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Gold-Catalyzed Regiodivergent [2 + 2 + 2]-Cycloadditions of Allenes with Triazines

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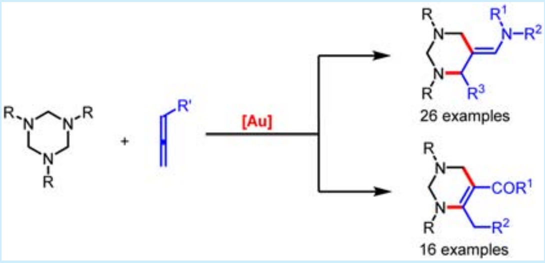
Supporting Information

ABSTRACT: Gold-catalyzed regiodivergent cycloadditions of functionalized allenes with 1,3,5-triazines, providing diverse N-heterocycles in moderate to excellent yields under mild reaction conditions, are reported. Importantly, different types of allenes exhibit distinct selectivity and reactivity for the reactions. Mechanistic investigations reveal that all of the cycloadditions proceed through a stepwise [2 + 2 + 2]-cycloaddition process.



The soft carbophilic character of gold complexes enables them to be ideal catalysts for activating carbon−carbon multiple bonds for a wide range of organic transformations.[1] In particular, cycloadditions of two or more unsaturated components under gold catalysis present important roles for the construction of various cyclic compounds.[2,3] However, the regioselective cycloaddition of the orthogonal π-systems of allenes remains challenging since different regioisomers form during the addition process.[4] Nevertheless, since the properties of allenes have been strongly influenced by the functional groups located at one or both double bonds, the allene involved cycloadditions might be controlled regioselectively.[4]

On the other hand, as stable and readily available surrogates for aryl imines, 1,3,5-tris(aryl)hexahydro-1,3,5-triazines have been utilized as effective reagents in aminomethylation and hydroaminomethylation reactions by incorporating the aminomethyl group into a functionalized molecule. For example, Krische and co-workers described the hydroaminomethylations of allenes and 1,3-dienes through ruthenium-catalyzed processes (Scheme 1, a).[5] Feng and co-workers reported the aminomethylation reaction of β-keto esters/amides by using those triazines as excellent Mannich-type reagents (Scheme 1, a).[6] Recently, Huang and co-workers developed an elegant palladium-catalyzed aminomethylamination of allenes employing tetrabenzylmethanediamine as the key substrate.[7] Our group discovered that 1,3,5-triazines can also serve as formal 1,4-dipoles in gold-catalyzed formal [4 + 1]/[4 + 3]-cycloadditions with diazo compounds.[8] Inspired by former reports and in continuation with our ongoing interest in gold catalysis,[9] we report the gold-catalyzed cycloadditions of 1,3,5-tris(aryl/benzyl)hexahydro-1,3,5-triazines with *N*-allenamides and allenoates, which resulted in the discovery of unprecedented regioselective [2 + 2 + 2]-cycloadditions.

N-Allenamides are versatile building blocks and have been utilized in various gold-catalyzed cycloadditions.[9] Initially, triazine **1a** and allenamide **2a** were utilized as model substrates to achieve the optimal reaction conditions (Table 1). First, without the addition of gold catalyst, the reaction did not react in dichloromethane (DCM) at room temperature (entry 1). The addition of 5 mol % of Ph_3PAuCl afforded **3a** in 47% yield (entry 2). The yield was improved moderately when AgOTf

Scheme 1. Previous Reports and Our Utilization of 1,3,5-Triazines

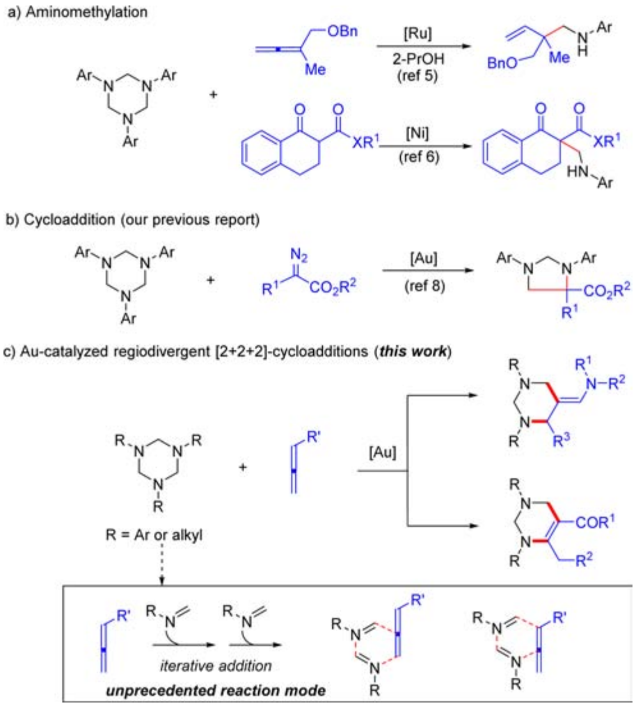


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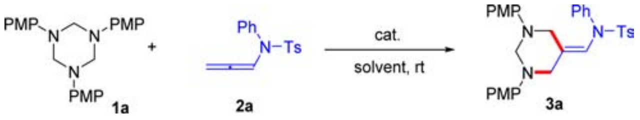
Table 1. Optimization of the Reaction Conditions[a]



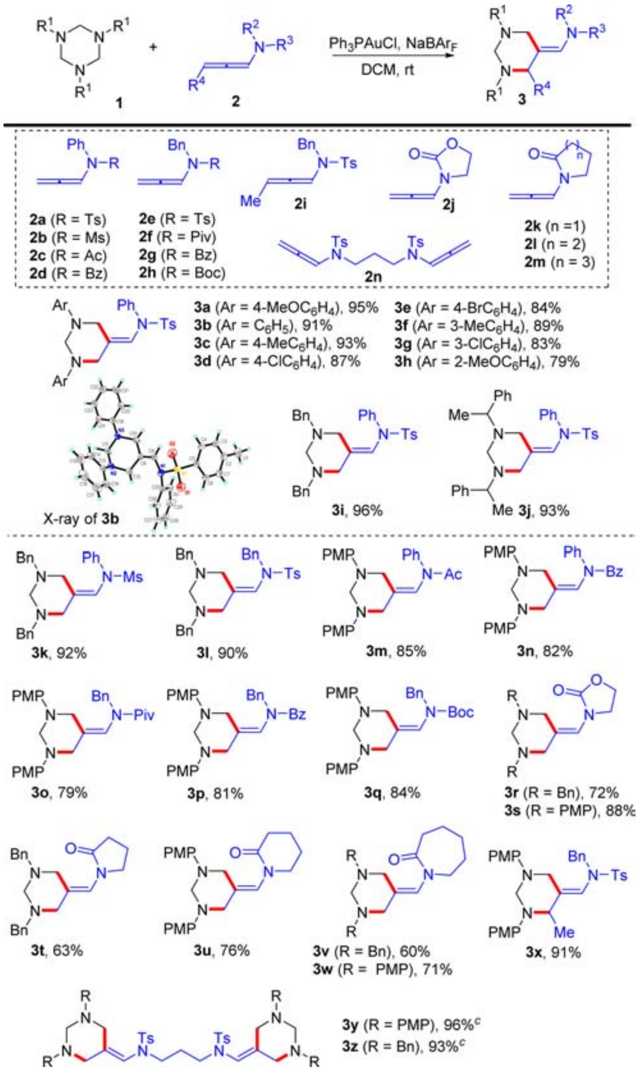
entry	catalyst	additive	solvent	yield[b] (%)
1			DCM	
2	Ph_3PAuCl		DCM	47
3	Ph_3PAuCl	AgOTf	DCM	73
4	Ph_3PAuCl	$AgSbF_6$	DCM	79
5	Ph_3PAuCl	$NaBAr_F$	DCM	95
6	IPrAuCl	$NaBAr_F$	DCM	<10
7	$(PhO)_3PAuCl$	$NaBAr_F$	DCM	91
8	XPhosAuCl	$NaBAr_F$	DCM	82
9	$BINAP(AuCl)_2$	$NaBAr_F$	DCM	73
10	$XantPhos(AuCl)_2$	$NaBAr_F$	DCM	66
11	Ph_3PAuCl	$NaBAr_F$	DCE	81
12	Ph_3PAuCl	$NaBAr_F$	THF	27
13	Ph_3PAuCl	$NaBAr_F$	toluene	56
14	Ph_3PAuCl	$NaBAr_F$	1,4-dioxane	30
15[c]	Ph_3PAuCl	$NaBAr_F$	DCM	56
16[d]	Ph_3PAuCl	$NaBAr_F$	DCM	87

[a] Reaction conditions: **1a** (0.2 mmol), **2a** (0.2 mmol), catalyst (5 mol %), additive (5 mol %), solvent (2.0 mL), rt, 12 h. [b] Isolated yields. [c] At 0 °C, 48 h. [d] Catalyst (2 mol %), 48 h.

and $AgSbF_6$ were used as additives (entries 3 and 4). Gratifyingly, when 5 mol % of $NaBAr_F$ (Ar_F: tetrakis[3,5-bis(trifluoromethyl)phenyl]borate) was added as an additive, the yield of **3a** was increased to 95% (entry 5). Next, different gold catalysts were examined with $NaBAr_F$ as the additive. The N-heterocyclic carbene gold catalyst was inactive in this reaction (entry 6). Other phosphite and phosphine gold catalysts were also examined, delivering **3a** in moderate to good yields (entries 7−10). Next, solvent screening showed that DCM remained the best choice (entries 12−14). Lower temperature or catalyst loading decreased the reaction efficiency (entries 15 and 16).

With the optimal conditions in hand, we next set out to investigate the generality of this reaction (Scheme 2). The reactions of **2a** with different substituted 1,3,5-triaryl-1,3,5-triazines bearing either electron-donating or electron-withdrawing substituents at the aryl moiety all proceeded smoothly to afford the cycloaddition products in good to excellent yields. Typically, tribenzyl-1,3,5-triazine and trimethylbenzyl-1,3,5-triazine both reacted well and delivered the corresponding products **3i** and **3j** in excellent yields. Next, various substituted *N*-allenamides were subjected to this reaction. First, by changing the substituent group from *p*-toluenesulfonyl (Ts) to other groups such as methylsulfonyl (Ms), acetyl (Ac), benzoyl (Bz), pivaloyl (Piv), and *tert*-butoxycarbonyl (Boc), the cycloadditions proceeded well to give the final products in good to excellent yields (**3k**−**q**). Second, the allenes bearing different lactam groups were also tolerated, providing the corresponding products in moderate to good yields (**3r**−**w**). Furthermore, the reaction of **1a** with bis-substituted *N*-allenamide **2i** furnished **3x** in 91% yield. Notably, the bis-allenamide **2n** also worked well in the reaction and afforded **3y** and **3z** in excellent yields. The structure of **3b** was confirmed by X-ray analysis.[10]

Scheme 2. Scope for Reaction of Triazines with Allenamides[a,b]

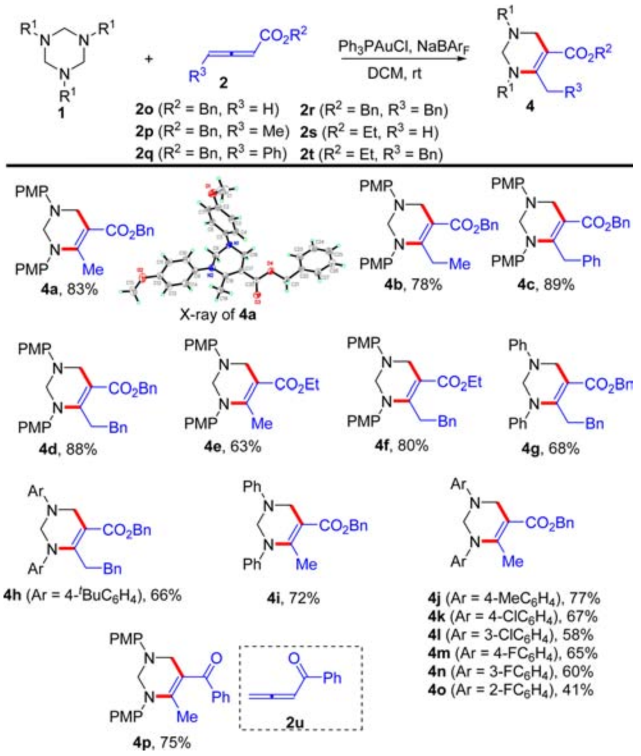


[a] Reaction conditions: **1** (0.2 mmol), **2** (0.2 mmol), Ph_3PAuCl (5 mol %), and $NaBAr_F$ (5 mol %) in DCM (2 mL) at rt for 12 h. [b] Isolated yields. [c] **1** (0.4 mmol) was used.

The electron-deficient allenoates are also versatile intermediates in organic synthesis. In particular, gold-catalyzed cycloisomerizations of allenoates are well-known procedures for the formation of butenolides.[1g,11a,b] Moreover, the reactions of allenoates with imines resulted in the formation of amino esters[11c] or [3 + 2]-cycloaddition products[11d] in the presence of a nucleophilic catalyst. Then the allenoates were examined in the gold-catalyzed cycloadditions (Scheme 3). The reactions of **1a** with different allenoates **2o**−**t** were performed, and the corresponding products **4a**−**f** were isolated in moderate to good yields in 48 h. Various triazines were tested, and the corresponding products were also obtained in moderate to good yields (**4g**−**o**). Notably, the allenic ketone **2u** was also tolerated, and the product **4p** was obtained in 75% yield. The structure of **4a** was confirmed by X-ray analysis.[10]

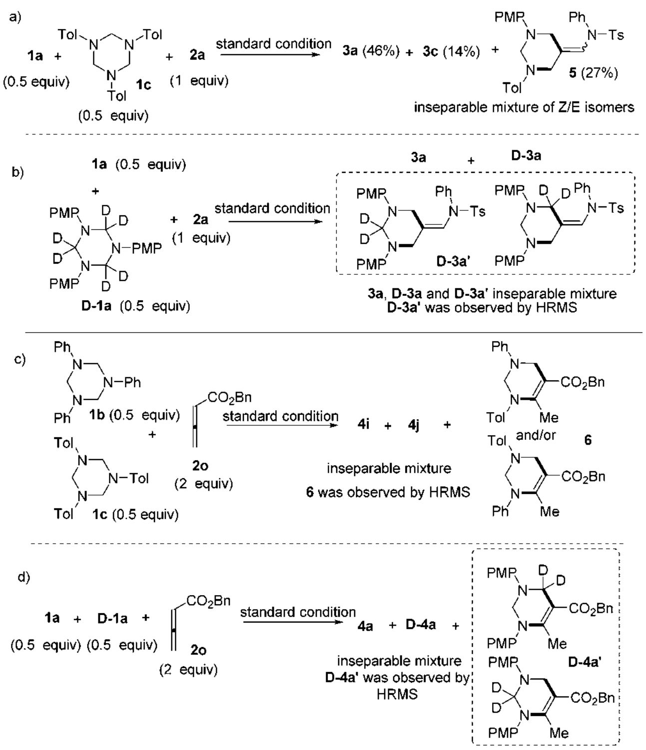
To further understand the cycloaddition processes, control and deuterium-labeling experiments were conducted (Scheme 4). The reaction of **1a** and **1c** with **2a** was performed under standard reaction conditions and afforded **3a** and **3c** in 46% and 13% yields, respectively (Scheme 4a). The cross-cyclization product **5** was also detected as an inseparable *Z*/*E* mixture, which was determined by ^1H NMR and HRMS analysis of the

Scheme 3. Scope for Reaction of Triazines with Allenoates[a,b]



[a]Reaction conditions: **1** (0.2 mmol), **2** (0.4 mmol), Ph$_3$PAuCl (5 mol %), and NaBAr$_F$ (5 mol %) in DCM (2 mL) at rt for 48 h. [b]Yields of isolated products.

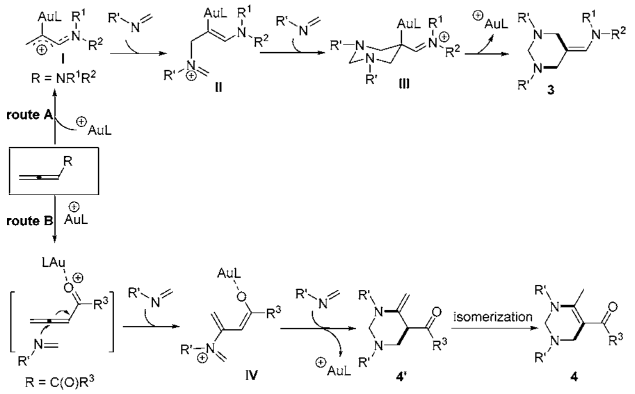
Scheme 4. Control Experiments



crude product. Moreover, the reaction of **1a** and **D-1a** with **2a** delivered the cycloaddition products as an inseparable mixture of **3a**, **D-3a**, and **D-3a′** observed by HRMS analysis (Scheme 4b). Next, the reaction of **1b**, **1c**, and **2o** was conducted, and the cross-cycloaddition product **6** was confirmed by HRMS analysis (Scheme 4c). A similar situation was observed for the reaction of **1a**, **D-1a**, and **2o**. **D-4a′** was determined by NMR and HRMS analysis (Scheme 4d). The above experiments indicated that the formation of six-membered N-heterocycles proceeded through iterative additions of formaldimines with allenes, which is quite different compared with literature reports.[5,6]

On the basis of former investigations, a plausible reaction mechanism has been proposed. As shown in Scheme 5, the reaction of cationic gold complex with *N*-allenamide generates gold species **I** (route A). The nucleophilic addition of formaldimine to **I** produces intermediate **II**. Subsequent reaction with another molecule of formaldimine gives rise to intermediate **III**. Then cyclization and deauration furnish **3** as the final product. Alternatively, as a Lewis acid catalyst, the gold complex can activate the carbonyl group of allenoate (route B). The nucleophilic addition of formaldimine to allenoate (Michael addition) generates intermediate **IV**. Subsequent addition to another molecule of formaldimine and deauration provides **4′**, which would isomerize to **4** as the final product.

Scheme 5. Proposed Reaction Mechanism



In summary, we have developed gold-catalyzed regiodivergent cycloadditions of 1,3,5-triazines with allenes, providing the six-membered N-heterocycles in moderate to excellent yields under mild reaction conditions. Mechanism investigations revealed that these cycloadditions proceed through stepwise and iterative additions of formaldimines to the allene moieties. Importantly, different functionalized allenes present quite different cycloaddition pathways.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b03691.

Experimental procedures along with characterizing data and NMR spectra (PDF)

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Notes

The authors declare no competing financial interest.

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■ REFERENCES

(1) For selected reviews, see: (a) Hashmi, A. S. K.; Hutchings, G. J. *Angew. Chem., Int. Ed.* **2006**, *45*, 7896. (b) Fürstner, A.; Davies, P. W. *Angew. Chem., Int. Ed.* **2007**, *46*, 3410. (c) Hashmi, A. S. K. *Chem. Rev.* **2007**, *107*, 3180. (d) Jiménez-Núñez, 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) Corma, A.; Leyva-Pérez, A.; Sabater, M. J. *Chem. Rev.* **2011**, *111*, 1657. (g) Krause, N.; Winter, C. *Chem. Rev.* **2011**, *111*, 1994. (h) Rudolph, M.; Hashmi, A. S. K. *Chem. Soc. Rev.* **2012**, *41*, 2448. (i) Muratore, M. E.; Homs, A.; Obradors, C.; Echavarren, A. M. *Chem. - Asian J.* **2014**, *9*, 3066. (j) Dorel, R.; Echavarren, A. M. *Chem. Rev.* **2015**, *115*, 9028. (k) Zheng, Z.; Wang, Z.; Wang, Y.; Zhang, L. *Chem. Soc. Rev.* **2016**, *45*, 4448. (l) Pan, F.; Shu, C.; Ye, L.-W. *Org. Biomol. Chem.* **2016**, *14*, 9456.

(2) For reviews on gold-catalyzed cycloadditions of two or more unsaturated components, see: (a) Ma, S.; Yu, S.; Gu, Z. *Angew. Chem., Int. Ed.* **2006**, *45*, 200. (b) López, F.; Mascareñas, J. L. *Beilstein J. Org. Chem.* **2011**, *7*, 1075. (c) López, F.; Mascareñas, J. L. *Beilstein J. Org. Chem.* **2013**, *9*, 2250. (d) Asiri, A. M.; Hashmi, A. S. K. *Chem. Soc. Rev.* **2016**, *45*, 4471.

(3) For selected examples on gold-catalyzed cycloadditions, see: (a) Suárez-Pantiga, S.; Hernández-Díaz, C.; Piedrafita, M.; Rubio, E.; González, J. M. *Adv. Synth. Catal.* **2012**, *354*, 1651. (b) Montserrat, S.; Faustino, H.; Lledós, A.; Mascareñas, J. L.; López, F.; Ujaque, G. *Chem. - Eur. J.* **2013**, *19*, 15248. (c) Bernal-Albert, P.; Faustino, H.; Gimeno, A.; Asensio, G.; Mascareñas, J. L.; López, F. *Org. Lett.* **2014**, *16*, 6196. (d) Ocello, R.; De Nisi, A.; Jia, M.; Yang, Q.-Q.; Monari, M.; Giacinto, P.; Bottoni, A.; Miscione, G. P.; Bandini, M. *Chem. - Eur. J.* **2015**, *21*, 18445. (e) Zheng, Z.; Zhang, L. *Org. Chem. Front.* **2015**, *2*, 1556. (f) Wang, Y.; Zheng, Z.; Zhang, L. *J. Am. Chem. Soc.* **2015**, *137*, 5316. (g) Dorel, R.; Echavarren, A. M. *J. Org. Chem.* **2015**, *80*, 7321. (h) Xu, W.; Wang, W.; Wang, X. *Angew. Chem., Int. Ed.* **2015**, *54*, 9546. (i) Huple, D. B.; Mokar, B. D.; Liu, R.-S. *Angew. Chem., Int. Ed.* **2015**, *54*, 14924. (j) Tokimizu, Y.; Oishi, S.; Fujii, N.; Ohno, H. *Angew. Chem., Int. Ed.* **2015**, *54*, 7862. (k) Nakamura, I.; Gima, S.; Kudo, Y.; Terada, M. *Angew. Chem., Int. Ed.* **2015**, *54*, 7154. (l) Chen, M.; Chen, Y.; Sun, N.; Zhao, J.; Liu, Y.; Li, Y. *Angew. Chem., Int. Ed.* **2015**, *54*, 1200. (m) Shu, C.; Wang, Y.-H.; Zhou, B.; Li, X.-L.; Ping, Y.-F.; Lu, X.; Ye, L.-W. *J. Am. Chem. Soc.* **2015**, *137*, 9567. (n) Li, L.; Zhou, B.; Wang, Y.-H.; Shu, C.; Pan, Y.-F.; Lu, X.; Ye, L.-W. *Angew. Chem., Int. Ed.* **2015**, *54*, 8245. (o) Zhou, A.-H.; He, Q.; Shu, C.; Yu, Y.-F.; Liu, S.; Zhao, T.; Zhang, W.; Lu, X.; Ye, L.-W. *Chem. Sci.* **2015**, *6*, 1265. (p) Mei, L.-Y.; Wei, Y.; Tang, X.-Y.; Shi, M. *J. Am. Chem. Soc.* **2015**, *137*, 8131. (q) Zi, W.; Toste, F. D. *Angew. Chem., Int. Ed.* **2015**, *54*, 14447. (r) Zhang, L.; Wang, Y.; Yao, Z.-J.; Wang, S.; Yu, Z.-X. *J. Am. Chem. Soc.* **2015**, *137*, 13290. (s) Rao, W.; Susanti, D.; Ayers, B. J.; Chan, P. W. H. *J. Am. Chem. Soc.* **2015**, *137*, 6350. (t) Jiménez, T.; Carreras, J.; Ceccon, J.; Echavarren, A. M. *Org. Lett.* **2016**, *18*, 1410. (u) Hosseyni, S.; Wojtas, L.; Li, M.; Shi, X. *J. Am. Chem. Soc.* **2016**, *138*, 3994. (v) Ferrer, S.; Echavarren, A. M. *Angew. Chem., Int. Ed.* **2016**, *55*, 11178. (w) Jin, H.; Tian, B.; Song, X.; Xie, J.; Rudolph, M.; Hashmi, A. S. K. *Angew. Chem., Int. Ed.* **2016**, *55*, 12688. (x) Mokar, B. D.; Huple, D. B.; Liu, R.-S. *Angew. Chem., Int. Ed.* **2016**, *55*, 11892. (y) Jin, H.; Huang, L.; Xie, J.; Rudolph, M.; Rominger, F.; Hashmi, A. S. K. *Angew. Chem., Int. Ed.* **2016**, *55*, 794.

(4) For selected reviews on allene chemistry, see: (a) Ma, S. *Chem. Rev.* **2005**, *105*, 2829. (b) Ma, S. *Acc. Chem. Res.* **2009**, *42*, 1679. (c) López, F.; Mascareñas, J. L. *Chem. Soc. Rev.* **2014**, *43*, 2904. (d) Lledó, A.; Pla-Quintana, A.; Roglans, A. *Chem. Soc. Rev.* **2016**, *45*, 2010. (e) Kitagaki, S.; Inagaki, F.; Mukai, C. *Chem. Soc. Rev.* **2014**, *43*, 2956. (f) Wang, Z.; Xu, X.; Kwon, O. *Chem. Soc. Rev.* **2014**, *43*, 2927. (g) Yang, W.; Hashmi, A. S. K. *Chem. Soc. Rev.* **2014**, *43*, 2941. (h) Zimmer, R.; Reissig, H.-U. *Chem. Soc. Rev.* **2014**, *43*, 2888. (i) Cañeque, T.; Truscott, F. M.; Rodriguez, R.; Maestri, G.; Malacria, M. *Chem. Soc. Rev.* **2014**, *43*, 2916.

(5) (a) Oda, S.; Sam, B.; Krische, M. J. *Angew. Chem., Int. Ed.* **2015**, *54*, 8525. (b) Oda, S.; Franke, J.; Krische, M. J. *Chem. Sci.* **2016**, *7*, 136.

(6) Lian, X.; Lin, L.; Fu, K.; Ma, B.; Liu, X.; Feng, X. *Chem. Sci.* **2017**, DOI: 10.1039/C6SC03902B.

(7) Hu, J.; Xie, Y.; Huang, H. *Angew. Chem., Int. Ed.* **2014**, *53*, 7272.

(8) Zhu, C.; Xu, G.; Sun, J. *Angew. Chem., Int. Ed.* **2016**, *55*, 11867.

(9) For selected gold-catalyzed annulations of allenamides, see: (a) Faustino, H.; López, F.; Castedo, L.; Mascareñas, J. L. *Chem. Sci.* **2011**, *2*, 633. (b) Faustino, H.; Bernal, P.; Castedo, L.; López, F.; Mascareñas, J. L. *Adv. Synth. Catal.* **2012**, *354*, 1658. (c) Zhou, W.; Li, X.-X.; Li, G.-H.; Wu, Y.; Chen, Z. *Chem. Commun.* **2013**, *49*, 3552. (d) Faustino, H.; Alonso, I.; Mascareñas, J. L.; López, F. *Angew. Chem., Int. Ed.* **2013**, *52*, 6526. (e) Li, G.-H.; Zhou, W.; Li, X.-X.; Bi, Q.-W.; Wang, Z.; Zhao, Z.-G.; Hu, W.-X.; Chen, Z. *Chem. Commun.* **2013**, *49*, 4770. (f) Faustino, H.; Varela, I.; Mascareñas, J. L.; López, F. *Chem. Sci.* **2015**, *6*, 2903. (g) Wang, Y.; Zhang, P.; Qian, D.; Zhang, J. *Angew. Chem., Int. Ed.* **2015**, *54*, 14849. (h) Jia, M.; Monari, M.; Yang, Q.-Q.; Bandini, M. *Chem. Commun.* **2015**, *51*, 2320. (i) Wang, Y.; Zhang, P.; Liu, Y.; Xia, F.; Zhang, J. *Chem. Sci.* **2015**, *6*, 5564. (j) Hernández-Díaz, C.; Rubio, E.; González, J. M. *Eur. J. Org. Chem.* **2016**, *2016*, 265.

(10) CCDC 1517335 (**3b**) and CCDC 1517336 (**4a**) contain the supplementary crystallographic data for this paper and can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

(11) (a) Kang, J.-E.; Lee, E.-S.; Park, S.-I.; Shin, S. *Tetrahedron Lett.* **2005**, *46*, 7431. (b) Piera, J.; Krumlinde, P.; Strübing, D.; Bäckvall, J.-E. *Org. Lett.* **2007**, *9*, 2235. (c) Cowen, B. J.; Saunders, L. B.; Miller, S. J. *J. Am. Chem. Soc.* **2009**, *131*, 6105. (d) Xu, Z.; Lu, X. *Tetrahedron Lett.* **1999**, *40*, 549.