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Gold-catalyzed *endo*-selective cyclization of alkynylcyclobutanecarboxamides: synthesis of cyclobutane-fused dihydropyridones†

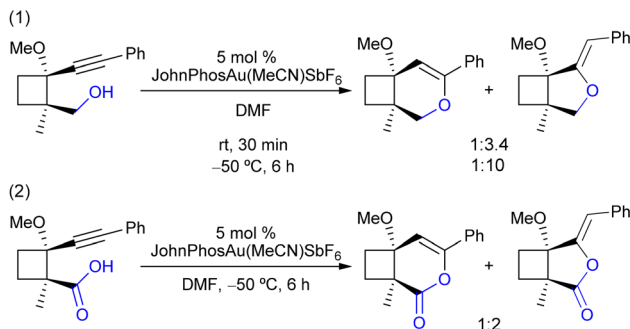
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Cyclobutane-fused dihydropyridones can be efficiently synthesized by a completely *endo*-selective gold-catalyzed cyclization of alkynylcyclobutanes bearing an appended amide, which proceeds under mild conditions. The observed selectivity, which is reversed from that previously observed for the cyclization of related alcohols and acids, is supported by DFT calculations.

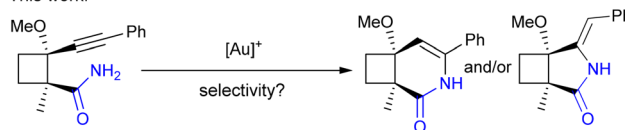
The cyclization of functionalized alkynes under gold catalysis has become a powerful tool in organic synthesis for the preparation of both carbo- and heterocyclic relevant structures.¹ These reactions, which rely on the selective activation of the triple bond by a carbophilic Lewis acidic gold complex, allow a significant increase in molecular complexity under mild conditions and show remarkable functional group tolerance, which has prompted their extensive use in total synthesis.² Nevertheless, in some occasions and depending on the nature of the starting materials, the *endo/exo* selectivity of the cyclization event can be difficult to predict and control.³ In this regard, we have recently described the gold-catalyzed cycloisomerization of alkynylcyclobutanes bearing an appended hydroxyl group (Scheme 1, 1), which showed moderate *exo* selectivity at room temperature that could be significantly improved by performing the reaction at $-50\text{ }^{\circ}\text{C}$.⁴ However, the selectivity of this cyclization turned out to be considerably dependent on the nature of the substitution on the starting material, and for example, when the hydroxyl group was replaced with a carboxylic acid moiety, little selectivity was achieved, even at low temperature (Scheme 1, 2).⁴

In this context, we became interested in evaluating the possibility of performing a selective cyclization of related alkynylcyclobutane carboxamides under gold catalysis. The products obtained in this transformation would be cyclobutane-fused N-heterocycles, which are interesting building blocks in medicinal chemistry.⁵ Thus, the cyclobutane unit is present in many natural products, including terpenoids, steroids, and alkaloids, which display versatile biological activities such as antimicrobial, antibacterial, antiviral and anticancer activities.⁶ Particularly interesting would be the achievement of an *endo*-selective cyclization, as it would provide a dihydropyridone ring, which can also be found in different drugs with valuable biological activities.⁷ Specifically, the 3-azabicyclo[4.2.0]octan-2-one motif is present in some natural products, such as sophoraline A, which shows hepatoprotective activity,⁸ and melicodenine G, with anti-proliferative activity against DLD-1 human colon cancer cells (Scheme 2).⁹

Previous results:



This work:



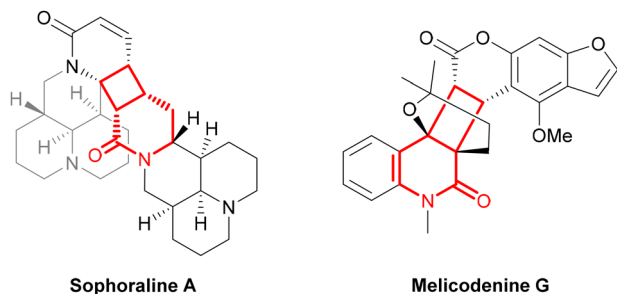
Scheme 1 Previously reported *endo/exo* selectivity in gold-catalyzed cyclization of alkynylcyclobutanes and the proposed strategy.

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† Electronic supplementary information (ESI) available: Experimental details and NMR spectra of all new compounds (PDF). See DOI: <https://doi.org/10.1039/d3ob00051f>





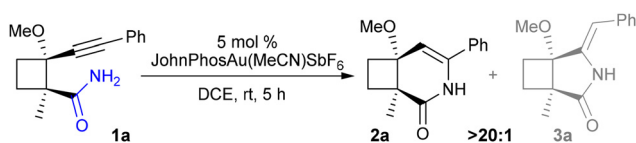
Scheme 2 Biologically active natural products containing the 3-azabicyclo[4.2.0]octan-2-one motif.

The strategy proposed in this work for the construction of cyclobutane-fused N-heterocycles relies on the modification of a pre-existing four-membered carbocyclic ring. This approach¹⁰ has been gaining interest in the last few years for complementing common approaches, usually based on [2 + 2] cycloaddition.¹¹

Herein we report our results on the gold-catalyzed cycloisomerization of alkynylcyclobutane carboxamides, and provide an explanation, based on DFT calculations, for the observed selectivity.

At the outset, the reaction of model alkynylcyclobutane **1a**, bearing an appended carboxamide group, was tested under the conditions previously determined as optimal for the cycloisomerization of related hydroxymethyl-substituted alkynylcyclobutanes (5 mol% JohnPhosAu(MeCN)SbF₆ as the catalyst at –50 °C in dimethylformamide), but the reaction was too sluggish. Therefore, it was necessary to increase the temperature to get useful conversions. Thus, full conversion was reached at room temperature after 5 h in dichloroethane, and remarkably, complete regioselectivity was achieved under these conditions, obtaining cyclobutane-fused dihydropyridone **2a**, coming from a 6-*endo* cyclization, as the only observable product in the crude reaction mixture (Scheme 3).¹²

DFT studies were performed to rationalize the high *endo* selectivity obtained in the cyclization of alkynylcyclobutane carboxamide **1a** and the reversal of selectivity observed with respect to the cycloisomerization of related hydroxymethyl substituted alkynylcyclobutanes. The formation of the 6-*endo* product was preferred over the 5-*exo* product with $\Delta\Delta G^\ddagger = +3.6 \text{ kcal mol}^{-1}$ for **1a**, justifying the exclusive formation of the product 6-*endo* **2a** (Fig. 1). For the alcohol derivative, calculations at room temperature and –50 °C were performed, which showed that in both cases the formation of the 5-*exo* product is favoured over the 6-*endo* product.¹³ Therefore, the



Scheme 3 Initial result: selective *endo* cyclization.

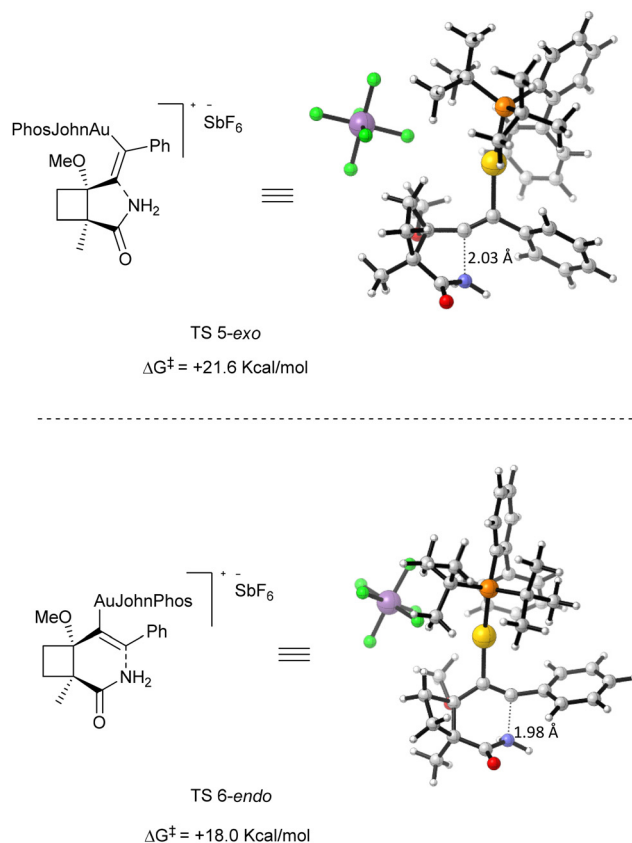
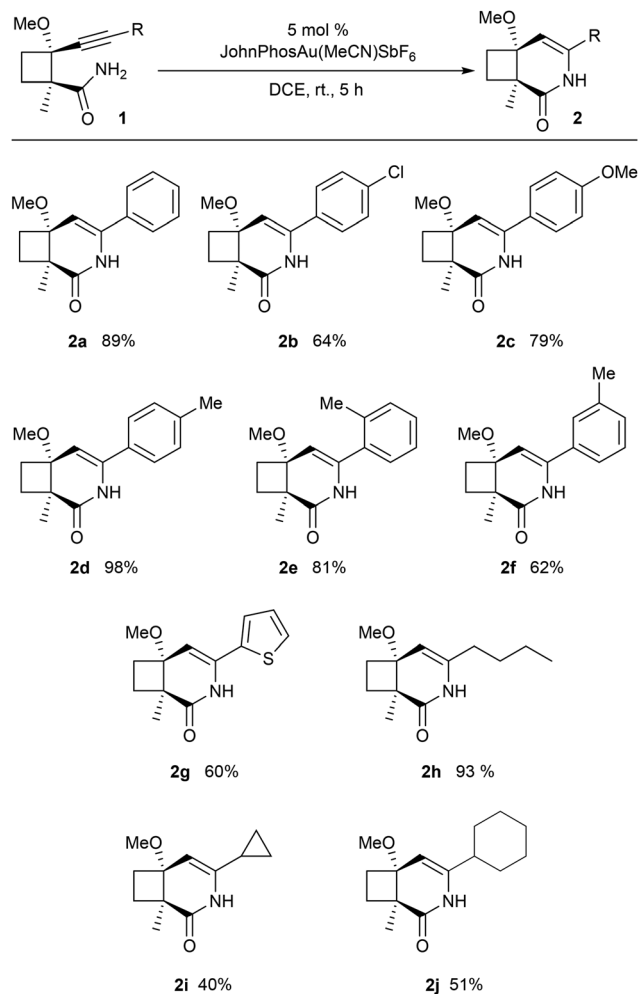


Fig. 1 Transition states for the 5-*exo* and 6-*endo* cyclization.

nature of the nucleophilic group is the determinant of the *endo/exo* selectivity. As the transition states were found to be late ones,¹³ the selectivity could be attributed to the higher stability of the product coming from a 6-*endo* cyclization than that of the one that comes from a 5-*exo* process. This difference in stability could be due to a higher strain in the five-membered ring, which shows a larger deviation from the ideal sp^2 angle for the carbonyl carbon atom. This strain would not be present in the products obtained from the cyclization of hydroxymethyl-substituted alkynylcyclobutanes.

Next, we explored the scope of the gold-catalyzed cyclization of alkynylcyclobutanecarboxamides **1** to check if complete *endo*-selectivity was maintained when varying the nature of the substituent of the triple bond and assess its usefulness for the synthesis of cyclobutane-fused dihydropyridones. Noteworthy, different 3-azabicyclo[4.2.0]oct-4-en-2-ones **2** could be obtained in good yields by stirring a solution of the corresponding starting material **1** in dichloroethane at room temperature in the presence of 5 mol% JohnPhosAu(MeCN)SbF₆ (Scheme 4). Phenyl rings with either electron-withdrawing (**2b**) or electron-donating groups (**2c–f**), located in the *ortho*, *meta* or *para* position, are well tolerated as substituents of the triple bond of the starting material. Heteroaromatics (**2g**) and alkyl groups, either linear (**2h**) or cyclic (**2i** and **2j**), are also suitable groups for this transformation, although cyclic alkyl groups provided somewhat lower yields. Remarkably, a com-

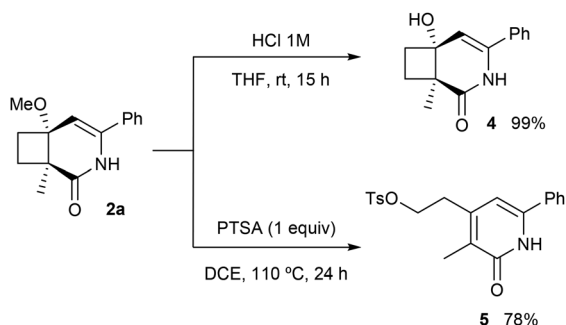




Scheme 4 Synthesis of cyclobutane-fused dihydropyridones by gold-catalyzed 6-*endo* cyclization of alkynylcyclobutanecarboxamides **1**.

pletely 6-*endo* selective cyclization was observed in all cases, regardless of the nature of the alkyne substituent.

Finally, considering the push-pull nature of the cyclobutane moiety present in 3-azabicyclo[4.2.0]oct-4-en-2-one **2a**,¹⁴ we performed some experiments aimed at evaluating the stability of this ring and the possibility of achieving a selective



Scheme 5 Further transformations of cyclobutane-fused dihydropyridone **2a**.

ring-opening to access novel building blocks (Scheme 5).¹⁵ No conversion was observed upon heating **2a** to 110 °C, showing significant thermal stability of this structure. Reaction of **2a** with 1 M HCl at room temperature did not lead to ring opening, but provided quantitatively compound **4**, in which the ether moiety was cleaved. Lastly, heating **2a** to 110 °C in the presence of PTSA produced the cyclobutane ring-opening, giving rise to 3,4,6-trisubstituted pyridin-2-one **5** in a high yield.¹⁶

Conclusions

In conclusion, gold-catalyzed reactions of alkynylcyclobutanes with a pendant amide group proceed selectively through a 6-*endo* cyclization, providing in good yields cyclobutane-fused pyridones, fragments with potential interest in medicinal chemistry. The high selectivity observed for these reactions is noteworthy, considering that the cyclization of alkynylcyclobutanes having a pendant alcohol provides mixtures of *endo/exo* products, with the one coming from an *exo* cyclization being the major one. DFT calculations are in agreement with the observed selectivity, which is maintained regardless of the substituent of the triple bond of the starting material. The cyclobutane ring present in the obtained products shows remarkable stability, despite having push-pull character. It is stable upon heating or in the presence of a strong acid at room temperature, and only when heating in the presence of an acid is the ring opening observed.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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References

- (a) C. M. Hendrich, K. Sekine, T. Koshikawa, K. Tanaka and A. S. K. Hashmi, *Chem. Rev.*, 2021, **121**, 9113–9163; (b) R. L. Reyes, T. Iwai and M. Sawamura, *Chem. Rev.*, 2021, **121**, 8926–8947; (c) D. Campeau, D. F. León Rayo, A. Mansour, K. Muratov and F. Gagosz, *Chem. Rev.*, 2021,



- 121, 8756–8867; (d) D. Li, W. Zang, M. J. Bird, C. J. T. Hyland and M. Shi, *Chem. Rev.*, 2021, **121**, 8685–8755; (e) M. Mato, A. Franchino, C. García-Morales and A. M. Echavarren, *Chem. Rev.*, 2021, **121**, 8613–8684; (f) C. C. Chintawar, A. K. Yadav, A. Kumar, S. P. Sancheti and N. T. Patil, *Chem. Rev.*, 2021, **121**, 8478–8558; (g) E. Aguilar and J. Santamaria, *Org. Chem. Front.*, 2019, **6**, 1513–1540; (h) R. Dorel and A. M. Echavarren, *Chem. Rev.*, 2015, **115**, 9028–9072.
- 2 (a) K. Holzschneider and S. F. Kirsch, *Isr. J. Chem.*, 2018, **58**, 596–607; (b) V. Mouriès-Mansuy and L. Fensterbank, *Isr. J. Chem.*, 2018, **58**, 586–595; (c) P. Y. Toullec and V. Michelet, *Isr. J. Chem.*, 2018, **58**, 578–585; (d) P. McGee, J. Brousseau and L. Barriault, *Isr. J. Chem.*, 2018, **58**, 511–520; (e) A. Fürstner, *Angew. Chem., Int. Ed.*, 2018, **57**, 4215–4233; (f) K. Sugimoto and Y. Matsuya, *Tetrahedron Lett.*, 2017, **58**, 4420–4426; (g) D. Pflästerer and A. S. K. Hashmi, *Chem. Soc. Rev.*, 2016, **45**, 1331–1367.
- 3 (a) S. K. Nanda and R. Mallik, *Chem. – Eur. J.*, 2021, **27**, 15571–15604; (b) Y. Yang, Y. Liu, R. Zhu, C. Liu and D. Zhang, *J. Org. Chem.*, 2019, **84**, 9705–9713; (c) J. A. Goodwin and A. Aponick, *Chem. Commun.*, 2015, **51**, 8730–8741.
- 4 M. S. Garre, D. Sucunza, E. Aguilar, P. García-García and J. J. Vaquero, *J. Org. Chem.*, 2019, **84**, 5712–5725.
- 5 (a) M. S. Oderinde, E. Mao, A. Ramirez, J. Pawluczyk, C. Jorge, L. A. M. Cornelius, J. Kempson, M. Vetrichelvan, M. Pitchai, A. Gupta, A. K. Gupta, N. A. Meanwell, A. Mathur and T. G. Murali Dhar, *J. Am. Chem. Soc.*, 2020, **142**, 3094–3103; (b) B. Cox, K. I. Booker-Milburn, L. D. Elliott, M. Robertson-Ralph and V. Zdorichenko, *ACS Med. Chem. Lett.*, 2019, **10**, 1512–1517.
- 6 (a) Y.-Y. Fan, X.-H. Gao and J.-M. Yue, *Sci. China: Chem.*, 2016, **59**, 1126–1141; (b) V. M. Dembitsky, *Phytomedicine*, 2014, **21**, 1559–1581; (c) V. M. Dembitsky, *J. Nat. Med.*, 2008, **62**, 1–33.
- 7 (a) K. T. Homan, K. M. Larimore, J. M. Elkins, M. Szklarz, S. Knapp and J. J. G. Tesmer, *ACS Chem. Biol.*, 2015, **10**, 310–319; (b) X. Huang, S. Broadbent, C. Dvorak and S.-H. Zhao, *Org. Process Res. Dev.*, 2010, **14**, 612–616; (c) K. B. Goodman, *et al.*, *J. Med. Chem.*, 2007, **50**, 6–9; (d) P. G. Nantermet, J. C. Barrow, H. G. Selnick, C. F. Homnick, R. M. Freidinger, R. S. L. Chang, S. S. O'Malley, D. R. Reiss, T. P. Broten, R. W. Ransom, D. J. Pettibone, T. Olah and C. Forray, *Bioorg. Med. Chem. Lett.*, 2000, **10**, 1625–1628.
- 8 X. Yuan, J. Jiang, Y. Yang, X. Zhang, Z. Feng and P. Zhang, *Chin. Chem. Lett.*, 2022, **33**, 2923–2927.
- 9 K.-i. Nakashima, M. Oyama, T. Ito, Y. Akao, J. R. Witono, D. Darnaedi, T. Tanaka, J. Murata and M. Iinuma, *Tetrahedron*, 2012, **68**, 2421–2428.
- 10 (a) T. J. Osberger, S. L. Kidd, T. A. Kinga and D. R. Spring, *Chem. Commun.*, 2020, **56**, 7423–7426; (b) M. Wang, J. Chen, Z. Chen, C. Zhong and P. Lu, *Angew. Chem., Int. Ed.*, 2018, **57**, 2707–2711.
- 11 (a) For a revision on catalytic approaches to assemble cyclobutane motifs in natural product synthesis: M. Wang and P. Lu, *Org. Chem. Front.*, 2018, **5**, 254–259; (b) For a revision on synthesis of cyclobutanes by olefin [2 + 2] photocycloaddition: S. Poplata, A. Tröster, Y. Q. Zou and T. Bach, *Chem. Rev.*, 2016, **116**, 9748–9815.
- 12 We have previously observed for related alkynylcyclopropanes that the 5-*exo* cyclization pathway is somehow favored when using OH as an internal nucleophile, compared to the use of CONH₂, although the effect was less pronounced than that in the current case: J. M. Fernández-García, H. A. Garro, L. Fernández-García, P. García-García, M. A. Fernández-Rodríguez, I. Merino and E. Aguilar, *Adv. Synth. Catal.*, 2017, **359**, 3035–3051.
- 13 See the ESI† for details.
- 14 (a) N. Vemula and B. L. Pagenkopf, *Org. Chem. Front.*, 2016, **3**, 1205–1212; (b) H.-U. Reissig and R. Zimmer, *Angew. Chem., Int. Ed.*, 2015, **54**, 5009–5011.
- 15 For a gold-catalyzed cyclization of related cyclopropanes which proceeds with ring-opening to yield azepinones, see ref. 12.
- 16 For a similar acid-catalyzed ring opening of alkoxy-cyclobutanes: L. Serusi, M. Bonnans, A. Luridiana, F. Secci, P. Caboni, T. Boddaert, D. J. Aitken and A. Frongia, *Adv. Synth. Catal.*, 2019, **361**, 1908–1902.

