Unusual Regioselectivity in the Gold(I)-Catalyzed [3+2] Carbocycloaddition Reaction of VinylDiazo Compounds and N-Allenamides

Enol López, a,b Javier González, a Luis A. López a,b,*

a Departamento de Química Orgánica e Inorgánica, Universidad de Oviedo, c/ Julián Clavería, 8, 33006-Oviedo
b Instituto Universitario de Química Organometálica “Enrique Moles”, Universidad de Oviedo, c/ Julián Clavería, 8, 33006-Oviedo
E-mail: lalg@uniovi.es

Received: ((will be filled in by the editorial staff))

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/adsc.201####. ((Please delete if not appropriate))

Abstract. The reaction of N-allenamides with alkenyldiazo compounds in the presence of gold catalysts provided methylidenecyclopentene derivatives resulting from a formal intermolecular [3+2] carbocyclization, a rare process in the gold chemistry of allenes. The participation of the Cα=Cβ of the allenamide represents a very unusual regioselectivity in gold-catalyzed cycloaddition reactions of this type of allenic scaffolds. A stepwise mechanism involving initial activation of the diazo component has been proposed.

Keywords: Allenes; Carbenes; [3+2] Cycloaddition; Diazocompounds; Gold

Over the past decades, significant progress has been made toward developing efficient and selective transition metal-catalyzed synthetic methodologies involving allenamides.[1] However, catalytic methods based on the use of gold complexes as catalysts have only recently become available.[2] From a mechanistic point of view,[3] it is generally accepted that the coordination of the allenamide to gold renders an electrophilic species, which is able to participate in nucleophilic additions and cycloaddition reactions (Scheme 1, a). Specifically, a number of gold-catalyzed carbocycloadditions of allenamide derivatives, including [2+1],[4] [2+2],[5] and [4+2][6] cycloadditions, have been recently reported. Additionally, the synthesis of some heterocyclic compounds through gold-catalyzed [3+2][7] and [2+2+2][8] cycloaddition reactions of allenamide derivatives has also been disclosed. Interestingly, all of the above-mentioned cyclization processes share the characteristic of being highly regioselective, the allene Cβ=Cγ bond being solely involved (Scheme 1, b).

On the other hand, the transition metal-catalyzed transformations of stabilized vinyldiazo derivatives have received in the last years great attention. In most cases, the so-generated metal vinylcarbene species show a typical carbene reactivity transferring the carbene unit to saturated and unsaturated substrates.[9] Vinyllogous reactivity, although less developed, has evolved in the last years as another synthetically useful pathway for metal vinylcarbene intermediates.
generated from vinyldiazo compounds.\[^{10}\]\n
Surprisingly, despite impressive recent progress in this field, to the best of our knowledge, the cycloaddition between vinyldiazor derivatives and allene derivatives remains unexplored. In this regard, we realized that the recent introduction of gold complexes as efficient catalysts for the activation of diazo compounds\[^{11}\]\ could pave the way for the successful development of a selective cycloaddition of vinyldiazocompounds and allenamides.\[^{12}\] However, such a metal-catalyzed process could pose some challenges. In particular, regioselectivity issues have to be addressed as both reagents have multiple reaction sites. In the case of the allenic partner, the selectivity problems arise from the presence of two reactive orthogonal double bonds. Regarding the vinyldiazocomponent, both retention of its diazo function,\[^{13}\]\ and decomposition into an electrophilic gold-carbene intermediate can be envisioned. This fact along with the above-mentioned dichotomy of the postulated carbene intermediate species (carbene vs vinylogous reactivity) could greatly increase the complexity of the process. On the other hand, a number of non-productive self-coupling processes representing potential competitive pathways should be avoided\[^{14,15}\]. In the most favourable scenario, the selected catalyst should facilitate the preferential activation of one of the two substrates which, once activated, should react in a selective way with the second component while suppressing the above-mentioned side reactions.

Herein, we report the realization of this goal; specifically, we describe the gold-catalyzed \([3+2]\) cycloaddition of allenamides toward vinyldiazocompounds. This process represents not only a rare example of intermolecular gold-catalyzed carbo \([3+2]\) cyclization reaction involving allenamides but also an extremely unusual reactivity pattern in the chemistry of this type of allene derivatives.\[^{16}\]\ Notably, the observed participation of the Cα=Cβ bond represents an extremely infrequent regioselectivity pattern in gold-catalyzed cyclizations of allenamides. In this regard, a recent report by Zhang et al reporting the gold(I)-catalyzed cyclization of 2-(1-alkynyl)-2-alken-1-ones with allenamides through the Cα=Cβ bond has prompted us to release our results (Scheme 1, c).\[^{17}\]

We initially studied the reaction of benzyl 2-diazobut-3-enoate (1a) and N-tosylallenamide 2a (EWG = Ts, R^1 = Ph, R^4 = H) as model substrates. In accordance with our previous research NHC-based gold(I) complexes in dichloromethane were initially selected as the catalytic systems. To our delight, we found that stirring a mixture of vinyldiazocompound 1a and N-tosylallenamide 2a (4 equiv) in the presence of IPr(MeCN)AuSbF\(_6\) (10 mol%) in dichloromethane at room temperature gave the \([3+2]\) cycloadduct 3a in 40% yield after column chromatography (Scheme 2). Very significantly, under these reaction conditions no other regioisomeric products were observable by \(^1H\)-NMR spectroscopy.\[^{18}\]

To our delight, a significant increase in the yield of 3a (81% after chromatographic purification) was achieved when JohnPhosAuNTf\(_2\) was used under otherwise similar conditions (10 mol%, \(\text{CH}_2\text{Cl}_2\), RT). Lowering the catalyst loading to 2.5 mol% resulted in longer reaction time (16 h) and a lower yield (46%). Other gold catalysts tested were found to be less efficient for this transformation (see the Supporting Information for full details on the screening and optimization study).

The structure of compound 3a was ascertained by NMR methods, which clearly demonstrated the participation of the Cα=Cβ bond of the allenamide.

![Scheme 2](image_url)

Scheme 2. Gold(I)-catalyzed \([3+2]\) cycloaddition of stabilized vinyldiazocompounds 1a and allenamide 2a: Summary of catalyst optimization.

The reaction was then extended to other combinations of vinyldiazocompounds and allenamides (Scheme 3). First, we found that the nature of the ester substituent has little impact on the outcome of the reaction with allenamide 2a. Thus, ethyl substituted vinyldiazocompound 1b (R^1 = Et, R^4 = H) undergoes the cyclization process affording the corresponding cycloadduct 3b in 66% yield. Somewhat lower yield was obtained when using tert-butyl 2-diazobut-3-enoate (1e; R^1 = 'Bu, R^4 = H). Vinyl substitution was tolerated, as demonstrated in the formation of cycloadduct 3d in 61% yield when vinyldiazocompound 1d (R^1 = Et, R^4 = Me) was subjected to the standard conditions.

Next, we investigated the scope of this gold-catalyzed \([3+2]\) cyclization reaction with regard to the allenamide partner. Indeed, a number of aryl substituted tosylallenamides (EWG = Ts, R^3 = aryl group, R^4 = H) were compatible with this protocol and those with both electron-rich (allenamides 2b and 2e; R^3 = 4-MeC\(_6\)H\(_4\) and R^3 = 3,5-Me\(_2\)C\(_6\)H\(_3\), respectively) and electron-deficient aryl groups (allenamide 2d; R^3 = 4-FC\(_6\)H\(_4\)) reacted with vinyldiazocompounds 1a-c to give the expected cycloadducts 3e-i in moderate yields (42-68%). A naphthyl-containing cycloadduct 3j was also available from the corresponding tosylallenamides 2e (R^3 = 2-naphthyl, R^4 = H). Reactions with N-alkyl substituted tosylallenamides (allenamides 2f and 2g; R^3 = Me and R^3 = Bn, respectively) also proceeded smoothly to afford the corresponding \([3+2]\) cycloadducts 3k-m in moderate yields (34-59%).
Variation of the tosyl group was also tolerated as demonstrated the preparation of compound 3n bearing a 2,4,6-tris(isopropyl)phenyl group. Besides, 1-(1,2-propadienyl)pyrrolidin-2-one (2i) was also a suitable substrate in this gold-catalyzed [3+2] cycloaddition leading to product 3o. Finally, this gold-catalyzed [3+2] cyclization tolerated substitution at the allenyl moiety as demonstrated the formation of product 3p in 45% yield from allenamide 2j (EWG = Ts, R³ = Ph, R⁴ = Et). Remarkably, this reaction proceeded with total Z-selectivity.

Single-crystal analysis of compound 3g unambiguously confirmed our initial structural assignment (Figure 1).\(^\text{[19]}\)

A mechanistic proposal to rationalize the obtained results is depicted in Scheme 4. Although different mechanistic scenarios can be envisioned for the formation of the [3+2]-carbocycloadducts 3, the structure of the final products would suggest that it is the activation of the diazo compound rather than of the allene that, very likely, accounts for the cyclization event. As a result, the mechanism would begin with the reaction of the vinyldiazo compound with the gold complex to afford a gold-vinyl carbene intermediate I.\(^\text{[20]}\) In agreement with previous reports, this intermediate would show an enhanced tendency to react through the vinylogous position. Consequently, nucleophilic attack of the central carbon atom of the allenamide to this position would generate intermediate II.\(^\text{[21]}\) This complex would undergo cyclization through attack of the vinyl-gold to the electrophilic iminium atom carbon to release the final product and regenerate the gold-catalyst.

**Scheme 3.** Gold(I)-catalyzed [3+2] cycloaddition of stabilized vinyldiazo derivatives 1 and allenamides 2. Reaction conditions: 1 (0.5 mmol), 2 (2.0 mmol), (JohnPhosAu)NTf₂ (10 mol%), CH₂Cl₂ (0.05 M), RT. Values in parenthesis are the yields of isolated products. Naph = naphthyl. Tripp = 2,4,6-tris(isopropyl)phenyl.

**Scheme 4.** Proposed mechanism for the synthesis of compounds 3 from vinyldiazo compounds 1 and N-allenamides 2.
Taking into account that previous [n+2] cyclization reactions involving allenamides are proposed to proceed by activation of the allenic partner by the gold catalyst, the divergent regiochemical outcome observed in our case would be a consequence of the preferential activation of the diaco partner. This proposal is supported by a preliminary computational DFT study (see Supporting Information for details) which shows that the formation of gold(I) carbene-type intermediate I (Scheme 4) is clearly favoured as compared with the activation of the N-allenamide partner. The coordination of the nucelophilic diazo compound to the gold(I) catalytic species leads to an unstable intermediate, which loses a dinitrogen molecule, in a reaction showing a very low activation barrier (the predicted $\Delta G^*$ values being in the range of 4-6 kcal mol$^{-1}$). In addition, the elimination of N$_2$ makes the reaction for the formation of gold(I) carbene intermediate, quite exothermic.

In summary, we have found new reactivity patterns in gold allene chemistry. Specifically, the reaction of allenamide derivatives with vinylidiazocompounds afforded five-membered rings arising from a [3+2] carbocycloaddition, an uncommon process in gold allene chemistry. Notably, the participation of the Cs=C@B represents an extremely infrequent regioselectivity pattern in gold-catalyzed cyclizations of allenamides. These results are fully consistent with a mechanistic pathway involving initial activation of the vinylidiazopartner. Studies to gain further insight into the reaction mechanism and to develop an enantioselective version of the present reaction are ongoing.

**Experimental Section**

**Representative procedure (3a):** JohnPhosAuNTf$_2$ (39 mg, 0.05 mmol, 10 mol%) was added to a solution of benzyl 2-diazobut-3-enolate (1a; 101 mg, 0.5 mmol) and allenamide 2a (570 mg, 2.0 mmol) in CH$_2$Cl$_2$ (5 mL). The mixture was stirred at room temperature until the disappearance of 1a (monitored by TLC; 1h). The solvent was removed under reduced pressure and the resulting residue was purified by flash chromatography (silica gel, hexanes/ethyl acetate 10:1) to yield compound 3a (186 mg, 81%). $^1$H-NMR (CDCl$_3$, 300 MHz): 2.42 (s, 3H), 2.77 (d, $J = 22.8$ Hz, 1H), 2.96 (d, $J = 22.8$ Hz, 1H), 5.03 (d, $J = 12.0$ Hz, 1H), 5.32 (d, $J = 12.0$ Hz, 1H), 5.39 (br s, 1H), 5.80 (br s, 1H), 6.19 (br s, 1H), 6.77 (br s, 1H), 6.91 (d, $J = 8.4$ Hz, 2H), 7.07-7.12 (m, 2H), 7.19-7.37 (m, 8H), 7.66 (d, $J = 7.5$ Hz, 2H). $^1$C-NMR (CDCl$_3$, 75 MHz): 21.6, 37.6, 66.0, 66.3, 114.4, 128.1, 128.3, 128.5, 129.0, 132.0, 134.3, 136.0, 136.5, 138.2, 142.8, 146.6, 147.1, 163.2. HRMS (EI) calculated for [C$_5$H$_9$N$_2$O$_5$S]$: (M$^+$): 459.1504, found 459.1507.

**Acknowledgements**

Financial support from Ministerio de Economía y Competitividad (MINECO) and Principado de Asturias (grants CTQ2013-41511-P, GRUPIN14-013) is gratefully acknowledged. E. L. thanks the Principado de Asturias for a predoctoral grant (Severo Ochoa Program). We thank Prof. J. M. González and Prof. A. Ballesteros for interesting discussions and Dr. J. Borge for his assistance in the collection of the X-ray data.

**References**

[1] Selected reviews on allene chemistry: a) L.-L. Wei, H. Xiong, R. P. Huang, *Acc. Chem. Res.* 2003, 36, 773; b) S. Ma, *Chem. Rev.* 2005, 105, 2829; c) B. Alcaide, P. Almendros, C. Aragoncillo, *Chem. Soc. Rev.* 2010, 39, 783; d) S. Ma, *Acc. Chem. Res.* 2009, 42, 1679; e) N. Krause, C. Winter, *Chem. Rev.* 2011, 111, 1994; f) S. Yu, S. Ma, *Angew. Chem. Int. Ed.* 2012, 51, 3074.

[2] Recent reviews on gold catalysis: a) R. Dorel, A. M. Echavarren, *Chem. Rev.* 2015, 115, 9028; b) C. Obradors, A. M. Echavarren, *Acc. Chem. Res.* 2014, 47, 902; c) A. S. K. Hashmi, *Acc. Chem. Res.* 2014, 47, 864; d) L. Zhang, *Acc. Chem. Res.* 2014, 47, 877; e) Y.-M. Wang, A. D. Lackner, F. D. Toste, *Acc. Chem. Res.* 2014, 47, 889; f) D.-H. Zhang, X.-Y. Tang, M. Shi, *Acc. Chem. Rev.* 2014, 47, 913; g) A. Fürstner, *Acc. Chem. Res.* 2014, 47, 925; h) B. Alcaide, P. Almendros, *Acc. Chem. Res.* 2014, 47, 939; i) L. Fensterbank, M. Malacria, *Acc. Chem. Res.* 2014, 47, 953; j) F. López, J. L. Mascareñas, *Beilstein J. Org. Chem.* 2011, 7, 1075; k) D. Garayalde, C. Nevado, *ACS Catal.* 2012, 2, 1462.

[3] For a recent excellent review on the reaction mechanisms of gold-catalyzed transformations of allenes, see: W. Yang, A. S. K. Hashmi, *Chem. Soc. Rev.* 2014, 43, 2941.

[4] J. Sabbatini, X. Huang, L. F. Veiros, N. Maulide, *Chem. Eur. J.* 2014, 20, 10636.

[5] Selected intermolecular [2+2] cycloadditions: a) X.-X. Li, L.-L. Zhu, W. Zhou, Z. Chen, *Org. Lett.* 2012, 14, 436; b) S. Suárez-Pantiga, C. Hernández-Díaz, M. Piedrafita, E. Rubio, J. M. González, *Adv. Synth. Catal.* 2012, 354, 1651; c) H. Faustino, P. Bernal, L. Castedo, F. López, J. L. Mascareñas, *Adv. Synth. Catal.* 2012, 354, 1658; d) S. Suárez-Pantiga, C. Hernández-Díaz, E. Rubio, J. M. González, *Angew. Chem. Int. Ed.* 2012, 51, 11552; e) P. Bernal-Albert, H. Faustino, A. Gimeno, G. Asensio, J. L. Mascareñas, F. López, *Org. Lett.* 2014, 16, 6196; f) M. Jia, M. Monari, Q.-Q. Yang, M. Bandini, *Chem. Commun.* 2015, 51, 2320.

[6] Selected examples of intermolecular [4+2] cycloadditions involving allenamides: a) H. Faustino, F. López, J. Castedo, J. L. Mascareñas, *Chem. Sci.* 2011, 2, 633; b) J. Francos, F. Grande-Carmona, H. Faustino, J. Iglesias-Sigüenza, E. Díez, I. Alonso, R. Fernández, J. M. Lassaletta, F. López, J. L. Mascareñas, *J. Am. Chem. Soc.* 2012, 134, 14322; c) V. Pirovano, L. Decataldo, E. Rossi, R. Vicente, *Chem. Commun.* 2013, 49, 3594; d) Y. Wang, P. Zhang, Y. Liu, F. Xia, J. Zhang, *Chem. Sci.* 2015, 6, 5564.

[7] a) W. Zhou, X.-X. Li, G.-H. Li, Y. Wu, Z. Chen, *Chem. Commun.* 2013, 49, 3552; b) G.-H. Li, W. Zhou, X.-X. Li, Q.-W. Bi, Z. Wang, Z.-G. Zhao, W.-X. Hu, Z. Chen, *Chem. Commun.* 2013, 49, 4770.

[8] H. Faustino, I. Varela, J. L. Mascareñas, F. López, *Chem. Sci.* 2015, 6, 2903.
[9] For a selection of relevant recent contributions on the applications of vinyldiazoacetates: a) S. N. Karad, R.-S. Liu, Angew. Chem. Int. Ed. 2014, 53, 5444; b) N. S. Y. Loy, A. Singh, X. Xu, C.-M. Park, Angew. Chem. Int. Ed. 2013, 52, 2212; c) X. Xu, P. Y. Zavalij, W. Hu, M. P. Doyle J. Org. Chem. 2013, 78, 1583; d) X. Xu, P. Y. Zavalij, M. P. Doyle, Angew. Chem. Int. Ed. 2012, 51, 9829.

[10] For selected recent examples of vinylogous reactivity of metal vinylicarbene intermediates, see: a) C. Qin, H. M. L. Davies, Org. Lett. 2013, 15, 6152; b) X. Xu, P. Y. Zavalij, M. P. Doyle, Angew. Chem. Int. Ed. 2013, 52, 12664; c) J. H. Hansen, H. M. L. Davies, Chem. Sci. 2011, 2, 457; d) J. Barluenga, G. Lonzi, L. Riesgo, L. A. López, M. Tomás, J. Am. Chem. Soc. 2010, 132, 13200.

[11] For a seminal contribution on gold-catalyzed carbene transfer from ethyl diazoacetate to unsaturated substrates, see: a) M. R. Fructos, T. R. Belderrain, P. de Frémont, N. M. Scott, S. P. Nolan, M. M. Díaz-Requejo, P. J. Pérez, Angew. Chem. Int. Ed. 2005, 44, 5284. For some relevant recent examples, see: b) J. F. Briones, H. M. L. Davies, J. Am. Chem. Soc. 2012, 134, 11916; c) Z. Yu, B. Ma, M. Chen, H.-H. Wu, L. Liu, J. Zhang, J. Am. Chem. Soc. 2014, 136, 6904; d) Y. Xi, Y. Su, Z. Yu, B. Dong, E. J. McClain, Y. Lan, X. Shi, Angew. Chem. Int. Ed. 2014, 53, 9817.

[12] For selected gold-catalyzed reactions of stabilized vinyldiazocompounds involving alkenylgold carbene intermediates, see: a) E. López, G. Lonzi, L. A. López, Organometallics, 2014, 33, 5924; b) J. F. Briones, H. M. L. Davies, J. Am. Chem. Soc. 2013, 135, 13314; c) G. Lonzi, L. A. López, Adv. Synth. Catal. 2013, 355, 1948; d) J. Barluenga, G. Lonzi, M. Tomás, L. A. López, Chem. Eur. J. 2013, 19, 1573; e) V. V. Pagar, A. M. Jadhav, R.-S. Liu, J. Am. Chem. Soc. 2011, 133, 20728.

[13] For selected gold-catalyzed reactions of stabilized vinyldiazocompounds that do not involve initial diazo decomposition into alkenylgold carbene intermediates, see: a) A. M. Jadhav, V. V. Pagar, R.-S. Liu, Angew. Chem. Int. Ed. 2012, 51, 11809; b) V. V. Pagar, A. M. Jadhav, R.-S. Liu, J. Org. Chem. 2013, 78, 5711; c) V. V. Pagar, R.-S. Liu, Angew. Chem. Int. Ed. 2015, 54, 4923.

[14] The gold(I)-catalyzed dimerization of vinyldiazocompounds has been recently reported: D. Zhang, G. Xu, D. Ding, C. Zhu, J. Li, J. Sun, Angew. Chem. Int. Ed. 2014, 53, 11070. See also, G. Xu, C. Zhu, W. Gu, J. Li, J. Sun, Angew. Chem. Int. Ed. 2015, 54, 883.

[15] For the gold(I)-catalyzed dimerization of allenamide derivatives, see references [5a-c]. The gold(I)-catalyzed allenamide [2+2+2]-cyclotrimmerization has been recently disclosed: C. Hernández-Díaz, E. Rubio, J. M. González, Eur. J. Org. Chem. 2016, 265.

[16] Some [3+2] cycloaddition reactions of chromium alkenyl(methoxy)carbene complexes with allenamides have been reported, see: J. Barluenga, R. Vicente, L. A. López, M. Tomás, J. Am. Chem. Soc. 2006, 128, 7050.

[17] Y. Wang, P. Zhang, D. Qian, J. Zhang, Angew. Chem. Int. Ed. 2015, 54, 14849.

[18] Along with the [3+2] cycloadduct 3a, products arising from the [2+2]-cycloaddition (dimerization) and [2+2+2]-cyclotrimmerization of the allenamide were also detected in the crude reaction mixture. Side products resulting from the dimerization of the vinyldiazocompound were also identified in minor amounts.

[19] CCDC-1427930 (3g) 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.

[20] For an interesting recent discussion on the nature of gold carbenoids, see: Y. Wang, M. E. Muratore, A. M. Echavarren, Chem. Eur. J. 2015, 21, 7332.

[21] The participation of allylic cations in the intramolecular reaction of α-oxo gold carbenes, generated in situ from the corresponding alkyne, and allenes has been recently postulated by Liu et al: R. K. Kawade, R.-S. Liu, Org. Lett. 2013, 15, 4094.
COMMUNICATION

Unusual Regioselectivity in the Gold(I)-Catalyzed [3+2] Carbocycloaddition Reaction of Vinyldiazo Compounds and N-Allenamides

Adv. Synth. Catal. Year, Volume, Page – Page

Enol López, Javier González, Luis A. López*