Gold(I)-Catalyzed Intramolecular [4+3]-Cycloaddition Reactions with Furan Propargyl Esters as the Substrates: Carbenoid vs. Stabilized Allyl Cation

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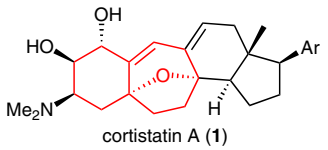
Abstract: The tricyclic ring system with an oxabicyclo[3.2.1]octadiene and a fused six-membered ring was produced efficiently using the readily available propargyl ester furan substrate in the presence of a Au(I) complex. The reaction involves a tandem 3,3-rearrangement of the propargyl ester followed by an intramolecular [4+3]-cycloaddition reaction. Both the primary ligand of the gold complex (N-heterocyclic carbene; NHC) and a neutral dynamic ligand (PhCN) are important for the success of the reaction.

Key words: gold-catalyzed, cycloadditions, furan, propargyl ester, carbenoid

Our interest in applying a transannular [4+3]-cycloaddition reaction to obtain the core structure of the potent anticancer agent cortistatin A (Figure 1)[1] led us to investigate the Au(I)-catalyzed cycloadditions with furan propargyl esters as the precursors.[2,3] To expand the scope of this method, we have studied the intramolecular version of this reaction. In the last several years the arsenal of new gold-catalyzed methods is increasingly applied in organic synthesis.[4]



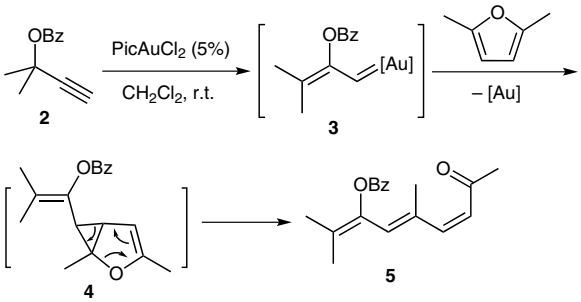
cortistatin A (**1**)

Figure 1 Potent antiangiogenesis natural product, cortistatin A, featuring a oxabicyclo[3.2.1]octene core structure fused with two six-membered rings

Other recent studies of gold-catalyzed intramolecular [4+3]- and [4+2]-cycloadditions involved the employment of preassembled allene dienes.[5] It was demonstrated that a selective [4+3] or [4+2] products could be achieved by employing either $Ar_3PAu(I)$- or $(ArO)_3PAu(I)$-type of catalysts. However there is still a lack of synthetic methodologies that produce the desired 6-7 ring system with the oxabicyclo[3.2.1]octane structure. A recent report on an efficient synthesis of cortistatin J employed an intramolecular [4+3]-cycloaddition reaction with a furan functional group adding to a (*Z*)-2-(trialkylsilyloxy)-2-enal three-carbon moiety.[6] This prompted us to show that the desired 6-7 fused rings in combination with the oxabicyclo[3.2.1]octane core structures could also be obtained by using the Au(I)-catalyzed tandem 3,3-rearrangement/intramolecular [4+3]-cycloaddition of the furan propargyl esters.

Propargyl esters have been shown to rearrange to either a gold carbenoid or an acetoxyallene in the presence of a gold complex through a 1,2- or 1,3-shift of the ester group.[7,8] The two reaction pathways are proposed to be competitive, and that the key intermediates in rapid equilibrium. We previously reported successful transannular [4+3]-cycloaddition reactions with the furan propargyl ester precursors.[3] However, in the study of intermolecular reactions, we observed that internal propargyl esters preferentially rearrange to α-ylidene-β-diketones in the presence of gold complexes, rather than the anticipated [4+3]-cycloaddition with furan. Zhang and co-workers have reported this rearrangement without the presence of furan.[9] Recently, new rearrangements of propargylic esters have been reported.[10]

When dimethylfuran was allowed to react with terminal propargyl esters in the presence of $PicAuCl_2$ [dichloro(2-pyridinecarboxylato)gold],[11] a stepwise 1,2-ester shift and cyclopropanation followed by furan ring-opening reaction were observed (Scheme 1). Gold-catalyzed intermolecular reactions involving furans are very rare.[12] Ohe and co-workers have reported a similar ruthenium-catalyzed heterocycle opening reaction.[13] A carbenoid intermediate was reportedly involved and the mechanism of the gold-catalyzed phenol synthesis involves such ring openings, too.[14]



Scheme 1 Terminal propargyl ester **2** reacted with dimethylfuran in the presence of a gold catalyst to give triene **5**, most likely through the carbenoid **3**

The results from the intermolecular reactions are in contrast to our earlier successful transannular reactions.[3] En-

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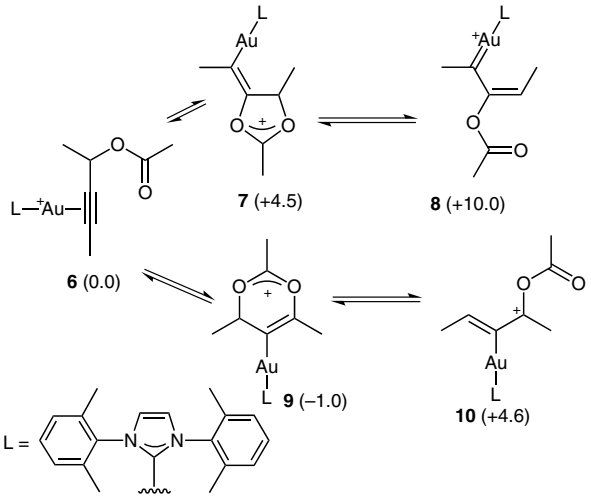
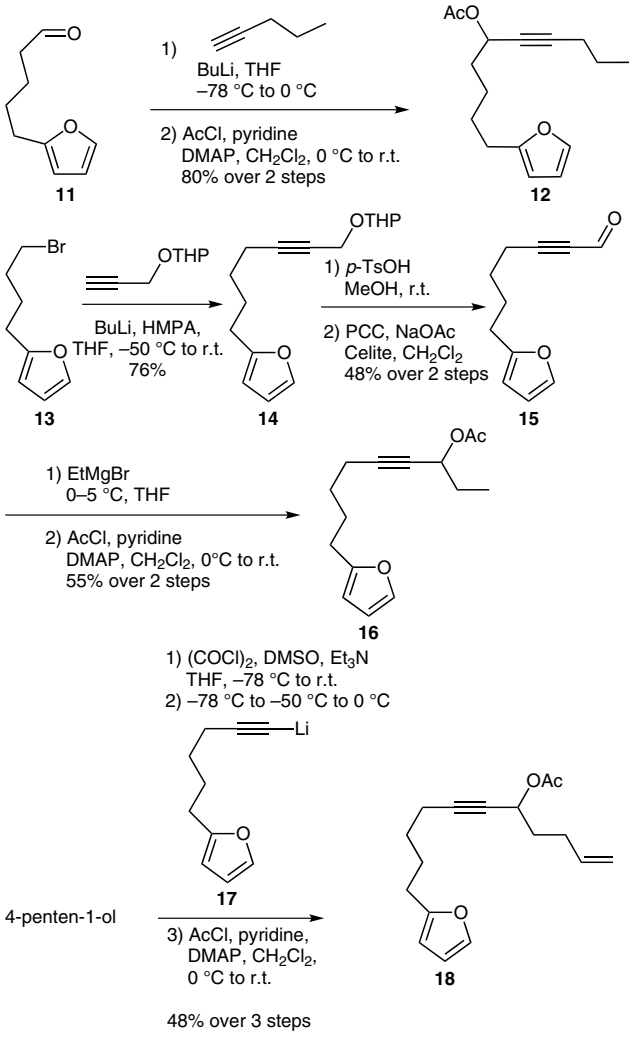
tropic effects are considered to play a major role in the difference in the two types of reactions. It was uncertain whether an intramolecular [4+3]-cycloaddition could be successfully carried out with gold-catalyzed furan propargyl esters.

Previous computations have shown that for terminal propargyl esters in the presence of a Au(I) catalyst, 1,2-acyl migration has a lower barrier than 1,3-acyl migration.[8] Since there is no report on computations of internal propargyl esters, we performed a DFT calculation for the prototype of substrate, such as **6** in Scheme 2, but with realistic NHC ligand considering the importance of steric effects. Our calculation shows that 1,3-migration of the ester group is preferred by the internal propargyl ester **6**. Not only the six-membered intermediate **9** is energetically favored over the five-membered intermediate **7**, but also the cationic allyl intermediate **10** is 5.4 kcal/mol more stable than the corresponding carbenoid intermediate **8**. These results indicate that internal propargyl esters should provide a better chance for [4+3]-cycloaddition reactions. Encouraged by the computational results, three substrates with an internal triple bond were prepared for performing the intramolecular [4+3]-cycloaddition reactions (Scheme 3).



Scheme 2 Computations were performed on 1,2- vs. 1,3-migration of the acetate group in the internal propargyl ester **6** to produce the carbenoid specie **8** vs. the cationic 1,3-dipole **10**. Relative to the L-Au coordinated alkyne **6**, the carbenoid **8** has a relative energy of 10 kcal/mol and the allyl cation **10** has an energy of 4.6 kcal/mol. The Becke's three parameter hybrid functional with the Lee–Yang–Parr correlation functional was used.[15] The 6-31G* basis set was used for main group atoms,[15] while the relativistic SDD effective core potential was used for the Au atom.[16]

Substrates **12** and **16** were designed to study the effect of the ester position on the connecting chain. Substrate **18** was aimed to test the carbenoid character of the reactive intermediate by possible trapping of the carbenoid intermediate with the terminal double bond. The synthesis of propargyl ester **12** started with the known furan aldehyde **11** (Scheme 3),[17] which was allowed to react with lithiated 1-pentyne to give the corresponding secondary propargyl alcohol. The desired propargyl ester **12** was obtained by acylation of the resulting secondary alcohol in 80% yield over two steps. Propargyl ester **16** was prepared starting from 1-(4-bromobutyl)furan (**13**; Scheme 3).[18] Substitution reaction with lithiated THP protected propargyl alcohol gave **14** in 76% yield.



Scheme 3 Preparation of furan propargyl esters **12**, **16**, and **18**

After removal of the THP ether protecting group from **14** with TsOH in MeOH, PCC oxidation of the resulting primary alcohol produced aldehyde **15** in 48% yield. Nucleophilic addition to the aldehyde with ethyl magnesium bromide followed by acylation afforded the desired propargyl ester **16** in 55% yield over two steps. The synthesis of propargyl ester **18** started with 4-pentenal (Scheme 3). After allowing 4-pentenal to react with the lithiated alkyne **17**,[19] acylation of the crude secondary alcohol gave the propargyl ester **18** in 48% yield over three steps.

Once the propargyl esters were in hand a brief screening of four gold complexes for the intramolecular [4+3]-cycloaddition reaction was performed. The different gold catalysts examined in this study are shown in Figure 2.

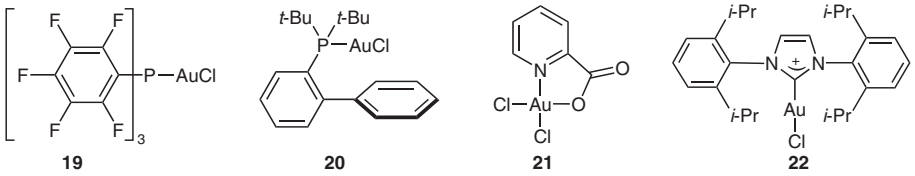


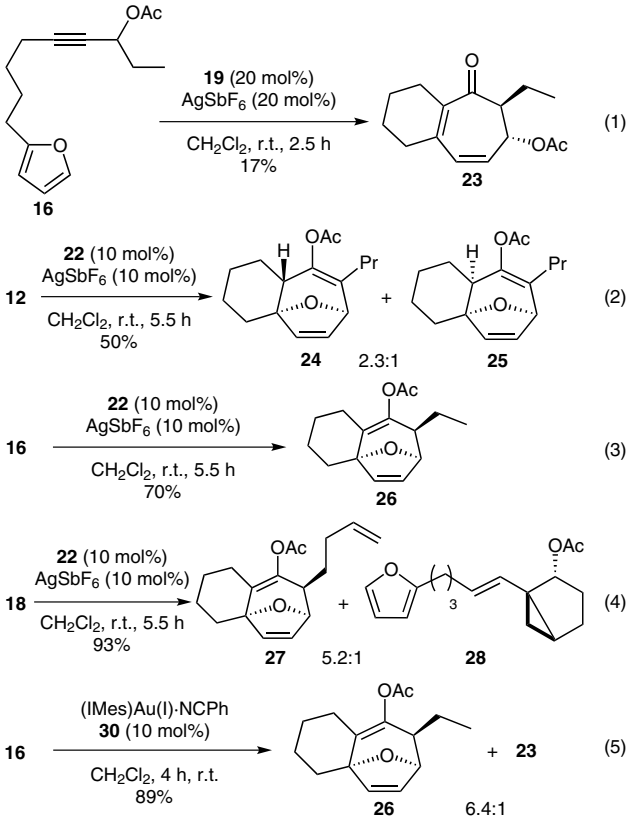
Figure 2 Gold complexes screened in this study

Disappointing results were obtained with complexes **19**–**21**. In the presence of the electron-deficient gold complex **19**, substrate **16** yielded 17% of the bicyclic ketone **23**.

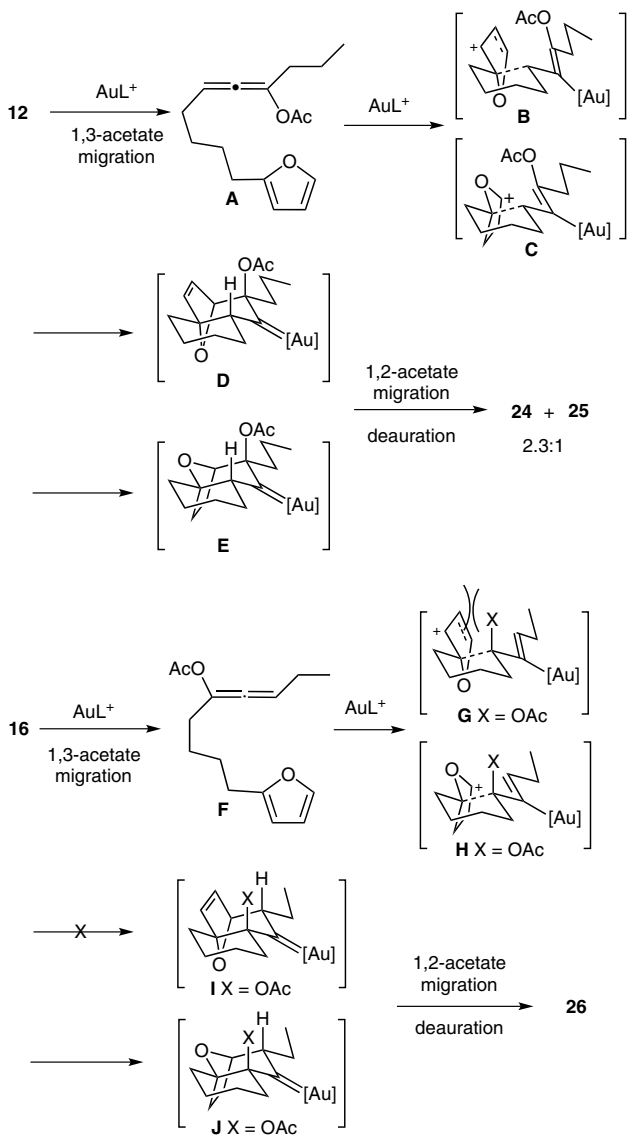
Compound **23** appears to be a secondary rearrangement product from an initial intramolecular [4+3]-cycloaddition product **26**. A similar ring-opening product was isolated by us previously.[20] Thus complex **19** appears to have a strong Lewis acid character, which caused decomposition of the substrate and the generation of the secondary reaction product. The gold complexes **20** and **21** were effective catalysts during our study of the transannular [4+3]-cycloaddition reactions.[3] In contrast, the reactions with substrates **12**, **16**, and **18** were sluggish in the presence of complexes **20** and **21**. Most of the starting materials decomposed after stirring for prolonged time. Some desired products (**24**) were observed with either complex **20** or **21**. Unfortunately the yield was low even with up to 20 mol% of catalyst loading and reaction time of up to four days. The best catalyst for the intramolecular [4+3]-cycloaddition was the gold complex (IPr)Au(I)Cl **22**. We were pleased to observe when in the presence of **22**/$AgSbF_6$ mixture,[21] the substrate **16** gave the desired [4+3]-cycloaddition product in 70% yield with catalyst loading at 10 mol% and a reaction time of five hours (Scheme 4, equation 3). In the presence of (IPr)Au(I)Cl (**22**)/$AgSbF_6$, furan propargyl ester **12** gave a mixture of two diastereomers **24** and **25** in 50% yield with a ratio of 2.3:1 in favor of **24** (Scheme 4, equation 2). Substrate **16** gave a single diastereomer **26** in 70% yield (Scheme 4, equation 3). Substrate **18** with a terminal alkene produced a mixture of two products in 93% combined yield with a ratio of 5.2:1 in favor of the desired [4+3]-cycloaddition product **27** (Scheme 4, equation 4). No interception of carbenoid intermediate was observed with **18**. However, product **28** was isolated, which resulted from a direct enyne cyclization without the migration of the acetate group. This is a rather unique 1,6-enyne isomerization product comparing to numerous previously reported similar type of reactions in that compound **18** is an internal alkyne and the acetate group remained on the same carbon after reaction.[22]

The formation of **27** should follow a similar pathway to the formation of **26** from **16**. The formation of **28** involves an initial activation of the internal alkyne by the Au(I) catalyst, which is followed by a nucleophilic attack by the pendant alkene resulting in the formation of a gold carbenoid species. The carbenoid intermediate undergoes a 1,2-hydride shift followed by elimination of AuL^+ to afford product **28**.

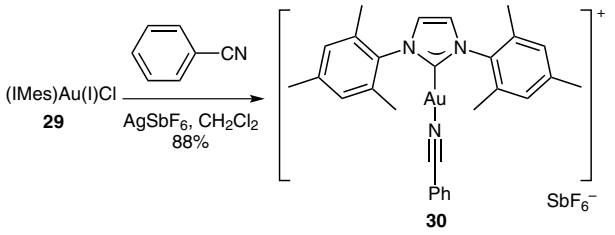
The observation of reactions of **12** producing two diastereoisomers and **16** producing only one diastereomer can be explained by considering the acetate location on the connecting chain between furan and the triple bond. Our suggested pathways are shown in Scheme 5. Initial Au(I)-catalyzed 1,3-acetate migration in substrates **12** and **16** leads to acetoxyallenes **A** and **F**, respectively. The location of the acetate is on the opposite end of the allene function in **12** and in **16**. As the Au(I) catalyst activates the acetoxyallene function into an allyl cation (**B**, **C**, **G**, or **H**), the formation of the first bond between furan and the allyl cation should be the one that forms a six-membered ring such as those shown in Scheme 5. It is reasonable to suggest that the energy difference between **B** and **C** is much smaller than that between **G** and **H** because of the location of the acetate group. Therefore, compounds **24** and **25** were both observed in the reaction of **12** and **26** was the only isolated product of **16**.



Scheme 4



Scheme 5 Proposed pathways for the observation of reactions of **12** producing two diastereoisomers and **16** producing only one diastereomer



Scheme 6 Preparation of PhCN-stabilized gold complex **30**

Some of the disadvantages of these cationic Au(I) catalysts, while remarkably active, is the lack of stability such as in complex **19**.[23] One of the important ligand properties is steric effects that protect the active cationic Au^+ species. For example the IPr NHC ligand (Figure 2)[24] has been found to be effective in many reactions. There is an additional approach to prolong the life of the active Au^+ catalyst. The groups of Nolan[25] and Echavarren have independently reported that a neutral ligand such as acetonitrile and benzonitrile can further improve the gold complex catalytic efficiency.[26] We prepared such a gold complex starting from the (IMes)Au(I)Cl (**29**)[21] as shown in Scheme 6.

When the substrate propargyl ester **16** was treated with the neutral gold complex **30** in CH_2Cl_2 at room temperature for four hours, an 89% yield of a mixture of **26** and **23** was obtained in a 6.4:1 ratio in favor of **26** (Scheme 4, equation 5), a better result than using **22** with $AgSbF_6$. As described above, compound **23** was formed as a secondary reaction product from **26**. The small amount of **23** isolated when using complex **30** could be a result of the more Lewis acidic Au(III)-promoted ring opening of **26**. Some minute amount of Au(III) species might have been formed in a disproportionation reaction of the complex **30**. The (IMes)Au(I) complex is not as sterically protected as the (IPr)Au(I) complex. Hence it is easier to undergo disproportionation to produce Au(III) and Au(0) species. This study shows that the desired 6-7 fused rings plus the oxabicyclo[3.2.1]octane core structures can be obtained in one operation by using the Au(I)-catalyzed tandem 3,3-rearrangement/intramolecular [4+3]-cycloaddition of the furan propargyl esters.[27] With continued improvement of the NHC ligand and a dynamic co-ligand, Au(I) catalysts should provide the most efficient route in the synthesis of the tricyclic products. Work along these lines is underway in our laboratories.

Acknowledgment

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Financial support from the Shoupp and CFR programs of Miami University is acknowledged.

Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synlett. Included are computational coordinates and experimental procedures as well as NMR spectra.

References and Notes

(1) Aoki, S.; Watanabe, Y.; Sanagawa, M.; Setiawan, A.; Kotoku, N.; Kobayashi, M. *J. Am. Chem. Soc.* **2006**, *128*, 3148.
(2) (a) Craft, D. T.; Gung, B. W. *Tetrahedron Lett.* **2008**, *49*, 5931. (b) Gung, B. W.; Craft, D. T. *Tetrahedron Lett.* **2009**, *50*, 2685.
(3) Gung, B. W.; Craft, D. T.; Bailey, L. N.; Kirschbaum, K. *Chem. Eur. J.* **2010**, *16*, 639.
(4) (a) Hashmi, A. S. K.; Rudolph, M. *Chem. Soc. Rev.* **2008**, *37*, 1766. (b) Rudolph, M.; Hashmi, A. S. K. *Chem. Soc. Rev.* **2012**, *41*, 2448.
(5) (a) Mauleon, P.; Zeldin, R. M.; Gonzalez, A. Z.; Toste, F. D. *J. Am. Chem. Soc.* **2009**, *131*, 6348. (b) Alonso, I.; Trillo, B.;

Lopez, F.; Montserrat, S.; Ujaque, G.; Castedo, L.; Lledos, A.; Mascarenas, J. L. *J. Am. Chem. Soc.* **2009**, *131*, 13020.
(6) Nilson, M. G.; Funk, R. L. *J. Am. Chem. Soc.* **2011**, *133*, 12451.
(7) (a) Zhang, L. *J. Am. Chem. Soc.* **2005**, *127*, 16804. (b) Zhao, J.; Hughes, C. O.; Toste, F. D. *J. Am. Chem. Soc.* **2006**, *128*, 7436. (c) Buzas, A.; Gagosz, F. *J. Am. Chem. Soc.* **2006**, *128*, 12614. (d) Oh, C. H.; Kim, A.; Park, W.; Park, D. I.; Kim, N. *Synlett* **2006**, 2781. (e) Yu, M.; Zhang, G. Z.; Zhang, L. M. *Tetrahedron* **2009**, *65*, 1846.
(8) Correa, A.; Marion, N.; Fensterbank, L.; Malacria, M.; Nolan, S. P.; Cavallo, L. *Angew. Chem. Int. Ed.* **2008**, *47*, 718.
(9) Wang, S. Z.; Zhang, L. M. *J. Am. Chem. Soc.* **2006**, *128*, 8414.
(10) Hashmi, A. S. K.; Yang, W. B.; Yu, Y.; Hansmann, M. M.; Rudolph, M.; Rominger, F. *Angew. Chem. Int. Ed.* **2013**, *52*, 1329.
(11) Hashmi, A. S. K.; Weyrauch, J. P.; Rudolph, M.; Kurpejovic, E. *Angew. Chem. Int. Ed.* **2004**, *43*, 6545.
(12) Hashmi, A. S. K.; Blanco, M. C.; Kurpejovic, E.; Frey, W.; Bats, J. W. *Adv. Synth. Catal.* **2006**, *348*, 709.
(13) Miki, K.; Fujita, M.; Uemura, S.; Ohe, K. *Org. Lett.* **2006**, *8*, 1741.
(14) (a) Stephen, A.; Hashmi, K.; Frost, T. M.; Bats, J. W. *J. Am. Chem. Soc.* **2000**, *122*, 11553. (b) Hashmi, A. S. K.; Rudolph, M.; Siehl, H. U.; Tanaka, M.; Bats, J. W.; Frey, W. *Chem. Eur. J.* **2008**, *14*, 3703.
(15) Becke, A. D. *Phys. Rev. A: Atom. Mol. Optical Phys.* **1988**, *38*, 3098.
(16) (a) Haeussermann, U.; Dolg, M.; Stoll, H.; Preuss, H.; Schwerdtfeger, P.; Pitzer, R. M. *Mol. Phys.* **1993**, *78*, 1211. (b) Kuechle, W.; Dolg, M.; Stoll, H.; Preuss, H. *J. Chem. Phys.* **1994**, *100*, 7535.
(17) Ragan, J. A.; Murry, J. A.; Castaldi, M. J.; Conrad, A. K.; Jones, B. P.; Li, B.; Makowski, T. W.; McDermott, R.; Sitter, B. J.; White, T. D.; Young, G. R. *Org. Process Res. Dev.* **2001**, *5*, 498.
(18) Rogers, C.; Keay, B. A. *Can. J. Chem.* **1992**, *70*, 2929.
(19) Harwood, L. M.; Leeming, S. A.; Isaacs, N. S.; Jones, G.; Pickard, J.; Thomas, R. M.; Watkin, D. *Tetrahedron Lett.* **1988**, *29*, 5017.
(20) Gung, B. W.; Craft, D. T. *Tetrahedron Lett.* **2009**, *50*, 2685.
(21) de Fremont, P.; Scott, N. M.; Stevens, E. D.; Nolan, S. P. *Organometallics* **2005**, *24*, 2411.
(22) Shen, H. C. *Tetrahedron* **2008**, *64*, 7847.
(23) Gung, B. W.; Bailey, L. N.; Craft, D. T.; Barnes, C. L.; Kirschbaum, K. *Organometallics* **2010**, *29*, 3450.
(24) Jafarpour, L.; Stevens, E. D.; Nolan, S. P. *J. Organomet. Chem.* **2000**, *606*, 49.
(25) de Fremont, P.; Marion, N.; Nolan, S. P. *J. Organomet. Chem.* **2009**, *694*, 551.
(26) Amijs, C. H. M.; Lopez-Carrillo, V.; Raducan, M.; Perez-Galan, P.; Ferrer, C.; Echavarren, A. M. *J. Org. Chem.* **2008**, *73*, 7721.
(27) **General Procedure for the Au(I)-Catalyzed Intramolecular [4+3]-Cycloadditions**: To a round-bottom flask equipped with a stirring bar under an atmosphere of nitrogen were added $AgSbF_6$ (2 mg, 0.007 mmol) and IPrAuCl (0.007 mmol) in freshly distilled CH_2Cl_2 (0.5 mL) and stirred for 5 min. The propargyl ester (0.07 mmol) dissolved in freshly distilled CH_2Cl_2 (0.5 mL) was added dropwise to the reaction and stirred at r.t. and monitored with ^{1}H NMR. The reaction mixture was diluted with Et_2O, filtered through Celite, the solvent removed under reduced pressure, and the residue purified over silica gel column. **[4+3]-Cycloaddition Product 26**: ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.97 (t, *J* = 7.35 Hz, 3 H), 1.04–1.20 (m, 1 H), 1.22–1.48 (m, 3 H), 1.68–1.89 (m, 4 H), 1.97 (d, *J* = 13.5 Hz, 1 H), 2.17 (s, 3 H), 2.43 (d, *J* = 17 Hz, 1 H), 2.89–2.92 (m, 1 H), 5.02 (d, *J* = 4.5 Hz, 1 H), 5.93 (d, *J* = 6.0 Hz, 1 H), 6.67 (d, *J* = 6.0 Hz, 1 H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 11.90, 18.83, 20.45, 23.27, 24.29, 29.70, 32.21, 42.05, 80.00, 83.42, 126.75, 129.47, 139.44, 141.89, 168.66. LCMS: *m*/*z* [M + Na] calcd for $C_{15}H_{20}O_3$: 271.1; found: 271.1.
[4+3]-Cycloaddition Product 27: ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.24–1.46 (m, 4 H), 1.91–1.74 (m, 4 H), 1.99 (d, *J* = 13.0 Hz, 1 H), 2.11 (s, 3 H), 2.20–2.11 (m, 2 H), 2.45 (d, *J* = 14.5 Hz, 1 H), 3.05 (m, 1 H), 5.04 (m, 3 H), 5.81 (m, 1 H), 5.96 (d, *J* = 6.0 Hz, 1 H), 6.71 (d, *J* = 6.0 Hz, 1 H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 20.5, 23.2, 24.0, 24.4, 25.0, 31.4, 32.2, 39.9, 79.9, 83.4, 115.2, 126.6, 129.7, 137.8, 139.2, 142.0, 168.6. LCMS: *m*/*z* [M + Na] calcd for $C_{17}H_{22}O_3$: 297.1; found: 297.1.
Enyne Cyclization Product 28: ^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.75 (dd, *J* = 7.8, 5.4 Hz, 1 H), 1.04 (t, *J* = 4.8 Hz, 1 H), 1.10–1.38 (m, 2 H), 1.65–1.94 (m, 4 H), 2.04–2.06 (m, 2 H), 2.07 (s, 3 H), 2.14–2.25 (m, 1 H), 2.62 (t, *J* = 7.5 Hz, 2 H), 5.35 (d, *J* = 15.5 Hz, 1 H), 5.37–5.49 (m, 2 H), 5.98 (d, *J* = 3.0 Hz, 1 H), 6.29 (dd, *J* = 3.0, 1.8 Hz, 1 H), 7.31 (d, *J* = 1.5 Hz, 1 H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 13.00, 21.25, 24.36, 26.02, 26.77, 27.34, 27.78, 31.99, 32.06, 78.24, 104.73, 110.03, 127.36, 131.80, 140.69, 156.21, 171.42. LCMS: *m*/*z* [M + Na] calcd for $C_{17}H_{22}O_3$: 297.1; found: 297.1.

