, 45 °C) were required for the optimal results, this Au/Ga bimetallic system worked well with both cyclic and acyclic 1,3-dicorbonyl compounds. The cyclic *β*-ketoesters containing ring systems could successfully undergo this transformation (**6a**–**6i**). Remarkably, the addition to the

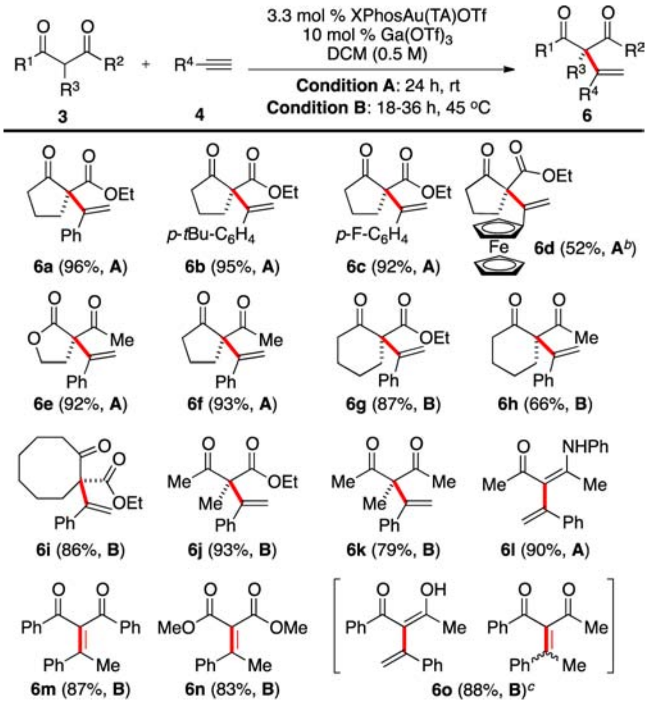


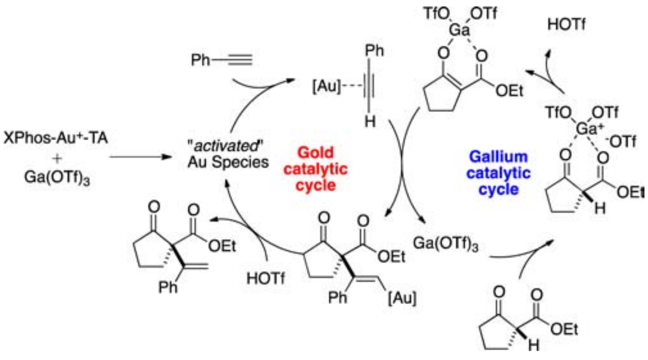
Figure 2. Scope of 1,3-Dicarbonyl Nucleophiles[a] [a] General reaction conditions: **3a** (0.4 mmol), 3.3 mol % XPhosAu(TA)OTf and 10 mol % $Ga(OTf)_3$ in dry DCM (0.8 mL), and Condition **A**: alkynes (2.0 equiv), rt; Condition **B**: alkynes (4.0 equiv), 45 °C; isolated yield. [b] 5 mol % XPhosAu(TA)OTf and 15 mol % $Ga(OTf)_3$, 12 h. [c] Obtained as a mixture of three known compounds and yield was determined by ^{1}H NMR.

ethynyl ferrocene gave a good yield, which highlighted the mild reaction conditions of this method. The acyclic α-alkyl-β-ketoester could also undergo this transformation, as well as 3-methyl-2,4-pentadione, dibenzoyl methane, and dimethyl malonate (**6j**, **6k**, **6m**−**6o**). The products of the latter two were the thermodynamically stable α,β-conjugated carbonyl compounds through olefin isomerization. Interestingly, the enamine derivative of 2,4-pentadione could also serve as an effective nucleophile in this transformation (**6l**), which provided the possibility for other carbon nucleophiles with broader synthetic applications. Notably, in most cases, an all-carbon quaternary center was efficiently generated.

It is too early to "call" the exact mechanism or the actual catalytic species in this transformation. However, based on the experimental results, it is highly likely that the Ga(III) interacted with the triazole-gold and helped the formation of catalytic active species. Based on the current results, a tentative mechanism is proposed in Scheme 3. We are currently investigating the actual catalytic components in this Au/Ga catalytic system.

The fact that the Nakamura reaction is successfully achieved at room temperature highlights the high efficiency of this new bimetallic catalyst. To test the limits of the gold catalyst in this bimetallic system, reactions were performed with a decreased gold loading while keeping the $Ga(OTf)_3$ at a similar amount as shown in Table 1. To our great delight, after some optimizations (see Table S6), we discovered that 0.05 mol % (500 ppm) was sufficient to promote this transformation if $Ga(OTf)_3$ was kept at the 5% level (at 45 °C). The scope at low Au loading is summarized in Figure 3. Notably, a loading as low as 100 ppm could promote the reaction (**5b**), albeit with a low yield (TON = 3600).

Scheme 3. Proposed Mechanism



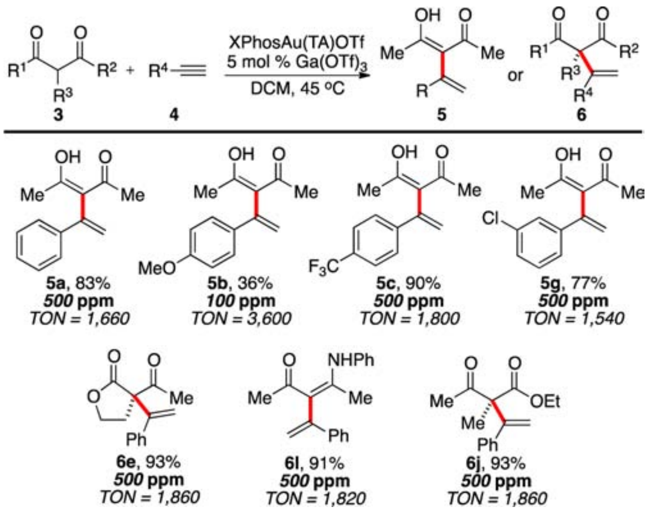


Figure 3. Nakamura reaction at low Au loading. The yields are determined by ^{1}H NMR and are the average of two runs.

For most cases in gold(I) homogeneous catalysis, the catalyst loadings are usually 1−5 mol %.[15] The high catalytic efficiency of the small gold cluster reported by Corma provided an alternative approach in reaching active gold catalysts with a low loading. Meanwhile, very recently, Hashmi reported a highly active mononuclear gold(I) catalyst which could promote the alkyne activation at a 0.01 ppm loading.[16] Thus, at this time, it is uncertain whether the gold cluster or the 'genuine' gold(I) cation serves as the active catalytic species in this Nakamura reaction.

In conclusion, we have unveiled synergistic gold/gallium catalysis in promoting an ambient Nakamura reaction. This is the first general protocol for an intermolecular reaction between 1,3-dicarbonyl compounds and unactivated alkynes at room temperature. Combining the low Au loading (500 ppm and as low as 100 ppm), the reported Au/Ga system provided a new practical approach to achieve a highly active catalytic system for alkyne activation. New reactivity with this bimetallic system for other challenging transformations (if using typical $[L-Au]^+$) is expected. A detailed mechanistic investigation is currently underway in our group.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Experimental details, NMR data, and crystal data CCDC 933135. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: Xiaodong.Shi@mail.wvu.edu.

Notes

The authors declare no competing financial interest.

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■ REFERENCES

(1) (a) *Modern Gold Catalyzed Synthesis*; Hashmi, A. S. K., Toste, F. D., Ed.; Wiley-VCH: Weinheim, 2012. (b) Hashmi, A. S. K.; Rudolph, M. *Chem. Soc. Rev.* **2012**, *41*, 2448. (c) Gorin, D. J.; Sherry, B. D.; Toste, F. D. *Chem. Rev.* **2008**, *108*, 3351. (d) Arcadi, A. *Chem. Rev.* **2008**, *108*, 3266. (e) Jiménez-Núñez, E.; Echavarren, A. M. *Chem. Rev.* **2008**, *108*, 3326. (f) Widenhoefer, R. A. *Chem.—Eur. J.* **2008**, *14*, 5382. (g) Hashmi, A. S. K. *Chem. Rev.* **2007**, *107*, 3180. (h) Fürstner, A.; Davies, P. W. *Angew. Chem., Int. Ed.* **2007**, *46*, 3410. (i) Zhang, L.; Sun, J.; Kozmin, S. A. *Adv. Synth. Catal.* **2006**, *348*, 2271. (j) Hashmi, A. S. K.; Hutchings, G. J. *Angew. Chem., Int. Ed.* **2006**, *45*, 7896.

(2) Oliver-Meseguer, J.; Cabrero-Antonino, J. R.; Domínguez, I.; Leyva-Pérez, A.; Corma, A. *Science* **2012**, *338*, 1452.

(3) Wang, W.; Hammond, G. B.; Xu, B. *J. Am. Chem. Soc.* **2012**, *134*, 5697.

(4) (a) Nakamura, M.; Endo, K.; Nakamura, E. *J. Am. Chem. Soc.* **2003**, *125*, 13002. (b) Endo, K.; Hatakeyama, T.; Nakamura, M.; Nakamura, E. *J. Am. Chem. Soc.* **2007**, *129*, 5264. An enantioseletive version has been reported: (c) Fujimoto, T.; Endo, K.; Tsuji, H.; Nakamura, M.; Nakamura, E. *J. Am. Chem. Soc.* **2008**, *130*, 4492.

(5) (a) Kennedy-Smith, J. J.; Staben, S. T.; Toste, F. D. *J. Am. Chem. Soc.* **2004**, *126*, 4526. (b) Staben, S. T.; Kennedy-Smith, J. J.; Toste, F. D. *Angew. Chem., Int. Ed.* **2004**, *43*, 5350.

(6) Allen, A. E.; MacMillan, D. W. C. *Chem. Sci.* **2012**, *3*, 633.

(7) (a) Kuninobu, Y.; Kawata, A.; Takai, K. *Org. Lett.* **2005**, *7*, 4823. (b) Tsuji, H.; Fujimoto, T.; Endo, K.; Nakamura, M.; Nakamura, E. *Org. Lett.* **2008**, *10*, 1219. (c) Onodera, G.; Kato, M.; Kawano, R.; Kometani, Y.; Takeuchi, R. *Org. Lett.* **2009**, *11*, 5038. (d) Tsuji, H.; Tanaka, I.; Endo, K.; Yamagata, K.-i.; Nakamura, M.; Nakamura, E. *Org. Lett.* **2009**, *11*, 1845. (e) Pennington-Boggio, M. K.; Conley, B. L.; Williams, T. J. *J. Organomet. Chem.* **2012**, *716*, 6. (f) Murahashi, S.; Naota, T.; Nakano, Y. *Synlett* **2009**, *20*, 3355. (g) Cheung, H. W.; So, C. M.; Pun, K. H.; Zhou, Z.; Lau, C. P. *Adv. Synth. Catal.* **2011**, *353*, 411.

(8) (a) Duan, H.; Sengupta, S.; Petersen, J. L.; Akhmedov, N. G.; Shi, X. *J. Am. Chem. Soc.* **2009**, *131*, 12100. (b) Chen, Y.; Yan, W.; Akhmedov, N. G.; Shi, X. *Org. Lett.* **2009**, *12*, 344. (c) Wang, D.; Ye, X.; Shi, X. *Org. Lett.* **2010**, *12*, 2088. (d) Wang, D.; Gautam, L. N. S.; Bollinger, C.; Harris, A.; Li, M.; Shi, X. *Org. Lett.* **2011**, *13*, 2618. (e) Wang, Q.; Aparaj, S.; Akhmedov, N. G.; Petersen, J. L.; Shi, X. *Org. Lett.* **2012**, *14*, 1334. (f) Wang, D.; Cai, R.; Sharma, S.; Jirak, J.; Thummanapelli, S. K.; Akhmedov, N. G.; Zhang, H.; Liu, X.; Petersen, J. L.; Shi, X. *J. Am. Chem. Soc.* **2012**, *134*, 9012.

(9) Luzung, M. R.; Markham, J. P.; Toste, F. D. *J. Am. Chem. Soc.* **2004**, *126*, 10858.

(10) For use of the combination of gold and a Lewis acid as a catalytic system, see: (a) Wang, Y.; Liu, L.; Zhang, L. *Chem. Sci.* **2013**, *4*, 739. (b) Wang, X.; Yao, Z.; Dong, S.; Wei, F.; Wang, H.; Xu, Z. *Org. Lett.* **2013**, *15*, 2234 and references cited therein.

(11) For a dual catalytic system involving gold and a second metal, see: (a) Shi, Y.; Peterson, S. M.; Haberaecker, W. W., III; Blum, S. A. *J. Am. Chem. Soc.* **2008**, *130*, 2168. (b) Lauterbach, T.; Livendahl, M.; Rosellón, A.; Espinet, P.; Echavarren, A. M. *Org. Lett.* **2010**, *12*, 3006. (c) Panda, B.; Sarkar, T. K. *Chem. Commun.* **2010**, *46*, 3131. (d) Hirner, J. J.; Shi, Y.; Blum, S. A. *Acc. Chem. Res.* **2011**, *44*, 603. (e) Weber, D.; Gagné, M. R. *Chem. Commun.* **2011**, *47*, 5172. (f) Hashmi, A. S. K.; Lothschütz, C.; Döpp, R.; Ackermann, M.; Becker, J. B.; Rudolph, M.; Scholz, C.; Rominger, F. *Adv. Synth. Catal.* **2012**, *354*, 133. For a conceptually novel use of a bimetallic system in Conia-ene reaction, see: (g) Gao, Q.; Zheng, B.-F.; Li, J.-H.; Yang, D. *Org. Lett.* **2005**, *7*, 2185.

(12) (a) Although gallium(III) halides (Cl, Br, and I) can serve as a π-acid in promoting alkyne-participating transformations, there have been no reports using $Ga(OTf)_3$ as a π-acid toward alkyne activation. Gandon reported a $GaCl_3$-catalyzed cycloisomerization/Friedel—Crafts tandem reaction: Li, H.-J.; Guillot, R.; Gandon, V. *J. Org. Chem.* **2010**, *75*, 8435. (b) However, this reaction cannot be catalyzed by $Ga(OTf)_3$. For a recent review on $Ga(OTf)_3$, see: Prakash, G. K. S.; Mathew, T.; Olah, G. A. *Acc. Chem. Res.* **2012**, *45*, 565.

(13) Low yield (<5%) was obtained with 1% HOTf.

(14) Unidentified products were obtained. This could be caused by $Ga(OTf)_3$-induced olefin isomerization.

(15) (a) Hashmi, A. S. K. *Science* **2012**, *338*, 1434. (b) Marion, N.; Ramón, R. S.; Nolan, S. P. *J. Am. Chem. Soc.* **2009**, *131*, 448.

(16) Jaimes, M. C. B.; Böhling, C. R. N.; Serrano-Becerra, J. M.; Hashmi, A. S. K. *Angew. Chem., Int. Ed.* **2013**, *52*, 7963.