Gold-Catalyzed Addition of Propargyl Acetates to Olefins via O -Acyl Migration/Cyclopropanation Sequence: Insight into the Diastereoselective Formation of the Alkene

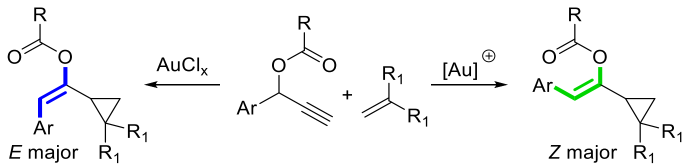
Marion Barbazanges, Yves Gimbert, Louis Fensterbank

Gold-catalyzed addition of propargyl acetates to olefins via *O*-acyl migration/cyclopropanation sequence: insight into the diastereoselective formation of the alkene

Marion Barbazanges,*‡ Yves Gimbert‡,§ and Louis Fensterbank‡

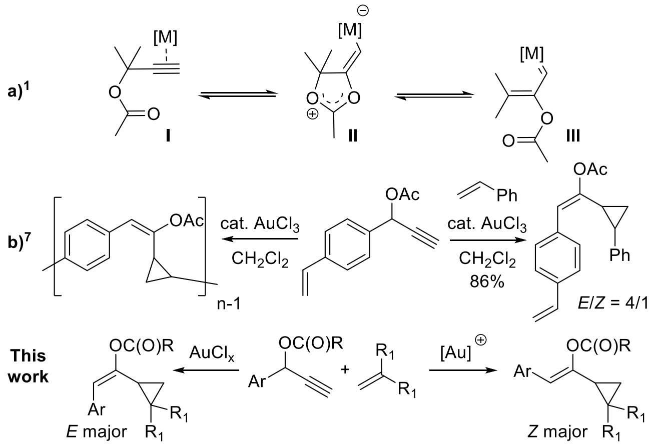
‡ Marion Barbazanges, Yves Gimbert, Louis Fensterbank, Institut Parisien de Chimie Moléculaire, Sorbonne Université, CNRS, Institut Parisien de Chimie Moléculaire (UMR CNRS 8232), 4 place Jussieu, 75252 Paris Cedex 05 (France). @IPCM_Sorbonne
e-mail: marion.barbazanges@sorbonne-universite.fr

§ Yves Gimbert, Département de Chimie Moléculaire (UMR CNRS 5250), Université Grenoble Alpes, F-38050 Grenoble, France



Abstract. This article discloses a study on the well-known addition of propargyl acetates to olefins via an *O*-acyl migration/cyclopropanation sequence. Herein, we show that the stereochemical outcome of the olefin is strongly dependent on the gold-catalyst and reaction parameters (concentration, temperature, alkene partner equivalents); *E* and the *Z* isomers can be selectively formed by judicious choice of reaction conditions.

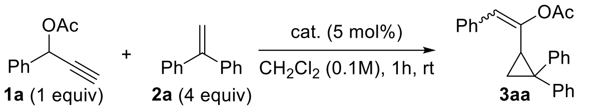
The electrophilic activation of propargyl acetates **I** by metals to generate metal carbenes **III** via 1,2-*O*-acyl migration constitutes a powerful and versatile tool for various valuable synthetic transformations generating molecular diversity (Scheme 1a).[1] The intramolecular transformation was first discovered in 1976 by Ohloff ($ZnCl_2$),[2] followed by Rautenstrauch in 1984 (palladium and platinum),[3] and re-evidenced by our group in 2002 with $PtCl_2$.[1j] The *intermolecular* trapping of carbene **III** by an alkene was first reported by Ohe and Uemura with a ruthenium(II) catalyst.[4] Subsequently, this reaction has witnessed intense developments due to the reactivity of π-acidic metals, mainly gold catalysts,[1] with applications in total syntheses of natural products[5] and in asymmetric catalysis.[6] In 2014, we reported the polymerization of bifunctional monomers via gold-catalyzed polycyclopropanation.[7] Using $AuCl_3$ as a catalyst, we obtained conjugated polymers integrating a cyclopropyl/vinyl/phenyl repeating unit. Notably, this transformation provided the *E* stereoisomer as the major product (Scheme 1b), which marked a sharp contrast with previously reported intermolecular reactions featuring only *Z*-isomer adducts, generally obtained by using cationic gold(I) catalysts.[1,6a,8] This piqued our interest since, contrary to cyclopropanation diastereoselectivity that has been well investigated,[8] alkene stereochemical outcome has rarely been discussed. Unsurprisingly, the only reported *E*-selective synthesis arose from intramolecular transformations yielding cyclic olefins.[1] To the best of our knowledge, only a few other intermolecular examples provide the *E*-isomer, yet always as the minor product.[9,1g] Moreover, *Z*-selectivity has also been observed when using $PtCl_2$,[10] cationic rhodium(I)[11] or $[RuCl_2(CO)_3]_2$[12] catalysts.[13]
This intriguing difference between our experimental observations and the results published in the literature led us to study the *Z*/*E* diastereoselectivity of this reaction, and its dependence on reaction conditions.[14,8a]



Scheme 1: Gold-Catalyzed Migration of Propargyl Acetate

In our study, we selected propargyl acetate **1a** and 1,1-disubstituted alkene **2a**, as the carbene acceptor, devoid of a prochiral face to suppress complex diastereomeric mixtures. We first screened the gold catalyst. Chlorinated gold complexes (Table 1, entries 1-5) demonstrated a preference for formation of the *E*-isomer (*E*/*Z* ratios ranging from 73/27 to 83/17). Using fully cationic and halide-free gold complexes (entries 6-9) induced an inversion of the stereoselectivity, preferentially furnishing the *Z*-isomer as the major product. When di-cationic $[Au(pic)][SbF_6]_2$ was used, only the *Z*-isomer was observed, albeit with very low conversion (entry 6). Using $[PPh_3Au][SbF_6]$ improved conversion, accompanied by the formation of numerous side-products, giving an *E*/*Z* ratio of 14/86. When JohnPhos was used as the ligand (entries 8-9), yields increased while the selectivity slightly decreased. Notably, the appearance of the reaction mixture was very different in both cases. When chlorinated gold complexes were used, the color of the reaction mixture turned to purple-to-black aspect only a few minutes after adding the alkyne partner (entries 1 to 5), whereas it remains light-yellow with fully cationic gold (entries 6 to 9). Thus, the *in-situ* formation of gold clusters or nanoparticles, that are known to catalyze such cycloisomerizations,[15] cannot be excluded in the case of chlorinated gold complexes that are known to be unstable in solution.[16]

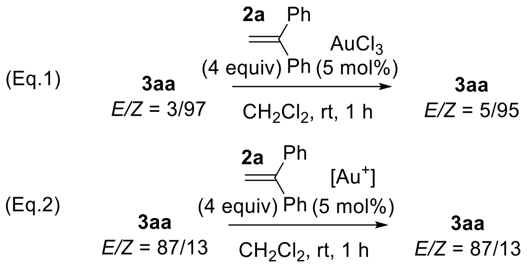
Table 1: Catalyst screening



	cat.	Yield (conversion)	E	Z
1[a]	**$AuCl_3$**	80%	82	18
2[a]	**AuCl**	74% (82%)	80	20
3[a]	**$NaAuCl_4$**	84%	73	27
4[a]	**$Au(pic)Cl_2$**	94%	81	19
5[a]	**$AupicCl_2$+$AgSbF_6$**	65% (80%)	83	17
6	**$AupicCl_2$+2$AgSbF_6$**	(3%)	0	100
7	**PPh_3AuCl + $AgSbF_6$**	34% (73%)	14	86
8	**$[Au]^+$**	89%	32	68
9	**[Au]+$AgSbF_6$**	70% (90%)	31	69

[a]: purple-to-black aspect of the reaction mixture. pic = 2-pyridinecarboxylato; $[Au]^+$: [*o*-Ph-C_6H_4-P(*t*Bu)$_2$Au(MeCN)][SbF_6]; [Au]: *o*-Ph-C_6H_4-P(*t*Bu)$_2$AuCl; cat.: catalyst; Conditions: **1a** (75 mg, 0.43 mmol, 1 equiv), **2a** (0.3 mL, 1.72 mmol, 4 equiv), cat. (22 µmol, 5 mol%), CH_2Cl_2 (4.3 mL), 1h, rt.

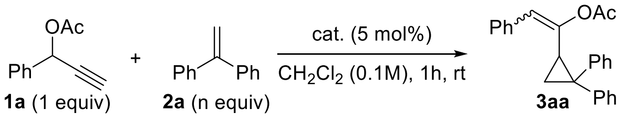
When the reaction is complete, the dr is constant and nearly no *E*-to-*Z* or *Z*-to-*E* isomerization was observed, even by re-subjecting products to reaction conditions (Scheme 2, and SI, section 2.2.3). In both cases, **3aa** was fully recovered.



Scheme 2: Configurational stability of cycloisomerization adducts; $[Au]^+$: [*o*-Ph-C_6H_4-P(*t*Bu)$_2$Au(MeCN)][SbF_6]; Conditions: (Eq.1): **3aa** (80 mg, 0.23 mmol, 1 equiv, *E*/*Z* = 3/97), **2a** (0.16 mL, 0.90 mmol, 4 equiv), $AuCl_3$ (3.4 mg, 11 µmol, 5 mol%), CH_2Cl_2 (4.5 mL), 1h, rt. (Eq.2): **3aa** (130 mg, 0.37 mmol, 1 equiv, *E*/*Z* = 87/13), **2a** (0.26 mL, 1.47 mmol, 4 equiv), $[Au]^+$ (14 mg, 18 µmol, 5 mol%), CH_2Cl_2 (4.5 mL), 1h, rt.

The influence of alkene partner stoichiometry was then evaluated. Interestingly, increasing equivalents of alkene resulted in greater the proportions of *E* diastereoisomer, independent of the catalyst used (Table 2). Changing alkene stoichiometry from 1 to 4 equivalents, increased ***E*/*Z*** dr from **50**/50 to **82**/18 when $AuCl_3$ was used (entries 1-3), and from **9**/91 to **32**/68 using a cationic gold catalyst (entries 4-6).

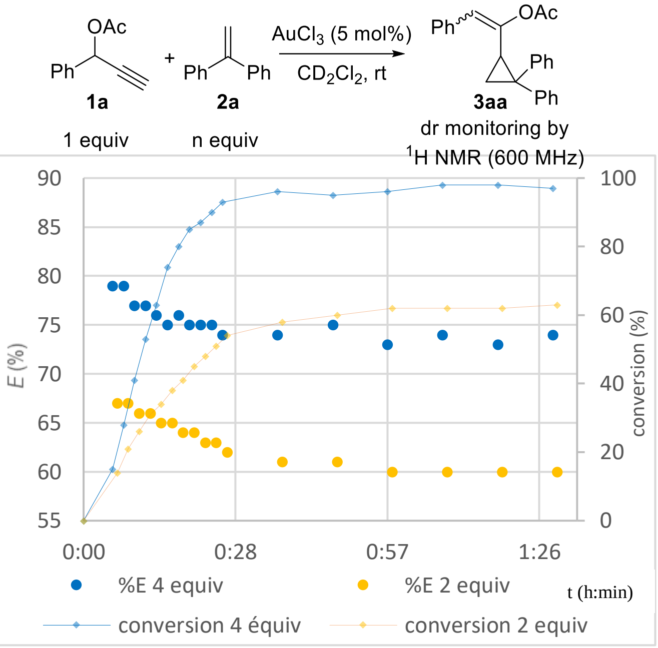
Table 2: Alkene stoichiometry



	n	cat.	Yield (conversion)	E	Z
1	**1**	$AuCl_3$	(55%)	50	50
2	**2**	$AuCl_3$	51% (59%)	71	29
3	**4**	$AuCl_3$	94%	82	18
4	**1**	$[Au]^+$	68%	9	91
5	**2**	$[Au]^+$	75%	19	81
6	**4**	$[Au]^+$	89%	32	68

$[Au]^+$: [*o*-Ph-C_6H_4-P(*t*Bu)$_2$Au(MeCN)][SbF_6]; Conditions: **1a** (75 mg, 0.43 mmol, 1 equiv), **2a** (n equiv), cat. (22 µmol, 5 mol%), CH_2Cl_2 (4.3 mL), 1h, rt.

Monitoring the dr during the reaction confirmed these findings as the percentage of *E* diastereoisomer slowly decreases with increasing conversion, which is consistent with the decrease of alkene equivalents (Figure 1).

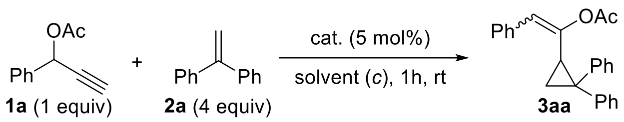


Conditions: **1a** (15 mg, 86 µmol, 1 equiv), **2a** (30µL, 0.17 mmol, 2 equiv (yellow) or 61µL, 0.34 mmol, 4 equiv (blue)), $AuCl_3$ (1.3 mg, 4.3 µmol, 5 mol%), CD_2Cl_2 (1mL), 300 K).

Figure 1: ^{1}H NMR monitoring of the diastereoisomeric ratio during the reaction (600 MHz, CD_2Cl_2, 293 K)

The effect of reaction concentration was also examined (Table 3). Higher concentrations favor formation of the *E* diastereoisomer, irrespective of the catalyst used. Using $AuCl_3$, the best drs were obtained in concentrated reaction mixtures (entries 1-2, *c* 0.2M), while with cationic gold dilute reaction mixtures resulted in higher diastereoselectivities (entries 9-10, *c* 0.05M). Toluene was found to be the solvent of choice for highest dr, whichever catalyst was used (entries 2 and 10, and SI, section 2.2.4).[17]

Table 3: Concentration



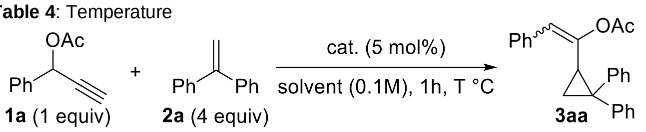
	cat.	solvent	*c*	Yield (conv)	E	Z
1	$AuCl_3$	CH_2Cl_2	**0.2M**	88%	88	12
2	$AuCl_3$	toluene	**0.2M**	60% (80%)	91	9
3	$AuCl_3$	CH_2Cl_2	**0.1M**	94%	82	18
4	$AuCl_3$	toluene	**0.1M**	95%	87	13
5	$AuCl_3$	CH_2Cl_2	**0.05M**	(67%)	76	24
6	$[Au]^+$	CH_2Cl_2	**0.2M**	74%	42	58
7	$[Au]^+$	CH_2Cl_2	**0.1M**	89%	32	68
8	$[Au]^+$	toluene	**0.1M**	51%	11	89
9	$[Au]^+$	CH_2Cl_2	**0.05M**	73%	21	79
10	$[Au]^+$	toluene	**0.05M**	77%	6	94

$[Au]^+$: [*o*-Ph-C_6H_4-P(*t*Bu)$_2$Au(MeCN)][SbF_6] ; Conditions: **1a** (75 mg, 0.43 mmol, 1 equiv), **2a** (0.3 mL, 1.72 mmol, 4 equiv), cat. (22 µmol, 5 mol%), solvent (*c*), 1h, rt.

Finally, the effect of temperature was also evaluated (Table 4). Irrespective of the catalyst, low temperature (0°C, entries 3-4 and

8) favors *E*-isomer formation while higher temperature (40°C, entries 1, 5-6) favors the *Z*-isomer. Once again toluene provided the highest dr (entries 3-4; 5-6).

Table 4: Temperature



	cat.	solvent	T	Yield (conversion)	*E*	*Z*
1	$AuCl_3$	CH_2Cl_2	**40°C**	(50%)	**70**	30
2	$AuCl_3$	CH_2Cl_2	**rt**	94%	**82**	18
3	$AuCl_3$	CH_2Cl_2	**0°C**	(77%)	**90**	10
4	$AuCl_3$	toluene	**0°C**	(38%)	**100**	0
5	$[Au]^+$	toluene	**40°C**	52% (75%)	4	**96**
6	$[Au]^+$	CH_2Cl_2	**40°C**	72%	21	**79**
7	$[Au]^+$	CH_2Cl_2	**rt**	89%	32	**68**
8	$[Au]^+$	CH_2Cl_2	**0°C**	75%	47	**53**

$[Au]^+$: [*o*-Ph-C_6H_4-P(*t*Bu)$_2$Au(MeCN)][SbF_6]; Conditions: **1a** (75 mg, 0.43 mmol, 1 equiv), **2a** (0.3 mL, 1.72 mmol, 4 equiv), cat. (22 µmol, 5 mol%), solvent (4.3 mL), 1h.

We then screened the scope and limitations (Figure 2). No change in reactivity was observed by changing the acetate function to a benzoate or a pivaloate: the transformation remains stereoselective and predominantly leads to the *E*-isomer when $AuCl_3$ is used as catalyst, whereas the *Z* product is generated with $[Au]^+$ (**3ba** and **3ca**). It was also possible to change the alkene partner to methylenecyclohexane (**3ab** and **3bb**) which displayed similar reaction outcomes, albeit requiring longer reaction times. On the other hand, when 2-methylene-1,3-diphenylpropane was used as the alkene partner, the *Z*-isomer was formed in all cases, an increase in the proportion of *E*-isomer being observed when $AuCl_3$ was used (**3ac**).
Introduction of a thiophene moiety led to numerous by-products and lower yields ranging from 28% and 48%, however the vinylcyclopropane **3da** was formed in the expected diastereoselective tendency respective of the gold catalyst used.

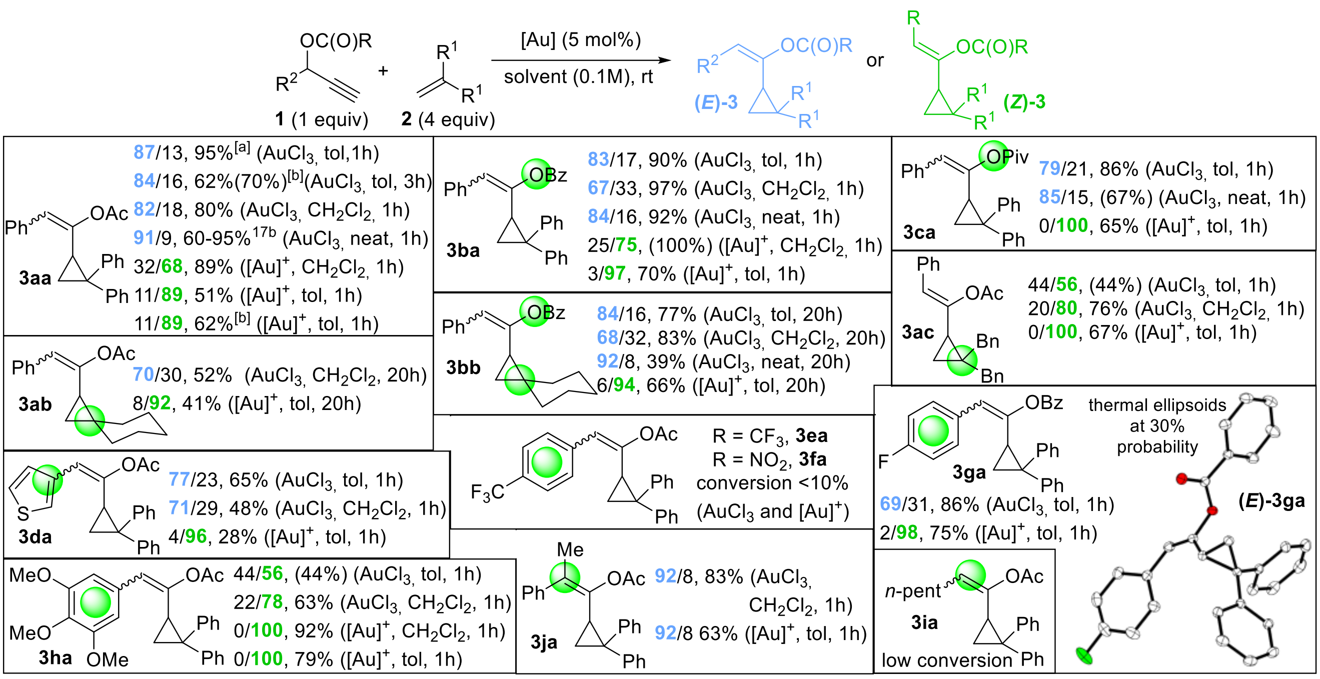
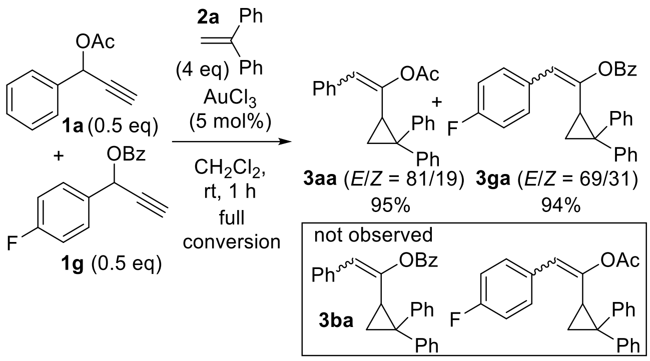


Figure 2. Scope and limitations; [a] **1** 0.43 mmol scale, *E*/*Z* measured on the crude material by ^{1}H NMR spectroscopy, yield (conversion) (catalyst, solvent, duration); [b] **1** 2 mmol scale; tol: toluene, $[Au]^+$: [*o*-Ph-C_6H_4-P(*t*Bu)$_2$Au(MeCN)][SbF_6].

Variation of substituents on the aryl group was next examined. Electron-withdrawing substituents such as *p*-nitro or *p*-trifluoromethyl groups drastically decreased reactivity (**3ea** and **3fa**). However, we succeeded in introducing a *p*-fluorine moiety that afforded full conversion, albeit with a small increase of the *Z*-isomer (**3ga** *vs* **3ba**). The introduction of electron-rich methoxy-substituents led to full conversion, and a selectivity always in favor of the *Z*-isomer, irrespective of the catalyst used (**3ha**). Nevertheless, a catalyst effect was observed, $[Au]^+$ only led to the *Z*-isomer, whereas $AuCl_3$ led to partial formation of the *E*-product (*E*/*Z* = 44/56). Introduction of an alkyl chain at the propargylic position led to very low conversion (**3ia**).[18] Finally, introduction of a quaternary center led to the same *E* selectivity in both cases (**3ja**). This last result could be explained by post-isomerization as suggested by Liu,[19] due to the tetrasubstituted nature of the alkene.

Given that ester scrambling could be responsible for the observed *E*-selectivity during the reaction with $AuCl_3$,[14c] we sought to rule out this possibility. When a 1:1 mixture of propargylic acetate **1a** and benzoate **1g** was subjected to reaction conditions, we only observed the expected products **3aa** and **3ga**, and no structure arising from ester elimination-re-addition (Scheme 3 and SI, section 2.2.6).



Scheme 3: Ester scrambling evaluation; Conditions: **1a** (37.5 mg, 0.215 mmol, 0.5 equiv), **1g** (55 mg, 0.215 mmol, 0.5 equiv), **2a** (0.3 mL, 1.72 mmol, 4 equiv), $AuCl_3$ (5.6 mg, 22 µmol, 5 mol%), CH_2Cl_2 (4 mL), rt, 1h.

From these experimental results, we can conclude that the use of a fully cationic Au-catalyst preferentially furnishes the *Z*-product, also favored under thermodynamic conditions (dilute reaction mixture, high temperature) while the use of a chlorinated catalyst such as $AuCl_3$ preferentially leads to the *E* product, generally formed under kinetic conditions (concentrated reaction mixture, low temperature, excess of alkene).

In this work, we focused on the gold-catalyzed 1,2-*O*-acyl migration/trapping of the intermediate carbene by a double bond leading to vinylcyclopropanes. Interestingly, only a scarce number reports have indicated a relationship between the stereochemistry of the double bond and the nature of the catalyst used; additionally, the formation of the *E* stereoisomer has rarely been reported in the literature for such an intermolecular transformation. Thus, we studied the factors influencing this and developed conditions allowing to obtain a stereoselective access to both isomers. Notably, we showed that the diastereomeric ratio is a direct function of the nature of the catalyst and substrates, alkene and alkyne equivalents, solvent, concentration and temperature. The stereochemistry of all obtained species is supported by 2D NOESY NMR spectroscopy and X-ray crystallography. The observation of the reaction mixture color, which turned from yellow to purple-to-black in a few minutes when a chlorinated gold catalyst was used suggests the *in-situ* formation of gold clusters or nanoparticles, which would be responsible of this unusual *E*-stereochemical outcome. Through a scrambling experiment, we proved that this selectivity did not arise from an ester elimination-re-addition process. DFT calculations are currently underway to rationalize our experimental observations.

Data availability Statement

The data underlying this study are available in the published article and its Supporting Information.

Supporting Information Statement

The Supporting Information is available free of charge at.
It includes synthetic procedures, ^1H and ^{13}C NMR spectra for all new compounds as well as non-commercially available cycloisomerization substrates and products, X-ray crystallographic analysis of **3ga** (CCDC 2095223), 2D NOESY analysis for diastereoisomers attribution, solvent evaluation, configurational stability study and NMR monitoring of the reaction.

Keywords

cycloisomerization • diastereoselectivity • gold • cyclopropane

Acknowledgements

This work was supported by the CNRS, Sorbonne Université and IUF. We are grateful to Dr. E. Derat, A. Guerault and Dr. H. Dossmann for fruitful discussion, G. Gontard for X-ray crystallography, G. Durosay, M. Ardin, P. de Sevin, C. Kaldhoun, and L. Gauthier for synthetic contribution, and O. Sadek for proof-reading the manuscript.

References

[1] For reviews: (a) Boyle, J. W.; Zhao, Y.; Chan, P. W. H. *Synthesis* **2018**, *50*, 1402-1416; (b)Day, D. P.; Chan, P. W. H. Gold-Catalyzed Cycloisomerizations of 1,n-Diyne Carbonates and Esters, *Adv. Synth. Catal*. **2016**, *358*, 1368–1384; (c) Shiroodi, R. K.; Gevorgyan, V. Metal-catalyzed double migratory cascade reactions of propargylic esters and phosphates, *Chem. Soc. Rev*. **2013**, *42*, 4991–5001; (d) Shu, X.-Z.; Shu, D.; Schienebeck, C. M.; Tang, W. Rhodium-catalyzed acyloxy migration of propargylic esters in cycloadditions, inspiration from the recent ‘‘gold rush’’, *Chem. Soc. Rev.* **2012**, *41*, 7698–7711; For representative examples, see: (e) Conyers, R. C.; Barnes, C. L.; Gung, B. W. Gold catalysis: up to six new bonds by a domino [3+2]/[2+1]/[2+1] cycloaddition, *Tetrahedron Lett.* **2015**, *56*, 3318–3321; (f) Conyers, R. C.; Gung, B. W. Gold(I)-Catalyzed Divergence in the Preparation of Bicyclic Enol Esters: From Exclusively [3C+2C]-Cycloaddition Reactions to Exclusive Formation of Vinylcyclopropanes, *Chem. Eur. J.* **2013**, *19*, 654–664; (g) Garayalde, D.; Krueger, K.; Nevado, C. Gold-Catalyzed Cyclopenta- and Cycloheptannulation Cascades: A Stereocontrolled Approach to the Scaffold of Frondosins A and B, *Angew. Chem. Int. Ed.* **2011**, *50,* 911–915; (h) Harrak, Y.; Makhlouf, M.; Azzaro, S.; Mainetti, E.; Lopez Romero, J. M.; Cariou, K.; Gandon, V.; Goddard, J.-P.; Malacria, M.; Fensterbank, L. New elements in the gold(I)-catalyzed cycloisomerization of enynyl ester derivatives embedding a cyclohexane template, *J. Organomet. Chem.* **2011**, *696*, 388–399; (i) Moreau, X.; Goddard, J.-P.; Bernard, M.; Lemière, G.; Lòpez-Romero, J. M.; Mainetti, E.; Marion, N.; Mouriès, V.; Thorimbert, S.; Fensterbank, L.; Malacria, M. Gold- vs. Platinum-Catalyzed Polycyclizations by *O*-Acyl Migration. Solvent-Free Reactions, *Adv. Synth. Catal.* **2008**, *350*, 43–48; (j) Mainetti, E.; Mouriès, V.; Fensterbank, L.; Malacria, M.; Marco-Contelles, J. The Effect of a Hydroxy Protecting Group on the $PtCl_2$-Catalyzed Cyclization of Dienynes–A Novel, Efficient, and Selective Synthesis of Carbocycles, *Angew. Chem. Int. Ed.* **2002**, *41*, 2132–2135.
[2] Strickler, H.; Davis, J. B.; Ohloff, G. Zur Cyclisierung von Dehydrolinalylacetat in Gegenwart von Zinkchlorid, *Helv. Chim. Acta* **1976**, *59*, 1328-1332.
[3] Rautenstrauch, V. 2-Cyclopentenones from 1-ethynyl-2-propenyl acetates, *J. Org. Chem*. **1984**, *49*, 950-952.
[4] Miki, K., Ohe, K.; Uemura, S. Ruthenium-Catalyzed Cyclopropanation of Alkenes Using Propargylic Carboxylates as Precursors of Vinylcarbenoids, *J. Org. Chem.* **2003**, *68*, 8505–8513.
[5] (a) Mouriès-Mansuy, V.; Fensterbank, L. Gold-Catalyzed Migration of Propargyl Acetate as an Entry into the Total Synthesis of Natural Products, *Isr. J. Chem.* **2018**, *58*, 586–595 and references therein; For a recent examples in total synthesis, see: (b) Jiang, Y.-L.; Yu, H.-X.; Li, Y.; Qu, P.; Han, Y.-X.; Chen, J.-H.; Yang, Z. Asymmetric Total Synthesis of Pre-schisanartanin C, *J. Am. Chem. Soc.* **2020**, *142*, 1, 573–580.

[6] For a seminal results in enantioselective transformation, see: (a) Johansson, M. J.; Gorin, D. J.; Staben, S. T.; Toste, F. D. Gold(I)-Catalyzed Stereoselective Olefin Cyclopropanation, *J. Am. Chem. Soc.* **2005**, *127*, 18002-18003; (b) Watson, I. D. G.; Ritter, S.; Toste, F. D. Asymmetric Synthesis of Medium-Sized Rings by Intramolecular Au(I)-Catalyzed Cyclopropanation. *J. Am. Chem. Soc.* **2009**, *131*, 2056–2057.

[7] For use in polymerization, see: Nzulu, F.; Bontemps, A.; Robert, J.; Barbazanges, M.; Fensterbank, L.; Goddard, J.-P.; Malacria, M.; Ollivier, C.; Petit, M.; Rieger, J.; Stoffelbach, F. Gold-Catalyzed Polymerization Based on Carbene Polycyclopropanation, *Macromolecules* **2014**, *47*, 6652−6656.

[8] For recent examples, see: (a) Reiersølmoen, A. C.; Csókás, D.; S. Øien-Ødegaard, Vanderkooy, A.; Kumar Gupta, A.; Carlsson, A.-C. C.; Orthaber, A.; Fiksdahl, A.; Pápai, I.; Erdélyi, M. Catalytic Activity of trans-Bis(pyridine)gold Complexes, *J. Am. Chem. Soc*. **2020**, 142, 6439−6446; (b) Reiersølmoen, A. C.; Fiksdahl, A. Pyridine- and Quinoline-Based Gold(III) Complexes: Synthesis, Characterization, and Application, *Eur. J. Org. Chem.* **2020**, 2867–2877; (c) Siah, H.-S. M.; Fiksdahl, A., Preparation and Catalytic Activity of Novel σ,π-Dual Gold(I) Acetylide Complexes, *Eur. J. Org. Chem.* **2020**, *2020*, 367–377; (d) Reiersølmoen, A. C.; Østrem, E.; Fiksdahl, A. Gold(III)-Catalysed Cis-to-Trans Cyclopropyl Isomerization, *Eur. J. Org. Chem.* **2018**, *2018*, 3317–3325.

[9] For intermolecular examples reporting the minor formation of the *E*-isomer: (a) Gung, B. W.; Bailey, L. N.; Craft, D. T.; Barnes, C. L.; Kirschbaum, K. Preparation and Characterization of Two New N-Heterocyclic Carbene Gold(I) Complexes and Comparison of Their Catalytic Activity to Au(IPr)Cl, *Organometallics* **2010**, *29*, 3450–3456; (b) Gorin, D. J.; Watson, I. D. G.; Toste, F. D. Fluorenes and Styrenes by Au(I)-Catalyzed Annulation of Enynes and Alkynes, *J. Am. Chem. Soc.* **2008**, *130*, 3736–3737; (c) for an exemple of major *E*-isomer in gold-catalyzed oxidative rearrangement, see: Witham, C. A.; Mauleón, P.; Shapiro, N. D.; Sherry, B. D.; Toste, F. D. Gold(I)-Catalyzed Oxidative Rearrangements, *J. Am. Chem. Soc.* **2007**, *129*, 5838–5839.

[10] (a) Nakanishi, Y.; Miki, K.; Ohe, K. Transition metal-catalyzed pentannulation of propargyl acetates via styrylcarbene intermediates, *Tetrahedron* **2007**, *63*, 12138–12148; (b) Marion, N.; Diez-Gonzalez, S.; de Frémont, P.; Noble, A. R.; Nolan, S. P. AuI-Catalyzed Tandem [3,3] Rearrangement–Intramolecular Hydroarylation: Mild and Efficient Formation of Substituted Indenes, *Angew. Chem. Int. Ed.* **2006**, *45*, 3647-3650.

[11] (a) Shibata, Y.; Noguchi, K.; Tanaka, K. Cationic Rhodium(I) Complex-Catalyzed [3 + 2] and [2 + 1] Cycloadditions of Propargyl Esters with Electron-Deficient Alkynes and Alkenes, *J. Am. Chem. Soc.* **2010**, *132*, 7896-7898; (b) Shu, X.-Z.; Huang, S.; Shu, D.; Guzei, I. A.; Tang, W. Interception of a Rautenstrauch Intermediate by Alkynes for [5+2] Cycloaddition: Rhodium-Catalyzed Cycloisomerization of 3-Acyloxy-4-ene-1,9-diynes to Bicyclo[5.3.0]decatrienes, *Angew. Chem. Int. Ed.* **2011**, *50*, 8153–8156.

[12] Miki, K.; Ohe, K.; Uemura, S. A new ruthenium-catalyzed cyclopropanation of alkenes using propargylic acetates as a precursor of vinylcarbenoids, *Tetrahedron Lett.* **2003**, *44*, 2019–2022.

[13] Interestingly, *E*/*Z* selectivity depending on the catalyst was reported by Toste and coworkers while performing gold-catalyzed oxidative propargylic ester migration, albeit with a different mechanistic proposal as the oxidation of the triple bound is supposed to occur *prior* to ester migration, see reference 9c.

[14] (a) Hines, J. M.; Eason, J. J.; Siebert, M. R. One Lump or Two? A Plurality of Pathways in Gold(III)-Catalyzed Cyclization Transforming Propargyl Acetates to a Carene-like Bicyclo[4.1.0]heptane, *Organometallics* **2017**, *36*, 920–926; (b) Swift, C. A.; Gronert, S. Gold(I)-Induced Rearrangements of Propargyl Derivatives: A Gas-Phase Study, *Organometallics* **2016**, *35*, 3844−3851; (c) Marion, N.; Lemière, G.; Correa, A.; Costabile, C.; Ramòn, R. S.; Moreau, X.; de Frémont, P.; Dahmane, R.; Hours, A.; Lesage, D.; Tabet, J.-C.; Goddard, J.-P.; Gandon, V.; Cavallo, L.; Fensterbank, L.; Malacria, M.; Nolan, S. P. Gold- and Platinum-Catalyzed Cycloisomerization of Enynyl Esters versus Allenenyl Esters: An Experimental and Theoretical Study, *Chem. Eur. J*. **2009**, *15*, 3243–3260; (d) Soriano, E.; Marco-Contelles, J. New Insights on the Mechanism of the Transition-Metal Stereoselective Olefin Cyclopropanation, *Chem. Eur. J.* **2008**, *14*, 6771–6779; (e) Correa, A.; Marion, N.; Fensterbank, L.; Malacria, M.; Nolan, S. P.; Cavallo, L. Golden carousel in catalysis: the cationic gold/propargylic ester cycle, *Angew. Chem. Int. Ed.* **2008**, *47*, 718–721; (f) Soriano, E.; Ballesteros, P.; Marco-Contelles, J. Theoretical Investigation on the Mechanisms of the $PtCl_2$-Mediated Cycloisomerization of Polyfunctionalized 1,6-Enynes-2-Propargylic Carboxylate, *Organometallics* **2005**, *24*, 3182–3191.

[15] Gross, E.; Liu, J. H.-C.; Toste, F. D.; Somorjai, G. A. Control of selectivity in heterogeneous catalysis by tuning nanoparticle properties and reactor residence time, *Nat. Chem.* **2012**, *4*, 947-952.

[16] (a) Hashmi, A. S. K.; Grundl, L. Gold catalysis: five new bonds by a domino hydroarylation/cycloisomerization, *Tetrahedron* **2005**, *61*, 6231–6236; (b) Hashmi, A. S. K.; Blanco, M. C.; Fischer, D.; Bats, J. W. Gold Catalysis: Evidence for the In-situ Reduction of Gold(III) During the Cyclization of Allenyl Carbinols *Eur. J. Org. Chem.* **2006**, 1387–1389; (c) Lemière, G.; Gandon, V.; Agenet, N.; Goddard, J.-P.; de Kozak, A.; Aubert, C.; Fensterbank, L.; Malacria, M. Gold(I)- and Gold(III)-Catalyzed Cycloisomerization of Allenynes: A Remarkable Halide Effect, *Angew. Chem. Int. Ed.* **2006**, *45*, 7596 –7599.

[17] (a) For dramatic solvent effects in gold catalyzed reactions, see: Zriba, R.; Gandon, V.; Aubert, C.; Fensterbank, L.; Malacria, M. Alkyne versus Allene Activation in Platinum- and Gold-Catalyzed Cycloisomerization of Hydroxylated 1,5-Allenynes, *Chem. Eur. J.* **2008**, *14*, 1482-1491; (b) Carrying the reaction neat in liquid 1,1-diphenylethylene led to similar dr, but reproducibility issues in terms of yields were observed, probably due to low solubility of the different species.

[18] In the literature, only intramolecular or tetrasubstituted examples such as **1ia** are reported in the alkyl series.

[19] Bhausaheb Wagh, S.; Liu, R.-S. Gold-catalyzed reactions of propargylic esters with vinylazides for the synthesis of *Z*- or *E*-configured buta-1,3-dien-2-yl esters *Chem.Commun*., **2015**, *51*, 15462–15464.