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Synthesis of Spiroaminals and Spiroketals with Bimetallic Relay Catalysis

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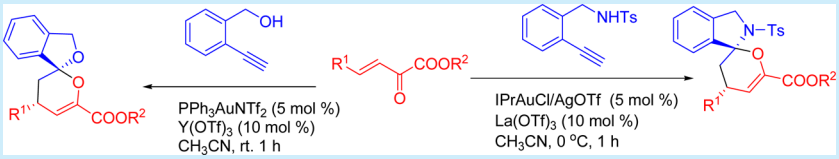
Supporting Information



ABSTRACT: A novel tandem metal relay catalytic system was developed by combining gold-catalyzed cycloisomerization with an early transition-metal-catalyzed inverse-electron-demand hetero-Diels–Alder (IED-HDA) reaction. Various biologically important spiroaminals and spiroketals were obtained with very high efficiency under mild conditions.

In every complex molecule or natural product synthesis, unstable, fragile, or arduously accessible subunits pose a challenge. Spiroketals and aminals are such structural units which are widely present in many bioactive molecules.[1]

Spiroketal containing natural products are widely found in insect pheromones, plants, bacterial, and marine sources. Many famous examples include okadaic acid,[2] berkelic acid,[3] altohyrtin,[4] aigialospirol,[5] and avermectin (Figure 1).[6] General

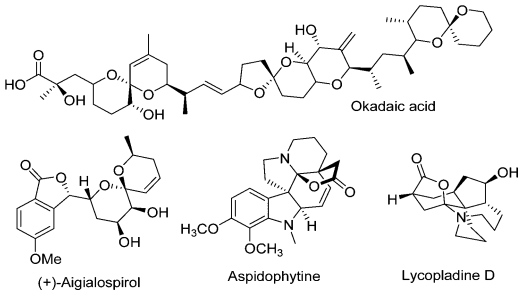


Figure 1. Natural products containing spiroketals and spiro-N,O-aminals.

strategies to access this key motif are through Bronsted acid or transition metal catalyzed intramolecular spiroacetalization of prefunctionalized substrates. For example, the Aponick group reported efficient gold- or palladium-catalyzed spiroketalization reactions of monopropargylic triols or ketoallylic diols.[7a,b] List[7d] and Nagorny[7e] independently reported enantioselective spiroketalization of hydroxyalkyl-substituted enol ethers by use of chiral phosphoric acid as the catalyst. Recently Barluenga[8] reported a palladium-catalyzed three-component cascade reaction of salicylaldehyde for the synthesis of spiroketals, and the Gong group[9] developed the asymmetric reaction using metal/phosphoric acid combined catalysis. However, unlike spiroketals, the synthesis of spiro-N,O-aminals has been much less explored. Very recently the Hashmi group reported an efficient gold-catalyzed tandem reaction toward tricyclic cagelike N,O-aminals.[10] Many N,O-aminals containing molecules such as pederin,[11a] psymberin,[11b,c] and aspidophytine[11d] showed important biological activities, thus the development of an efficient synthetic methodology toward spiro-N,O-aminals from readily available starting materials is in great demand. Herein, we report a bimetallic gold/early transition metal relay catalytic system for the synthesis of spiro-N,O-aminals and spiroketals. This process exhibits very high efficiency, high chemoselectivity and diastereoselectivity, and high atom and step economy.

Earlier, we reported an efficient gold/Lewis acid relay catalysis system[12] toward fused bicyclic aminals by combining π-acid gold catalysis[13] with another σ metal Lewis acid.[14] In this gold participating cascade reaction,[12a] the alkyne amines **2** underwent a gold-catalyzed 5-exo-dig intramolecular hydroamination cyclization to afford the enamide **M1**, followed by internal isomerization to enamide **M2**, and then reacted with another Lewis acid activated electrophile **1** through HDA reaction[15] to produce the fused bicyclic aminals (Scheme 1). Considering the biological and synthetic importance of spiroaminals and spiroketals, we were interested in developing an efficient method toward this type of molecules through bimetallic catalysis. Unfortunately, all efforts to obtain the spirocycle as the major product by fine-tuning the reaction conditions were unsuccessful. We reasoned that to obtain the spirocyclic product, the key issue is to inhibit the isomerization reaction. We therefore replaced substrate **2** by alkyne amine **3**, in which two saturated carbons were replaced by a benzene

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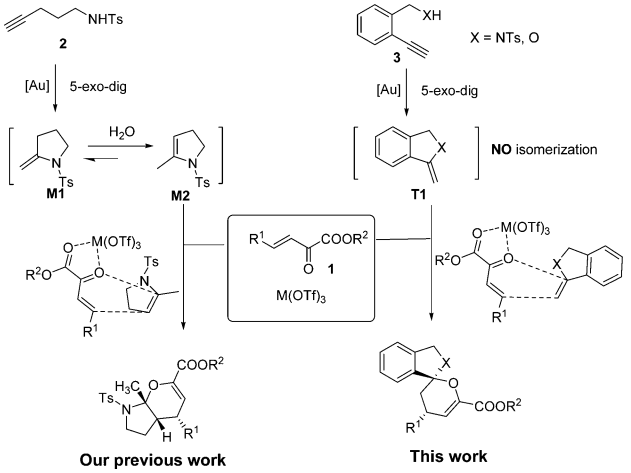
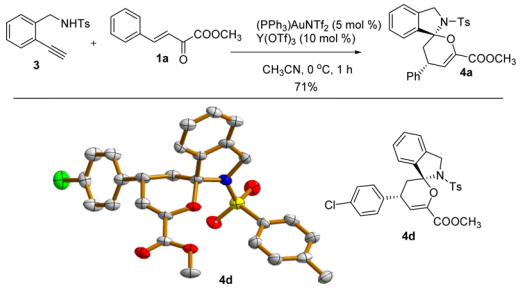
Scheme 1. Concept of the Bimetallic Lewis Acid Catalyzed Cascade Reaction



ring. In this way, the inward isomerization of the generated enamide **T1** is blocked, thus making it possible to react with activated electrophiles to generate spirocyclic products (Scheme 1).

To test this hypothesis, alkyne **3** and unsaturated keto-ester **1a** were subjected to this cascade reaction in the presence of $(PPh_3)AuNTf_2$ and $Y(OTf)_3$ in CH_3CN at room temperature (Scheme 2). It turned out to be a very messy reaction mixture.

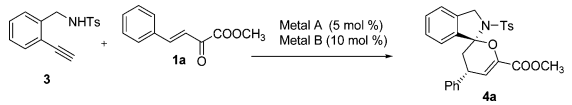
Scheme 2. Initial Formation of the Spiro-N,O-Aminal



To our delight, when we lowered the reaction temperature to 0 °C, the target spiro-N,O-aminal **4a** was isolated in 71% yield. The structure and stereochemistry were unambiguously characterized by NMR, mass spectrometry, and single X-ray crystallography. Remarkably, the diastereoselectivity was very good and only single endodiastereomer was detected in this reaction, which agrees well with the proposed transition state in Scheme 1.

Encouraged by these results, we continued to optimize the reaction conditions to develop an efficient bimetallic Lewis acid catalyzed system toward spiro aminals (Table 1). A series of different gold catalysts were examined (entries 1–5), and it was found that the combination of an NHC carbene ligated gold catalyst with AgOTf afforded the product in the highest yield (72%, entry 2). Other commonly used gold catalysts such as $AuCl{\cdot}PPh_3/AgOTf$, IMesAuCl/AgOTf, $AuCl(CH_3SCH_3)$, AuCl, and $AuCl_3$ resulted in lower yields (see Supporting Information). Different counterions were also explored and could not give better results (entry 2 vs entries 7, 8). Then we investigated different early transition metals such as $In(OTf)_3$, $Ga(OTf)_3$, $Sc(OTf)_3$, $La(OTf)_3$, and $Bi(OTf)_3$ together with the optimal gold catalyst (entries 9–13). Among all of them,

Table 1. Optimization of Reaction Conditions[a]



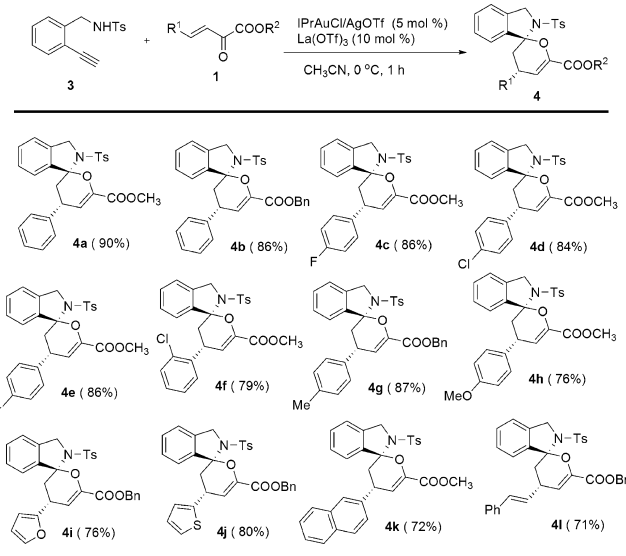
	catalyst			
entry	A	B	solvent	yield%[b]
1	PPh_3AuNTf_2	$Y(OTf)_3$	CH_3CN	71
2	IPrAuCl/AgOTf	$Y(OTf)_3$	CH_3CN	72
3	IMesAuCl/AgOTf	$Y(OTf)_3$	CH_3CN	46
4	$AuCl{\cdot}PPh_3/AgOTf$	$Y(OTf)_3$	CH_3CN	64
5	$AuCl(CH_3SCH_3)$	$Y(OTf)_3$	CH_3CN	14
6	AgOTf	$Y(OTf)_3$	CH_3CN	0
7	$IPrAuCl/AgSbF_6$	$Y(OTf)_3$	CH_3CN	64
8	$IPrAuCl/AgNTf_2$	$Y(OTf)_3$	CH_3CN	57
9	IPrAuCl/AgOTf	$In(OTf)_3$	CH_3CN	41
10	IPrAuCl/AgOTf	$Ga(OTf)_3$	CH_3CN	37
11	IPrAuCl/AgOTf	$Sc(OTf)_3$	CH_3CN	37
12	**IPrAuCl/AgOTf**	**$La(OTf)_3$**	**CH_3CN**	**90**
13	IPrAuCl/AgOTf	$Bi(OTf)_3$	CH_3CN	messy
14	IPrAuCl/AgOTf	$La(OTf)_3$	CH_2Cl_2	<10
15	IPrAuCl/AgOTf	$La(OTf)_3$	toluene	<10
16	IPrAuCl/AgOTf	–	CH_3CN	trace
17	–	$La(OTf)_3$	CH_3CN	0

[a]Reaction conditions: **3** (0.1 mmol), **1a** (0.12 mmol), catalyst **A** (5 mol %), catalyst **B** (10 mol %), solvent (1 mL) at 0 °C. [b]Isolated yield.

$La(OTf)_3$ was the best choice, and the target spiro-aminal **4a** was isolated in 90% yield. Control experiments confirmed that both the gold catalyst and $La(OTf)_3$ are necessary in this process (entries 16, 17). Without the early transition metal, a very messy reaction was observed; only a trace amount of the product was detected on TLC, and no product was formed without the gold catalyst.

With the optimized conditions established, the substrate scope was next examined (Scheme 3). The β,γ- unsaturated-α-keto-esters with different aromatic substituents at the γ-position

Scheme 3. Scope of the Au(I)–La(III) Catalyzed Cascade Reaction for Synthesis of Spiro-aminals[a]



[a]Reaction conditions: **3** (0.2 mmol), **1** (0.24 mmol), IPrAuCl/AgOTf (5 mol %), $La(OTf)_3$ (10 mol %), CH_3CN (2 mL) at 0 °C for 1 h.

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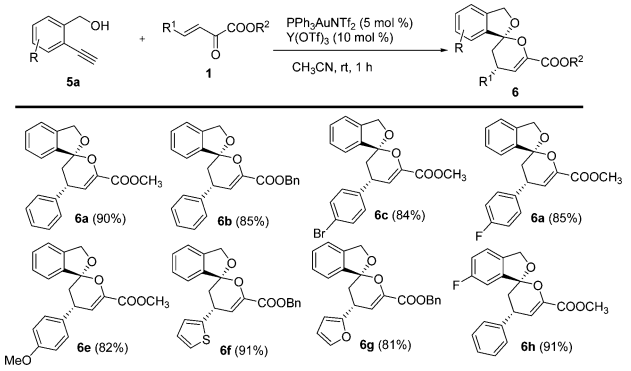
reacted smoothly with alkyne amine **3** to give the spiro-N,O-aminal **4** in good to excellent yields in less than 1 h. The diastereoselectivity was very good in all these reactions, and only the endo isomers were detected. Different ester groups and halogen groups at the *para* or *ortho* position of the phenyl ring did not affect the reaction (**4a**–**4f**). Substrates bearing an electron-donating group such as methyl and methoxyl were also suitable substrates, giving the corresponding spiro-aminals in 87% and 76% yield respectively (**4g**, **4h**). In addition, more sensitive substituents such as styryl, 2-furyl, and 2-thienyl were well tolerated in this mild transformation and the corresponding products were obtained in 71–80% yields (**4i**, **4j**, **4l**).

By simply switching the nucleophilic nitrogen to oxygen in substrate **3**, we are able to obtain spiroketals instead following this strategy. Through optimization, the desired spiroketal **6a** could be obtained in 90% yield in the presence of PPh_3AuNTf_2 (5 mol %) and $Y(OTf)_3$ (10 mol %) in acetonitrile at rt. If the $La(OTf)_3$ (the optimal Lewis acid for nitrogen-based substrates) was used, a slightly lower yield (71%) was obtained (for details, see Supporting Information). A series of unsaturated keto-esters were also subjected to these reaction conditions and gave the corresponding spiroketal in very good yields (82–91%) in 1 h (Scheme 4). The diastereoselectivities

Scheme 4. Scope of the Au(I)–Y(III) Catalyzed Cascade Reaction for Synthesis of Spiroketals[a]



[a]Reaction conditions: **5a** (0.2 mmol), **1** (0.24 mmol), PPh_3AuNTf_2 (5 mol %), $Y(OTf)_3$ (10 mol %), CH_3CN (2 mL) at rt for 1 h.

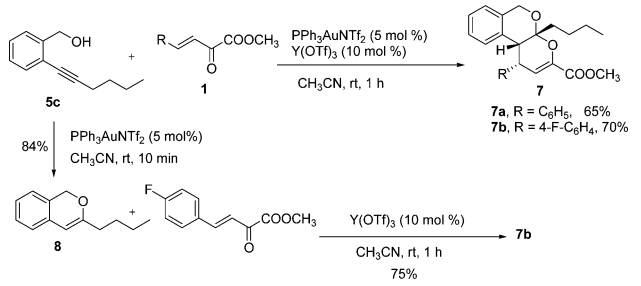
were also excellent. Different halogens at different positions, electron-donating groups, and heterocyclic substituents were also well tolerated in the transformation.

To further explore the scope of this methodology, we investigated the reactivity of the internal akyne **5c** bearing a terminal *n*-butyl group. Under standard conditions, fused bicyclic ketal **7** was obtained instead of spiroketals (Scheme 5). These results were not surprising, because this type of substrate went through 6-endo-dig cyclization more easily than the above 5-exo-dig mode.[16]

In order to better understand the reaction mechanism, the stepwise reactions were examined.[17] With the gold catalyst only, the alkyne **5c** could generate the alkene ether **8** in 84% yield in 10 min. This intermedate was subjected to an $Y(OTf)_3$ catalyzed HDA reaction, and the target product was formed in 75% yield in 1 h. These results clearly indicated the possible reaction pathway is the gold-catalyzed hydroamination and Lewis acid catalyzed HDA reaction cascade.

In summary, we have developed a new method for the synthesis of spiroaminals and spiroketals based on one-pot

Scheme 5. Cascade or Stepwise Reaction of the Internal Alkyne



gold/Lewis acid relay catalysis. The features of this protocol include very high efficiency, excellent diastereoselectivity, 100% atom economy, and simple one-pot operation which does not require an inert atmosphere. Application of this bimetallic strategy to other reactions is underway in our laboratory.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures, characterization data, and NMR spectra for new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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■ REFERENCES

(1) (a) For reviews of spiroketals, see: (a) Perron, F.; Albizati, K. F. *Chem. Rev.* **1989**, *89*, 1617. (b) Mead, K. T.; Brewer, B. N. *Curr. Org. Chem.* **2003**, *7*, 227. (c) Aho, J. E.; Pihko, P. M.; Rissa, T. K. *Chem. Rev.* **2005**, *105*, 4406.

(2) Tachibana, K.; Scheuer, P. J.; Tsukitani, Y.; Kikuchi, H.; Van Engen, D.; Clardy, J.; Gopichand, Y.; Schmitz, F. J. *J. Am. Chem. Soc.* **1981**, *103*, 2469.

(3) (a) Stierle, A. A.; Stierle, D. B.; Kelly, K. *J. Org. Chem.* **2006**, *71*, 5357. (b) Liu, J.; De Brabander, J. K. *J. Am. Chem. Soc.* **2009**, *131*, 12562. (c) Fananás, F. J.; Mendoza, A.; Arto, T.; Temelli, B.; Rodriguez, F. *Angew. Chem., Int. Ed.* **2012**, *51*, 4930.

(4) (a) Kobayashi, M.; Aoki, S.; Sakai, H.; Kawazoe, K.; Kihara, N.; Sasaki, T.; Kitagawa, I. *Tetrahedron Lett.* **1993**, *34*, 2795. (b) Evans, D. A.; Coleman, P. J.; Dias, L. C. *Angew. Chem., Int. Ed.* **1997**, *36*, 2738.

(5) (a) Vongvilai, P.; Isaka, M.; Kittakoop, P.; Srikitikulchai, P.; Kongsaeree, P.; Thebtaranonth, Y. *J. Nat. Prod.* **2004**, *67*, 457.

(6) Pitterna, T.; Cassayre, J.; Hüter, O. F.; Jung, P. M. J.; Maienfisch, P.; Kessabi, F. M.; Quaranta, L.; Tobler, H. *Bioorg. Med. Chem.* **2009**, *17*, 4085.

(7) (a) Aponick, A.; Li, C.-Y.; Palmes, J. A. *Org. Lett.* **2009**, *11*, 121. (b) Palmes, J. A.; Paioti, P. H. S.; de Souza, L. P.; Aponick, A. *Chem.—Eur. J.* **2013**, *19*, 11613. (c) Wang, X.; Han, Z.; Wang, Z.; Ding, K. *Angew. Chem., Int. Ed.* **2012**, *51*, 936. (d) Čorić, I.; List, B. *Nature* **2012**, *483*, 315. (e) Sun, Z.; Winschel, G. A.; Borovika, A.; Nagorny, P.

dx.doi.org/10.1021/ol4033286 | *Org. Lett.* XXXX, XXX, XXX–XXX

J. Am. Chem. Soc. **2012**, *134*, 8074. (f) Ho, J. H. H.; Choy, S. W. S.; Macgregor, S. A.; Messerle, B. A. *Organometallics* **2011**, *30*, 5978.

(8) (a) Barluenga, J.; Mendoza, A.; Rodriguez, F.; Fananás, F. J. *Angew. Chem., Int. Ed.* **2009**, *48*, 1644. For Povarov reaction type multicomponent reactions from alkynol, see: (b) Barluenga, J.; Mendoza, A.; Rodriguez, F.; Fananás, F. J. *Angew. Chem., Int. Ed.* **2008**, *47*, 7044. (c) Barluenga, J.; Mendoza, A.; Rodriguez, F.; Fananás, F. J. *Chem.—Eur. J.* **2008**, *14*, 10892. (d) Barluenga, J.; Calleja, J.; Mendoza, A.; Rodriguez, F.; Fananás, F. J. *Chem.—Eur. J.* **2010**, *16*, 7110.

(9) (a) Wu, H.; He, Y.-P.; Gong, L.-Z. *Org. Lett.* **2013**, *15*, 460. For represneted Au/organo relay catalysis, see: (b) Han, Z.; Chen, D.; Wang, Y.; Guo, R.; Wang, P.; Wang, C.; Gong, L.-Z. *J. Am. Chem. Soc.* **2012**, *134*, 6532. (c) Tu, X.; Gong, L.-Z. *Angew. Chem., Int. Ed.* **2012**, *51*, 11346. (d) Ren, L.; Lei, T.; Ye, J.; Gong, L.-Z. *Angew. Chem., Int. Ed.* **2012**, *51*, 771. (e) Wang, C.; Han, Z.; Luo, H.; Gong, L.-Z. *Org. Lett.* **2010**, *12*, 2266. (f) Han, Z.; Xiao, H.; Chen, X.; Gong, L.-Z. *J. Am. Chem. Soc.* **2009**, *131*, 9182. (g) Wu, X.; Li, M.; Gong, L.-Z. *Acta Chim. Sinica* **2013**, *71*, 1091.

(10) Hashmi, A. S. K.; Bührle, M.; Wölfle, M.; Rudolph, M.; Wieteck, M.; Rominger, F.; Frey, W. *Chem.—Eur. J.* **2010**, *16*, 9846.

(11) (a) Richter, A.; Kocienski, P.; Raubo, P.; Davies, D. E. *Anti-Cancer Drug Des.* **1997**, *12*, 217. (b) Jiang, X.; Williams, N.; De Brabander, J. K. *Org. Lett.* **2007**, *9*, 227. (c) Rech, J. C.; Floreancig, P. E. *Org. Lett.* **2005**, *7*, 5175. (d) He, F.; Bo, Y.; Altom, J. D.; Corey, E. J. *J. Am. Chem. Soc.* **1999**, *121*, 6771. (e) Ishiuchi, K.; Kutota, T.; Hoshino, T.; Kobayashi, J. *Bioorg. Med. Chem.* **2006**, *14*, 5995.

(12) (a) Wang, X.; Yao, Z.; Dong, S.; Wei, F.; Wang, H.; Xu, Z. *Org. Lett.* **2013**, *15*, 2234. For a Cu−Pd relay catalysis, see: (b) Song, C.; Ju, L.; Wang, M.; Liu, P.; Zhang, Y.; Wang, J.; Xu, Z. *Chem.—Eur. J.* **2013**, *19*, 3584. (c) Song, C.; Dong, S.; Feng, L.; Peng, X.; Wang, M.; Wang, J.; Xu, Z. *Org. Biomol. Chem.* **2013**, *11*, 6258. (d) Song, C.; Sun, D.; Peng, X.; Bai, J.; Zhang, R.; Hou, S.; Wang, J.; Xu, Z. *Chem. Commun.* **2013**, *49*, 9167.

(13) For reviews on gold catalysis, see: (a) Zhang, L.; Sun, J.; Kozmin, S. A. *Adv. Synth. Catal.* **2006**, *348*, 2271. (b) Fürstner, A.; Davies, P. W. *Angew. Chem., Int. Ed.* **2007**, *46*, 3410. (c) Li, Z.; Brouwer, C.; He, C. *Chem. Rev.* **2008**, *108*, 3239. (d) Jiménez- Núnez, E.; Echavarren, A. M. *Chem. Rev.* **2008**, *108*, 3326. (e) Gorin, D. J.; Sherry, B. D.; Toste, F. D. *Chem. Rev.* **2008**, *108*, 3351. (f) Hashmi, A. S. K.; Rudolph, M. *Chem. Soc. Rev.* **2008**, *37*, 1766. (g) Hashmi, A. S. K. *Angew. Chem., Int. Ed.* **2010**, *49*, 5232. (h) Aubert, C.; Fensterbank, L.; Garcia, P.; Malacria, M.; Simonneau, A. *Chem. Rev.* **2011**, *111*, 1954. (i) Patil, N. T.; Yamamoto, Y. *Chem. Rev.* **2008**, *108*, 3395. (j) Krause, N.; Winter, C. *Chem. Rev.* **2011**, *111*, 1994. (k) Rudolph, M.; Hashmi, A. S. K. *Chem. Soc. Rev.* **2012**, *41*, 2448. For recent examples, see: (l) Tkatchouk, E.; Mankad, N. P.; Benitez, D.; Goddard, W. A.; Toste, F. D. *J. Am. Chem. Soc.* **2011**, *133*, 14293. (m) Pagar, V. V.; Jadhav, A. M.; Liu, R.-S. *J. Am. Chem. Soc.* **2011**, *133*, 20728. (n) Chen, Y.; Chen, M.; Liu, Y. *Angew. Chem., Int. Ed.* **2012**, *51*, 6493. (o) Conyers, R. C.; Gung, B. W. *Chem.—Eur. J.* **2013**, *19*, 654. (p) Liu, F.; Qian, D.; Li, L.; Zhao, X.; Zhang, J. *Angew. Chem., Int. Ed.* **2010**, *51*, 6669. (q) Yang, T.; Campbell, L.; Dixon, D. J. *J. Am. Chem. Soc.* **2007**, *129*, 12070. (r) Ye, L.; He, W.; Zhang, L. *Angew. Chem., Int. Ed.* **2011**, *50*, 3236. (s) Ye, L.; Cui, L.; Zhang, G.; Zhang, L. *J. Am. Chem. Soc.* **2010**, *132*, 3258. (t) 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. (u) Wang, Q.; Aparaj, S.; Akhmedov, N. G.; Petersen, J. L.; Shi, X. *Org. Lett.* **2012**, *14*, 1334. (v) Wang, D.; Gautam, L. N. S.; Bollinger, C.; Harris, A.; Li, M.; Shi, X. *Org. Lett.* **2011**, *13*, 2618. (w) Xu, M.; Ren, T.-T.; Li, C.-Y. *Org. Lett.* **2012**, *14*, 4902. (x) Shu, C.; Liu, M.; Sun, Y.; Ye, L. *Org. Lett.* **2012**, *14*, 4958. (y) Cao, Z.; Wang, X.; Tan, C.; Zhao, X.; Zhou, J. *J. Am. Chem. Soc.* **2013**, *135*, 8197.

(14) Another four examples of gold participating cooperative dual metal catalysis, see: (a) Wang, Y.; Liu, L.; Zhang, L. *Chem. Sci.* **2013**, *4*, 739. (b) Egi, M.; Yamaguchi, Y.; Fujiwara, N.; Akai, S. *Org. Lett.* **2008**, *10*, 1867. (c) Ye, L.; Zhang, L. *Org. Lett.* **2009**, *11*, 3646. (d) Demir, A. S.; Emrullahoglu, M.; Buran, K. *Chem. Commun.* **2010**, *46*, 8032.

(15) (a) Xu, Z.; Liu, L.; Wheeler, K.; Wang, H. *Angew. Chem., Int. Ed.* **2011**, *50*, 3484. (b) Deng, Y.; Liu, L.; Sarkisian, R. G.; Wheeler, K.; Wang, H.; Xu, Z. *Angew. Chem., Int. Ed.* **2013**, *52*, 3663.

(16) (a) Ackermann, M.; Bucher, J.; Rappold, M.; Graf, K.; Rominger, F.; Hashmi, A. S. K. *Chem.—Asian J.* **2013**, *8*, 1786. (b) Hashmi, A. S. K.; Schäfer, S.; Wölfle, M.; Gil, C. D.; Fischer, P.; Laguna, A.; Blanco, M. C.; Gimeno, M. C. *Angew. Chem., Int. Ed.* **2007**, *46*, 6184. (c) Li, X.; Chianese, A. R.; Vogel, T.; Crabtree, R. H. *Org. Lett.* **2005**, *7*, 5437. (d) Asao, N.; Takahashi, K.; Lee, S.; Kasahara, T.; Yamamoto, Y. *J. Am. Chem. Soc.* **2002**, *124*, 12650.

(17) One reviewer suggested the stepwise reaction to understand the mechanism. Unfortunately, for substrate **3** and **5a**, the preformed enamide or vinyl ether is very reactive and could not be isolated. For dimerization of the enamide, see: Yu, Y.; Shu, C.; Shen, C.; Li, T.; Ye, L. *Chem.—Asian J.* **2013**, *8*, 2920.

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