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ARTICLE TYPE

Gold-Catalyzed Diastereoselective [2+2+2]-Cycloaddition of 1,7-Enynes with Carbonyl Compounds

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Deepak B. Huple and Rai-Shung Liu*

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Abstract: We report a gold-catalyzed [2+2+2]-cycloaddition of 1,7-enyne with carbonyl species; our experimental data ¹⁰ suggests that the resulting oxacyclic cycloadducts arose from an interception of gold-containing cyclobutenium intermediates with carbonyl species.

In the presence of gold and platinum catalysts, 1,n-enynes (n = 5-7) undergo cycloisomerizations with skeletal rearrangement, ¹⁵ giving various carbocycles with high chemoselectivity.^{1,2} For 1,6terminal enynes **I**, their key cyclopropyl gold-carbene intermediates **A** have a dipole character to react with suitable dipolarophiles to access bicyclic compounds **II**.³⁻⁶ The first realization of this valuable cycloaddition was reported by ²⁰ Echavarren et. al.³ on the gold-catalyzed cyclizations of 1,6enynes bearing a tethered carbonyl functionality (Nu-E = R_1R_2CO); this method has been applied to the total synthesis of naturally occurring compounds englerin A and B.⁴

$$X \xrightarrow{\mathbb{R}^{1}} \mathbb{R}^{2} \xrightarrow{Au^{+}} X \xrightarrow{\mathbb{R}^{2}} \mathbb{R}^{2} \xrightarrow{\mathbb{R}^{2}} \mathbb{R}^{1} + \bigcup_{E_{\delta^{+}}}^{\mathbb{N}_{u}} \xrightarrow{\mathbb{R}^{2}} \mathbb{R}^{2} \xrightarrow{\mathbb{R}^{2}} \xrightarrow{\mathbb{R$$

In contrast, gold-catalyzed intermolecular cycloadditions of 1,n-enynes with carbonyl species still remain a formidable task. ³⁰ With 1,6-enynes, Echavarren attempted to intercept intermediate **A** using external carbonyl compounds,⁵ but the reactions were inevitably accompanied with side products in significant proportions. Helmchen studied⁶ similar cycloadditions using unsubstituted 1,6-enynes, but carbonyl substrates were few and ³⁵ used in large proportion (20 equiv). To continue our work on gold-catalyzed cycloadditions on 1,n-enynes,^{7,8} we report an efficient intermolecular [2+2+2]-cycloaddition of 1,7-enynes **1** with carbonyl species, giving cycloadducts **2** stereoselectively; herein, the side reaction is the occurrence of cycloisomerization ⁴⁰ product,⁹ i.e., bicyclic cyclobutene species **3** that is not



Scheme 1. [2+2+2]-Cycloadditions of 1,7-enynes with carbonyls.

- ⁶⁰ convertible to acyclic diene **III** in this catalytic system. Our experimental results suggest that cycloadduct **2** is generated with an interception of cyclobutene-like cationic intermediate **B** with a carbonyl species, and its formation is unrelated to both cyclobutenes **3** and acyclic dienes **III**.
- Table 1 shows our efforts to realize the cycloaddition of 1,7-65 enyne 1a with benzaldehyde with commonly used gold and platinum catalysts. An optimized operation involves a slow addition (2 h) of a metal catalyst in dichloromethane to a mixture of 1,7-enyne (1 equiv) and benzaldehyde (2 equiv) in hot DCM 70 (35 °C). Workup of the solution followed immediately the end of the catalyst addition. Such an atypical addition drastically decreases the yields of cycloisomerization product 3a for most catalysts, but the reason for this phenomenon is still unclear. We first tested the reactions on $P(t-Bu)_2$ (o-biphenyl)AuNTf₂ (entry 1) 75 that gave desired oxacyclic adduct 2a in 81% yield together with byproduct **3a** (14% yield). With a standard reagent addition, we obtained cycloisomerization product 3a in 88% yield with cycloadduct 2a in a tractable proportion (2%). For IPrAuNTf₂ (IPr = 1,3-bis(diisopropyl phenylimidazol-2-ylidene, entry 2), we⁸⁰ recovered starting **1a** exclusively in hot DCM (35 ⁰C, 6 h, entry 2). The reaction chemoselectivity was further improved with more acidic P(t-Bu)₂(o-biphenyl)AuSbF₆ to give oxacyclic adduct 2a in 85% yield. PPh_3AuSbF_6 also showed a fair chemoselectivity to give compounds 2a and 3a in 71% and 20% 85 yields respectively (entry 4). A control experiment revealed that AgSbF₆ alone gave mainly cycloisomerization species 3a in 60% yield together with cycloadduct 2a in minor proportion (32%, entry 5). For AuCl₃ and PtCl₂/CO, their catalytic reactions gave mainly undesired cycloisomerization product 3a in 90% and 47%

Department of Chemistry, National Tsing-Hua University, Hsinchu, Taiwan, ROC E-mail: <u>rsliu@mx.nthu.edu.tw</u>

 [†] Electronic Supplementary Information (ESI) available: Experimental
 ⁴⁵ Procedures and characterization data for new compounds.CCDC 876013.
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| 1a | + H Ph (2 h, additi O DCM, 35 ((n equiv) ^a | alyst bon) bC, | | 9+ 3a |
|-------|--|----------------------------------|----------------------|------------------------------------|
| entry | catalyst | compounds (% yield) ^b | | |
| | | 1a | 2a | 3a |
| 1 | LAuCI/AgNTf2 | - | 81(<mark>2</mark>) | 14(<mark>88</mark>) ^c |
| 2 | IPrAuCI/AgNTf2 | 90 | | - |
| 3 | LAuCI/AgSbF ₆ | _ | 85 | trace |
| 4 | AuCIPPh3/AgSbF6 | - | 71 | 20 |
| 5 | AgSbF ₆ | _ | 32 | 60 |
| 6 | AuCl ₃ | | | 90 |
| 7 | PtCl ₂ /CO | 15 | 22 | 47 |
| 8 | LAuCI/AgSbF ₆ | - | | 90 ^d |

 $L = P(t-Bu)_2(o-biphenyl)$, DCM = dichloromethane. 1a (1 equiv., 0.01 M).^aPhCHO (2 equiv for entries 1-7). ^bYields are obtained after separation from a silica column. ^cThe values in parenthesis correspond to 15 a normal reagent treatment; the reaction duration is 5 min. ^dThis yield is given in the absence of benzaldehyde.

yields respectively (entries 6-7). In the absence of benzaldehyde, $P(t-Bu)_2$ (o-biphenyl)AuSbF₆ gave only cyclobutene derivative **3a** 20 in 90% yield. The molecular structure of compound 2a was confirmed by x-ray diffraction study.¹⁰

We prepared various 1,7-enynes 1b-1i to test the scope of substrates; their cycloadditions with benzaldehyde (2 equiv) were operated according to the preceding procedure. We obtained 25 cycloadducts 2b-2i nearly exclusively except entry 8 that gave cyclobutene compound **3i** in a small proportion (31%). For 1,7envne 1b bearing a cyclopentylidene moiety, we obtained its resulting oxacycle 2b in 80% yield. The gold-catalyzed cycloadditions also worked for 1,7-envnes 1c-1g bearing fluoro 30 and methoxy at the phenyl C(3)-C(5) carbons, giving resulting cycloadducts 2c-2g in 55-85% yields (entries 2-6). The reaction also worked well with all-carbon 1,7-envne 1h bearing a methylene bridge (X = CH_2 entry 7), producing compound **2h** in 78% yield. The cycloaddition on nitrogen-bridged 1,7-enyne 1i

35 gave cycloadduct 2i and cycloisomerization product 3i in 41% and 31% yields respectively. The yield of desired cycloadduct 2i was increased to 72% using benzaldehyde in excess proportion (6 equiv, entry 8).

We next investigated the scope of aldehydes (2 equiv) and 40 ketones (6 equiv.); the results are provided in Table 3. We examined the reactions on various 4-substituted benzaldehydes; satisfactory yields (86-88%) were obtained for methoxy- and methyl derivatives 4a and 4b (entries 1-2) whereas decreased yields (45-65%) were found for compounds 4c and 4d bearing X

- $_{45}$ = Cl, CO₂Me. In entry 4 (X = CO₂Me), we obtained also cycloisomerization byproduct 3a in 35% yield. These reactions were extensible to various aliphatic aldehydes (Rs = H) including R_{I} = methyl, ethyl, cyclopropyl and cyclohexyl; their resulting cycloadducts 4e-4h were produced in satisfactory yields (71-
- 50 82%, entries 5-8). The cycloadditions of heteroaryl aldehydes (R_L = 2 - .

Table 2. Gold-catalyzed cycloadditons with various 1,7-enynes



 $L = P(t-Bu)_2(o-biphenyl)$, DCM = dichloromethane, ^a[1a] = 0.01 M. ^bProduct yields are obtained after separation from a silica column.^c Cyclobutene species 3i was obtained in 31% yield. ^dPhCHO (6 equiv).

3-furanyl and 2-thienyl) gave expected oxacycles 4i-4k in 81-87% yields (entries 8-10). To our pleasure, these cycloadditions 75 worked well not only for alkenyl aldehydes but also for acetone; resulting oxacyclic products 41 and 4m were obtained in 84% and 78% yields respectively (entries 12-13).

According to our control experiments, oxacyclic cycloadduct 2a was not produced from the gold-catalyzed cycloaddition of ⁸⁰ bicyclic cyclobutene **3a** with benzaldehyde.¹¹ Like other 1,7envnes,⁹ an acyclic diene such as IIIh (eq 2) was unattainable in our catalytic system. To assure its absence, we prepared an

Table 3. [2+2+2]-Cycloadditions with varios carbonyl species



 $L = P(t-Bu)_2$ (o-biphenyl), DCM = dichloromethane, ^a [1a] = 0.01 M. ⁹⁰ ^bProduct yields are obtained after separation from a silica column.^c aldehyde. ^d Cyclobutene species **3a** was obtained in 35%. Acetone (6 equiv).

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authentic sample of acyclic diene IIIh from a separate procedure (eq 2). In the presence of $P(t-Bu)_2(o-biphenyl)AuSbF_6$ (5 mol %), this acyclic diene reacted slowly with benzaldehyde (2 equiv) in dichloromethane to produce two diasteromeric cycloadducts 2h ⁵ and 2h' in nearly equal proportion whereas 1,7-enyne 1h gave only oxacyclic product 2h (Table 2, entry 7). The proposed structure of species 2h' was inferred by the coupling constants of the OCHPh proton (dd, J = 4.4, 1.2 Hz). The poor diastereoselectivity of species IIIh precludes its participation in ¹⁰ this enyne cycloaddition.

As shown in Scheme 2, we postulate that cycloadduct 2a likely arose from the interception of gold-containing cyclobutenium-like intermediate B^{12} with benzaldehyde giving chair-like transition state C, ultimately giving observed product ¹⁵ 2a stereoselectively. This reaction model also rationalizes our observation on aldehyde substrates that electron-rich aryl aldehydes are more efficient than their electron-deficient analogues (Table 3, entries 1-4) in the cycloaddition reactions as the former shows great nucleophilicity to intercept species **B**.



Scheme 2. Stereochemical course and reaction mechanism

- ³⁵ In summary, we report a gold-catalyzed stereoselective cycloaddition of 1,7-enynes¹³ with various carbonyl species. This cycloaddition proceeds with a wide scope of enynes and carbonyl species in reasonable proportions with an efficient suppression of cycloisomerization byproduct. Based on our experimental data,
- ⁴⁰ we postulate that the formation of such [2+2+2]-cycloadducts arise from an efficient interception of cyclobutenium-like intermediate **B**. This work highlights the utility of gold catalysis in cycloaddition reactions.

Notes and references

- (a) E. Jiménez-Núñez, A. M. Echavarren, *Chem. Rev.* 2008, **108**, 3326 3350; (b) D. J. Gorin, B. D. Sherry, F. D. Toste, *Chem. Rev.* 2008, **108**, 3351-3378; (c) A. S. K. Hashmi, M. Rudolph, *Chem. Soc. Rev.* 2008, **37**, 1766-1775; (d) A. Fürstner, P. W. Davies, *Angew. Chem. Int. Ed.* 2007, **46**, 3410-3449; (e) L. Zhang, J. Sun, S. A. Kozmin, *Adv. Synth. Catal.* 2006, **348**, 2271-2296.
- For Au and Pt-catalyzed cycloisomerizations of 1,n-enynes (n = 5-7), see selected examples: (a) E. Jiménez-Núñez, K. Molawi, A. M. Echavarren, *Chem. Commun.* 2009, 7327-7329; (b) A. Fürstner, P. Hannen, *Chem. Eur. J.* 2006, 12, 3006-3019; (c) X. Linghu, J. J.
- 55 Kennedy-Smith, F. D. Toste, Angew. Chem. Int. Ed. 2007, 46,

View Online
7671-7673; (d) A. S. K. Hashmi, L. Ding, J. W. Bats, P. Fischer, W.
Frey, Chem. Eur. J. 2003, 9, 4339-4345; (e) L. Zhang, S. A.
Kozmin, J. Am. Chem. Soc. 2005, 127, 6962-6963; (f) J.-M. Tang,
S. Bhunia, S. M. A. Sohel, M.-Y. Lin, H.-Y. Liao, S. Datta, A. Das,
R.-S. Liu, J. Am. Chem. Soc. 2007, 129, 15677-15683; (g) F.
Gagosz, Org. Lett., 2005, 7, 4129-4132; (h) C. Nieto-Oberhuber,
M.P. Munoz, E. Bunuel, C. Nevado, D. J. Cardenas, A. M.
Echavarren, Angew. Chem. Int. Ed. 2004, 43, 2402-2406; (i) E.
Jimenez-Nunez, K. Olawi, A. M. Echavarren, Chem. Commun.,
2009, 7327-7327; (j) N. Chatani, T. Morimoto, T. Muto, S. Murai,
J. Am. Chem. Soc., 1994, 116, 6049-6050.

- E. J. Nunez, C. K. Claverie, C. Nieto-Oberhuber, A. M. Echavarren, Angew. Chem. Int. Ed., 2006, 45, 5452-5455.
- (a) K. Molawi, N. Delpont, A. M. Echavarren, *Angew Chem. Int. Ed.*, 2010, 49, 5317-3519; (b) L. Radtke, M.Willot, H. S. S. Ziegler, S. Saurland, C. Srohmann, R. Frohlich, P.Habenberger, H. Waldmann, M.Christmann, *Angew Chem. Int. Ed.*, 2011, 50, 3998-4002.
 - 5. A. Escribano-Cuesta, V. Lopez-Carrillo, D. Janssen, A. M. Echavarren, *Chem, Eur. J.*, 2009, **15**, 5646-5650.
- 75 6. M. Schelwies, A.L. Dempwolff, F. Rominger, G. Helmchen, *Angew Chem. Int. Ed.*, 2007, **46**, 5598-5601.
- Reviews for gold-catalyzed cycloaddition reactions, see: (a) a) A. S. K. Hashmi, *Chem. Rev.* 2007, **107**, 3180-3211; b) A. Fürstner, *Chem. Soc. Rev.* 2009, **38**, 3208-3221; c) N. T. Patil. Y. Yamamoto, *Chem. Rev.* 2008, **108**, 3395-3442; d) S. M. A. Sohel, R.-S. Liu, *Chem. Soc. Rev.* 2009, **38**, 2269–2281; e) F. López, J. L. Mascareñas, Beilstein, *J. Org. Chem.* 2011, **7**, 1075-1094; f) C. Aubert, L. Fensterbank, P. Garcia, M. Malacria, A. Simonneau, *Chem. Rev.* 2011, **111**, 1954.
- 85 8. We just reported [2+2+3]-cycloadditions of 1,6-enynes with nitrones, but these enynes gave only cycloisomerization products when benzaldehyde was used. See S. A. Gawade, S. Bhunia, R.-S. Liu, *Angew. Chem. Int. Ed.* 2012, **51**, 7835-38.
- (a) A. Fürstner, A. Schlecker, C. W. Lehmann, *Chem. Commun.*, 2007, 4277-4279; (b) G. B. Bajracharya, I. Nakamura, Y. Yamamoto, *J. Org. Chem.*, 2005, **70**, 892-897.
 - 10. Crystallogtaphic data of compound **2a** is deposited at Cambridge Crystallographic Data Center (CCDC 896604).
- Treatment of cyclobutene 3a with benzaldehyde (2 equiv) and P(t-Bu)₂(o-biphenyl)AuSbF₆ in DCM (25 °C, 12 h) gave unreacted 3a in 76% recovery.
- In Scheme 2, intermediate B is represented with two resonance structures B' and B"; this character will retard the conversion of this intermediate to bicyclic cyclobutadiene 3a via an elimination of gold
 fragment.



13. The [2+2+2] formal cycloadditions failed to work with substrates bearing 1,2-disubstituted alkenes including 2-substituted 4-methoxy-phenyl group.

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We report a gold-catalyzed [2+2+2]-cycloaddition of 1,7-enyne with carbonyl species; the resulting oxacyclic cycloadducts arose from an interception of gold-containing cyclobutenium intermediates with carbonyl species.