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Gold-Catalyzed Cycloisomerization and Diels–Alder Reaction of 1,6-Diyne Esters with Alkenes and Diazenes to Hydronaphthalenes and -cinnolines

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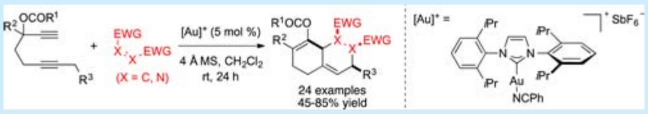
Supporting Information

ABSTRACT: A method for the efficient preparation of hydronaphthalene and -cinnoline derivatives by Au(I)-catalyzed cycloisomerzation of 1,6-diyne esters followed by a Diels–Alder reaction with alkenes or diazenes under mild conditions at room temperature with catalyst loadings as low as 1 mol % is described.



Partially hydrogenated naphthalenes and cinnolines are potentially useful building blocks in organic synthesis and drug discovery programs.[1] As illustrated in Figure 1, the two ring systems are also a key structural feature in a myriad of bioactive natural and pharmacologically interesting compounds.[2] For this reason, the targeting of elegant approaches to these two cyclic compound classes with selective control of substitution patterns by using readily accessible substrates remains among one of the central themes in organic chemistry.[1,3]

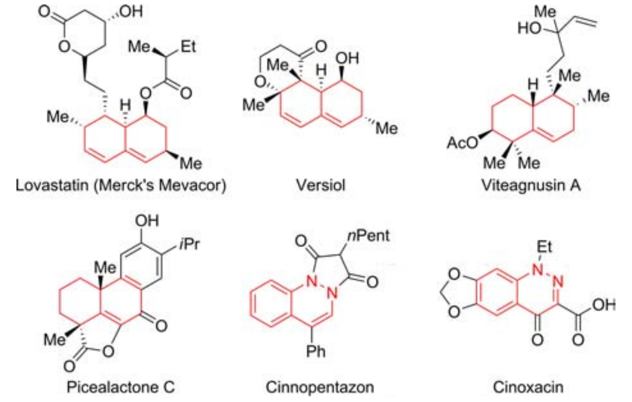
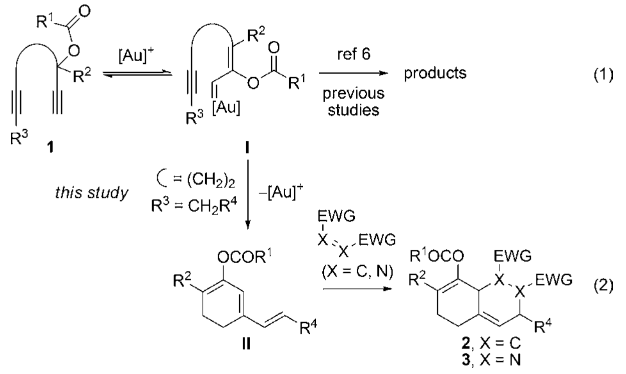


Figure 1. Examples of bioactive natural and synthetic compounds containing the hydronaphthalene and -cinnoline core.

1,*n*-Diyne ester cycloisomerizations catalyzed by Au(I) and Au(III) complexes have been highlighted in a number of recent studies as one of the most efficient and atom-economical methods for complex molecule synthesis in a single step.[4−7] For example, we and others reported the preparation of a variety of carbocyclic and heterocyclic compounds from gold(I)-catalyzed cycloisomerization of 1,*n*-diyne esters triggered by an initial 1,2-acyloxy migration step (Scheme 1, eq 1).[6] Building on these seminal works, we envisioned that the alkenyl gold carbenoid species **I**, derived from Au(I)-catalyzed rearrangement of 1,6-diyne ester **1**, might be susceptible to a pathway involving 1,2-hydride migration followed by deauration when $R^3 = CH_2R^4$ in the substrate (Scheme 1, eq 2). Subsequent Diels–Alder reaction of the ensuing triene intermediate **II** on subjecting it to a dienophile would then be anticipated to deliver the bicyclic product.[8,9] Herein we disclose the details of this chemistry that offers an expedient and chemoselective synthetic route to hydronaphthalenes and -cinnolines in good to excellent yields under mild conditions at room temperature.

Scheme 1. Gold-Catalyzed Reactivities of 1,*n*-Diyne Esters



We commenced our studies by examining the Au(I)-catalyzed reactions of **1a** with *N*-phenyl maleimide to establish

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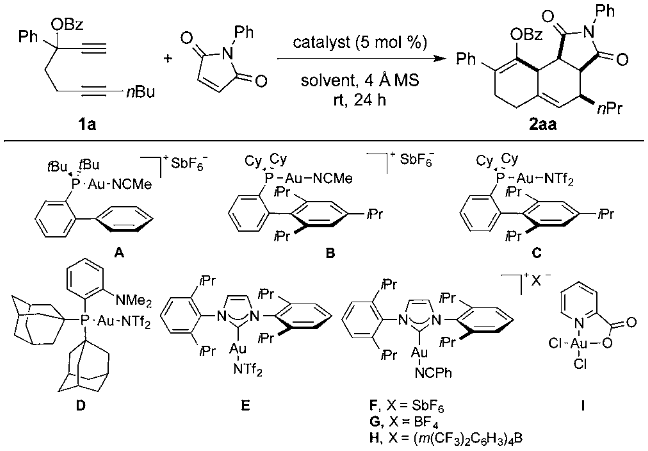
the reaction conditions (Table 1). This initially revealed that treating the 1,6-diyne ester and dienophile (2 equiv) with 5 mol % of Au(I) phosphine catalyst **A** and 4 Å molecular sieves (MS) in dichloromethane at room temperature for 24 h afforded **2aa** in 64% yield (entry 1). Lower product yields of 13−58% were observed when **A** was replaced with the Au(I) phosphine complexes **B**, **C**, **D**, or $Ph_3PAuNTf_2$ as the catalyst (entries 2−5). A similar outcome was found for reactions catalyzed by the NHC-gold(I) (NHC = *N*-heterocyclic carbene) complexes **E**, **G**, and **H** (entries 6, 11, and 12). Subsequent studies showed that repeating the reaction with the NHC−gold(I) complex **F** as the catalyst gave the best result, providing the hydronaphthalene adduct in 80% yield (entry 7). Under these latter catalytic conditions, an increase in the amount of the dienophile from 2 to 3 equiv led to a comparable product yield (entry 8). However, changing the solvent from dichloromethane to either 1,2-dichloroethane or toluene afforded **2aa** in lower yields of 50 and 69% yield (entries 9 and 10).

Table 1. Optimization of Reaction Conditions[a]



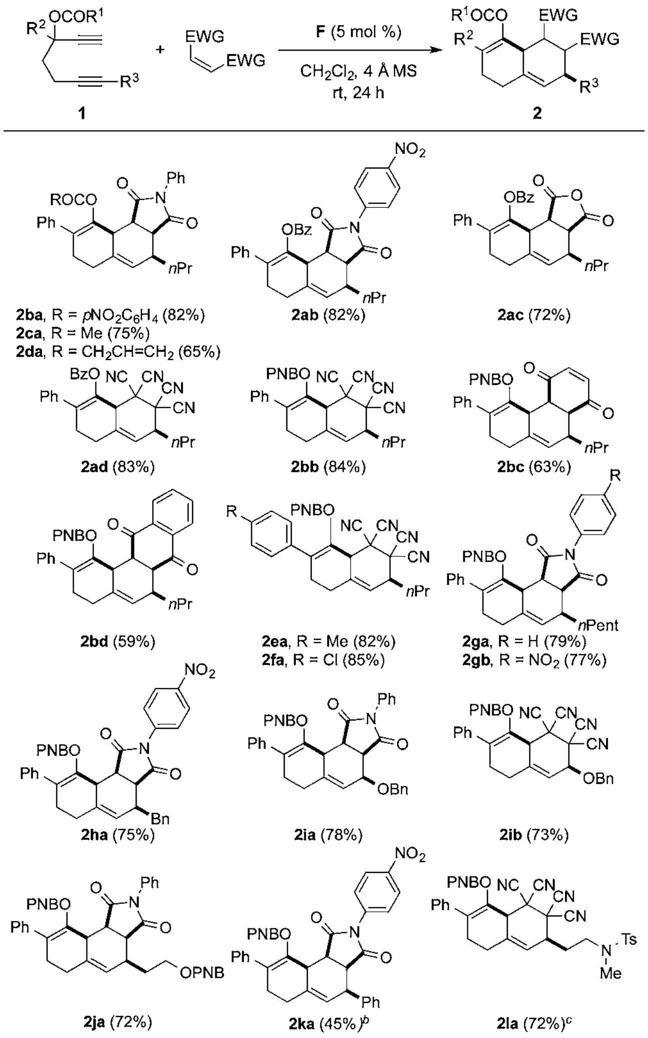
entry	catalyst	solvent	yield (%)[b]
1	**A**	CH_2Cl_2	64
2	**B**	CH_2Cl_2	39
3	**C**	CH_2Cl_2	58
4	**D**	CH_2Cl_2	50
5	$Ph_3PAuNTf_2$	CH_2Cl_2	13
6	**E**	CH_2Cl_2	52
7	**F**	CH_2Cl_2	80
8[c]	**F**	CH_2Cl_2	79
9[d]	**F**	$(CH_2Cl)_2$	50
10[e]	**F**	PhMe	69
11	**G**	CH_2Cl_2	33
12	**H**	CH_2Cl_2	62
13	AuCl	CH_2Cl_2	*f*
14	**I**	CH_2Cl_2	*g*
15	$PtCl_2$	CH_2Cl_2	*f*
16	$AgSbF_6$	CH_2Cl_2	*f*

[a] All reactions were conducted with 0.2 mmol of **1a** and 0.4 mmol of *N*-phenyl maleimide in the presence of 5 mol % of catalyst and 4 Å MS (100 mg) at room temperature for 24 h; Bz = benzyl. [b] Isolated product yield. [c] Reaction performed with 3 equiv of *N*-phenyl maleimide. [d] Reaction temperature = 60 °C. [e] Reaction temperature = 110 °C. [f] No reaction based on TLC or ^1H NMR analysis of the crude reaction mixture. [g] Unknown side product(s) were obtained based on ^1H NMR analysis of the crude mixture.

Similarly, a final set of control reactions mediated by AuCl, the Au(III) complex **I**, $PtCl_2$, or $AgSbF_6$ were found to result in either the recovery of the substrate or a mixture of unidentifiable decomposition products (entries 13−16).

The scope of the present procedure was next assessed with a variety of 1,6-diyne esters and alkenes, and the results are summarized in Scheme 2. Overall, these experiments demonstrated that the Au(I) complex **F**-catalyzed reaction conditions proved to be broad, affording a variety of substituted hydronaphthalenes in 45−85% yield from the corresponding 1,6-diyne esters **1a**−**l** and electron-deficient alkenes. Reactions of 1,6-diyne esters containing a PNB (**1b**), Ac (**1c**), or Alloc (**1d**) instead of a Bz migrating group with *N*-phenyl maleimide were found to proceed well, providing the corresponding bicycloadducts **2ba**−**da** in 65−82% yield. Likewise, the Diels−Alder reaction of the putative triene **II** generated in situ from either **1a** or **1b** with other dienophiles such as *N*-(4-

Scheme 2. Cycloisomerization of 1a−l Catalyzed by F and Diels−Alder Reaction with Alkenes[a]

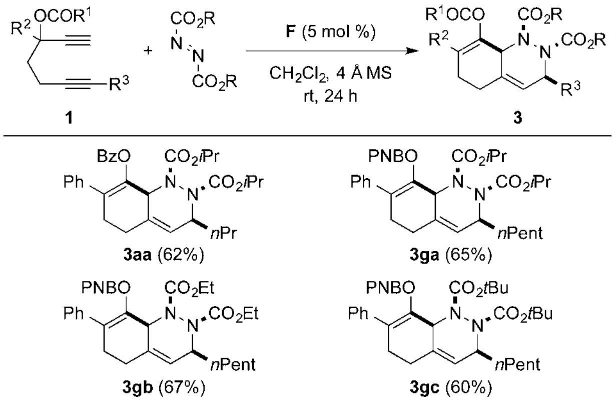


[a] All reactions were conducted at the 0.2 mmol scale with 5 mol % of **F** and 2 equiv of dienophile in dichloromethane in the presence of 4 Å MS (100 mg) at room temperature for 24 h. Values in parentheses denote isolated product yield. [b] Reaction temperature = 60 °C for 18 h followed by the addition of 1 equiv of $AlEt_2Cl$ in 1,2-dichloroethane for 1 h at room temperature. [c] Reaction performed with 5 mol % of **A**.

nitrophenyl)maleimide, maleic anhydride and tetracyanoethylene, 1,4-benzoquinone, and 1,4-naphthoquinone was found to be well-tolerated. In these transformations, the corresponding bi-, tri-, and tetracycloadducts **2ab–bd** were obtained in yields of 59–84%, and with the structure and relative *cis*-stereochemistry of **2ba** also being confirmed by single crystal X-ray analysis.[10] The presence of other aryl motifs (**1e**,**f**) at the *p*-nitrobenzoyl carbon center or an *n*-hexyl (**1g**), phenethyl (**1h**), or ether (**1i**,**j**) group at the R^3 position of the 1,6-diyne ester were found to have minimal influence on the course of the reaction. Under the present protocol, these reactions gave the corresponding hydronaphthalene derivatives **2ea–ja** in 72–85% yield. The only exceptions were the reactions of 1,6-diyne esters containing a Bn (**1k**) or sulfonamide (**1l**) moiety. The former required a reaction temperature of 60 °C for the cycloisomerization step followed by the addition of $AlEt_2Cl$ to promote the Diels–Alder reaction with *N*-(4-nitrophenyl)maleimide to give **2ka** in 45% yield. In the case of the latter, the gold(I) phosphine complex **A**-catalyzed reaction was found to furnish **2la** in 72% yield and with fewer impurities than the analogous transformation mediated by the NHC–gold(I) complex **F**. On other hand, no other cycloaddition products arising from a possible competitive Diels–Alder reaction at the ring diene motif of the posited triene intermediate were observed by TLC analysis and ^{1}H NMR spectroscopic measurements of the crude reaction mixtures. This was further corroborated by repeating the large-scale reaction of **1a** (1.5 g) with *N*-phenyl maleimide imide in the presence of 1 mol % of **F** under the present protocol, which gave **2aa** as the only product in 75% yield (1.7 g).

With 1,6-diyne esters **1a** and **1g** as representative examples, the scope of this new Au(I)-catalyzed cycloisomerization/Diels–Alder reaction method was further examined with diazene dienophiles (Scheme 3). By applying the NHC–gold(I) complex **F**-catalyzed protocol, this revealed the reactions of **1a** and **1g** with diisopropyl azodicarboxylate gave the corresponding hydrocinnolines **3aa** and **3ga** in 62 and 65% yield, respectively. Under similar conditions, experiments of **1g** with diethyl azodicarboxylate or di-*tert*-butyl azodicarboxylate provided the corresponding nitrogen heterocycles **3gb** and **3gc** in respective yields of 67 and 60%.

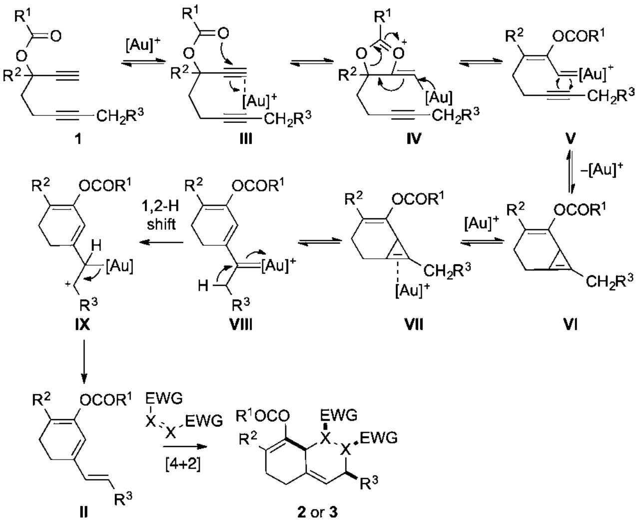
Scheme 3. Cycloisomerization of 1a and 1g Catalyzed by F and Diels–Alder Reaction with Diazenes[a]



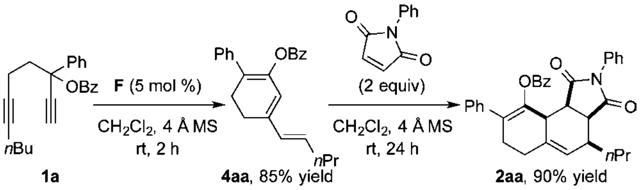
[a]All reactions were conducted at the 0.2 mmol scale with 5 mol % of **F** and 2 equiv of dienophile in dichloromethane in the presence of 4 Å MS (100 mg) at room temperature for 24 h. Values in parentheses denote isolated product yield.

A tentative mechanism for the present Au(I)-catalyzed cycloisomerization/Diels–Alder transformation is outlined in Scheme 4. Initially, this could involve activation of **1** by coordination of the gold catalyst to the C≡C bond of the substrate to give the gold(I)-coordinated species **III**.[6] This triggers *syn*-1,2-migration of the acyloxy moiety in the organogold adduct to give the gold carbenoid complex **V** via the 1,3-dioxol-1-ium species **IV**. Addition of the gold carbenoid moiety to the remaining alkyne moiety in this newly formed adduct might afford the cyclopropene **VI**. Further activation of the C=C bond of the bicyclic intermediate may give the gold(I)-coordinated complex **VII**, which is susceptible to electrophilic ring opening to afford the second gold carbenoid species **VIII**. A subsequent 1,2-hydride shift followed by protodeuteration of the ensuing putative organogold intermediate **IX** would then deliver the 1-vinylcyclohexa-1,3-diene adduct **II** that undergoes the Diels–Alder reaction with the dienophile to afford **2** or **3**. The proposed involvement of the triene intermediate is consistent with our findings for the control reactions depicted in Scheme 5. Subjecting **1a** with 5 mol % of Au(I) catalyst **F** and 4 Å MS in dichloromethane at room temperature for 2 h provided the 1-vinylcyclohexa-1,3-diene **4aa** (**II** in Schemes 1 and 4) in 85% yield. Treatment of this cycloadduct with *N*-phenyl maleimide (2 equiv) and 4 Å MS in dichloromethane at room temperature for 24 h then gave the expected Diels–Alder reaction product **2aa** in 90% yield.

Scheme 4. Proposed Mechanism for the Au(I)-Catalyzed Cycloisomerization/Diels–Alder Reaction of 1a–l with Electron-Deficient Dienophiles



Scheme 5. Control Experiment with 1a and *N*-Phenyl Maleimide



Added to this is the observed relative *cis*-stereochemistry of the product that would be in good agreement with Diels–Alder reactions involving a *trans,trans*-1,3-diene.

In summary, we have elucidated an efficient one-pot Au(I)-catalyzed cycloisomerization/Diels–Alder reaction process for the construction of hydronaphthalene and -cinnoline derivatives from 1,6-diyne esters and electron-deficient dienophiles. Efforts to explore the scope and synthetic applications of this transformation to other carbocyclic and heterocyclic systems are in progress and will be reported in due course.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b01935.

Detailed experiment procedures, characterization data and ^{1}H and ^{13}C NMR spectra for all starting materials and products (PDF)

CIF file of **2ba** (CIF)

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Notes

The authors declare no competing financial interest.

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■ REFERENCES

(1) Selected reviews: (a) de Bodinat, C.; Guardiola-Lemaitre, B.; Mocaër, E.; Renard, P.; Muñoz, C.; Millan, M. J. *Nat. Rev. Drug Discovery* **2010**, *9*, 628. (b) Cragg, G. M.; Grothaus, P. G.; Newman, D. J. *Chem. Rev.* **2009**, *109*, 3012. (c) Hanson, J. R. *Nat. Prod. Rep.* **2009**, *26*, 1156. (d) Cohen, P. *Nat. Rev. Drug Discovery* **2002**, *1*, 309.

(2) (a) Ono, M.; Yamasaki, T.; Konoshita, M.; Ikeda, T.; Okawa, M.; Kinjo, J.; Yoshimitsu, H.; Nohara, T. *Chem. Pharm. Bull.* **2008**, *56*, 1621. (b) Neuvonen, P. J.; Backman, J. T.; Niemi, M. *Clin. Pharmacokinet.* **2008**, *47*, 463. (c) Alvarez-Manzaneda, E.; Chahboun, R.; Cabrera, E.; Alvarez, E.; Alvarez-Manzaneda, R.; Lachkar, M.; Messouri, I. *Tetrahedron Lett.* **2007**, *48*, 989. (d) Scavone, J. M.; Gleckman, R. A.; Fraser, D. G. *Pharmacotherapy* **1982**, *2*, 266. (e) Fukuyama, K.; Tsukihara, T.; Katsube, Y.; Hamasaki, T.; Hatsuda, Y. *Tetrahedron Lett.* **1976**, *17*, 189. (f) Schatz, F.; Wagner-Jauregg, T. *Helv. Chim. Acta* **1968**, *51*, 1919.

(3) Selected reviews: (a) Vinogradova, O. V.; Balova, I. A. *Chem. Heterocycl. Compd.* **2008**, *44*, 501. (b) Chevallier, F.; Mongin, F. *Chem. Soc. Rev.* **2008**, *37*, 595. (c) de Koning, C. B.; Rousseau, A. L.; van Otterlo, W. A. L. *Tetrahedron* **2003**, *59*, 7.

(4) Selected reviews on gold catalysis: (a) Jia, M.; Bandini, M. *ACS Catal.* **2015**, *5*, 1638. (b) *Gold Catalysis: A Homogeneous Approach*; Toste, F. D., Michelet, V., Eds.; Imperial College Press: London, 2014. (c) Friend, C. M.; Hashmi, A. S. K. *Acc. Chem. Res.* **2014**, *47*, 729. (d) Braun, I.; Asiri, A. M.; Hashmi, A. S. K. *ACS Catal.* **2013**, *3*, 1902. (e) *Modern Gold Catalyzed Synthesis*; Hashmi, A. S. K., Toste, F. D., Eds.; Wiley-VCH: Weinheim, 2012. (f) Rudolph, M.; Hashmi, A. S. K. *Chem. Soc. Rev.* **2012**, *41*, 2448. (g) Krause, N.; Winter, C. *Chem. Rev.* **2011**, *111*, 1994. (h) Corma, A.; Leyva-Pérez, A.; Sabater, M. J. *Chem. Rev.* **2011**, *111*, 1657. (i) Fürstner, A. *Chem. Soc. Rev.* **2009**, *38*, 3208. (j) Gorin, D. J.; Sherry, B. J.; Toste, F. D. *Chem. Rev.* **2008**, *108*, 3351. (k) Hashmi, A. S. K.; Rudolph, M. *Chem. Soc. Rev.* **2008**, *37*, 1766. (l) Hashmi, A. S. K. *Chem. Rev.* **2007**, *107*, 3180. (m) Jiménez-Núñez, E.; Echavarren, A. M. *Chem. Commun.* **2007**, 333.

(5) Recent reviews on gold-catalyzed propargyl ester cycloisomerizations: (a) Ayers, B. J.; Chan, P. W. H. *Synlett* **2015**, *26*, 1305. (b) Fensterbank, L.; Malacria, M. *Acc. Chem. Res.* **2014**, *47*, 953. (c) Shiroodi, R. K.; Gevorgyan, V. *Chem. Soc. Rev.* **2013**, *42*, 4991. (d) Shu, X.-Z.; Shu, D.; Schienebeck, C. M.; Tang, W. *Chem. Soc. Rev.* **2012**, *41*, 7698. (e) Hashmi, A. S. K. *Angew. Chem.* **2010**, *122*, 5360. (f) Wang, S.; Zhang, G.; Zhang, L. *Synlett* **2010**, *2010*, 692. (g) Jiménez-Núñez, E.; Echavarren, A. M. *Chem. Rev.* **2008**, *108*, 3326.

(6) Examples of gold(I)-catalyzed reactions of 1,*n*-diyne esters via an initial 1,2-acyloxy migration step: (a) Liu, J.; Chen, M.; Zhang, L.; Liu, Y. *Chem. - Eur. J.* **2015**, *21*, 1009. (b) Rao, W.; Chan, P. W. H. *Chem. - Eur. J.* **2014**, *20*, 713. (c) Lauterbach, T.; Ganschow, M.; Hussong, M. W.; Rudolph, M.; Rominger, F.; Hashmi, A. S. K. *Adv. Synth. Catal.* **2014**, *356*, 680. (d) Oh, C. H.; Kim, J. H.; Piao, L.; Yu, J.; Kim, S. Y. *Chem. - Eur. J.* **2013**, *19*, 10501. (e) Rao, W.; Koh, M. J.; Li, D.; Hirao, H.; Chan, P. W. H. *J. Am. Chem. Soc.* **2013**, *135*, 7926. (f) Lauterbach, T.; Gatzweiler, S.; Nösel, P.; Rudolph, M.; Rominger, F.; Hashmi, A. S. K. *Adv. Synth. Catal.* **2013**, *355*, 2481.

(7) Recent examples of gold-catalyzed reactions of 1,*n*-diyne esters via an initial 1,3-acyloxy migration step: (a) Rao, W.; Susanti, D.; Ayers, B. J.; Chan, P. W. H. *J. Am. Chem. Soc.* **2015**, *137*, 6350. (b) Li, D.; Rao, W.; Tay, G. L.; Ayers, B. J.; Chan, P. W. H. *J. Org. Chem.* **2014**, *79*, 11301. (c) Yu, Y.; Yang, W.; Rominger, F.; Hashmi, A. S. K. *Angew. Chem., Int. Ed.* **2013**, *52*, 7586. (d) Hashmi, A. S. K.; Yang, W.; Yu, Y.; Hansmann, M. M.; Rudolph, M.; Rominger, F. *Angew. Chem., Int. Ed.* **2013**, *52*, 1329. (e) Rao, W.; Koh, M. J.; Kothandaraman, P.; Chan, P. W. H. *J. Am. Chem. Soc.* **2012**, *134*, 10811. (f) Chen, Y.; Chen, M.; Liu, Y. *Angew. Chem., Int. Ed.* **2012**, *51*, 6493. (g) Shi, H.; Fang, L.; Tan, C.; Shi, L.; Zhang, W.; Li, C.-C.; Luo, T.; Yang, Z. *J. Am. Chem. Soc.* **2011**, *133*, 14944. (h) Leboeuf, D.; Simonneau, A.; Aubert, C.; Malacria, M.; Gandon, V.; Fensterbank, L. *Angew. Chem., Int. Ed.* **2011**, *50*, 6868. (i) Zhang, D.-H.; Yao, L.-F.; Wei, Y.; Shi, M. *Angew. Chem., Int. Ed.* **2011**, *50*, 2583. (j) Luo, T.; Schreiber, S. L. *J. Am. Chem. Soc.* **2009**, *131*, 5667.

(8) Selected reviews on the Diels–Alder reaction: (a) Foster, R. A. A.; Willis, M. C. *Chem. Soc. Rev.* **2013**, *42*, 63. (b) Kotha, S.; Meshram, M.; Tiwari, A. *Chem. Soc. Rev.* **2009**, *38*, 2065. (c) Reymond, S.; Cossy, J. *Chem. Rev.* **2008**, *108*, 5359. (d) Wessig, P.; Müller, G. *Chem. Rev.* **2008**, *108*, 2051. (e) Takao, K.; Munakata, R.; Tadano, K. *Chem. Rev.* **2005**, *105*, 4779. (f) *The Diels-Alder Reaction: Selected Practical Methods*; Fringuelli, F., Taticchi, A., Eds.; Wiley: Hoboken, NJ, 2002. (g) *Cycloaddition Reactions in Organic Synthesis*; Kobayashi, S., Jørgensen, K. A., Eds.; Wiley-VCH: Weinheim, 2002.

(9) Selected recent examples of gold-initiated transformations involving a Diels–Alder reaction step: (a) Susanti, D.; Liu, L.-J.; Rao, W.; Lin, S.; Ma, D.-L.; Leung, C.-H.; Chan, P. W. H. *Chem. - Eur. J.* **2015**, *21*, 9111. (b) Zhou, L.; Zhang, M.; Li, W.; Zhang, J. *Angew. Chem., Int. Ed.* **2014**, *53*, 6542. (c) Wu, X.; Chen, S.-S.; Hu, Y.; Gong, L.-Z. *Org. Lett.* **2014**, *16*, 3820. (d) Malhotra, D.; Liu, L.-P.; Mashuta, M. S.; Hammond, G. B. *Chem. - Eur. J.* **2013**, *19*, 4043. (e) Liu, B.; Li, K.-N.; Luo, S.-W.; Huang, J.-Z.; Pang, H.; Gong, L.-Z. *J. Am. Chem. Soc.* **2013**, *135*, 3323. (f) Sanjuán, A. M.; García-García, P.; Fernández-Rodríguez, M. A.; Sanz, R. *Adv. Synth. Catal.* **2013**, *355*, 1955. (g) Han, Z.-Y.; Chen, D.-F.; Wang, Y.-Y.; Guo, R.; Wang, P.-S.; Wang, C.; Gong, L.-Z. *J. Am. Chem. Soc.* **2012**, *134*, 6532. (h) Song, X.-R.; Xia, X.-F.; Song, Q.-B.; Yang, F.; Li, Y.-X.; Liu, X.-Y.; Liang, Y.-M. *Org. Lett.* **2012**, *14*, 3344.

(10) CCDC 967743 (**2ba**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.