

cis-Selective Single-Cleavage Skeletal Rearrangement of 1,6-Enynes Reveals the Multifaceted Character of the Intermediates in Metal-Catalyzed Cycloisomerizations**

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Skeletal rearrangements which are catalyzed by electrophilic metals are the most emblematic transformations of enynes.^[1,2] For 1,6-enynes **1** two main types of products, **2** (single *exo*-cleavage) and **3** (double *exo*-cleavage), were initially identified (Scheme 1).^[3–10] A third type of product **4** (single *endo*-cleavage) was found when using Au^I,^[11] InCl₃,^[4e,f] Fe^{III},^[11b] or Ru^{II}^[12] as the catalysts. The factors that control the selectivity in this rearrangement manifold are not yet clearly understood.

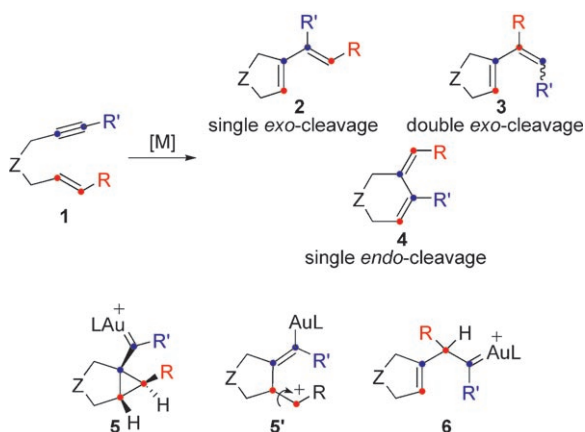
The single *exo*-cleavage rearrangement is superficially similar to the metathesis of enynes,^[13] although these reactions are very different.^[14] For Au^I, the rearrangement was proposed to proceed via intermediates **5** (Scheme 1)^[15] by a mechanism that is consistent with previous work.^[3–6] This

mechanism also explains the stereospecificity of this reaction, as observed with Au^I and other metal catalysts.^[2,11] On the other hand, the double *exo*-cleavage skeletal rearrangement usually leads to diene **3** with a predominant^[2–4,11] or exclusive *Z* configuration.^[16] For Au^I, formation of **3** was proposed to proceed by evolution of **5** to form a new rearranged carbene **6**, which undergoes proton loss and protodemetalation.^[15] Trapping of intermediate **6** has been carried out with olefins,^[17] indole,^[18] and carbonyl compounds.^[19] Proton loss from **6** can form a 1,4-diene in InCl₃-catalyzed reactions of substrate in which R' is an alkyl group.^[4f]

The Janus-like character of intermediates **5** has been recently discussed, stressing their carbocationic nature.^[1c,20] Conventionally, these intermediates are often depicted as cyclopropyl gold carbenes, although DFT calculations show that these species have highly distorted structures that are inbetween cyclopropyl gold carbenes and gold-stabilized homoallylic carbocations.^[11c,15,21] Intermediates of type **5** are involved in other processes such as nucleophilic additions of heteronucleophiles^[1,2b,11,20,22,23] inter- and intramolecular cyclopropanations,^[24] and intramolecular [4+2] cycloadditions of arylalkynes with alkenes.^[25] All of these processes are stereospecific.^[26]

If open cations such as **5'** are involved in the above-mentioned reactions, then the question of stereospecificity arises as bond rotation could occur prior to rearrangement. Herein, we show that this is indeed the case for 1,6-enynes (*E*)-**1** bearing R groups at the alkene moiety that are electron-donating, and which react non-stereospecifically with metal catalysts. Interestingly, the single-cleavage skeletal rearrangement of (*E*)- or (*Z*)-**1** give dienes (*Z*)-**2** in an unexpected *cis*-selective process (Scheme 2).

The reaction of cyclopropylenyne (*E*)-**7a** proceeded non-stereospecifically to give **8a** as a mixture of *E/Z* isomers, along with the product of *endo*-skeletal rearrangement **9a** (Table 1). Although (*Z*)-**8a** was formed as a minor product with moderately active AuCl (Table 1, entry 1), counterintuitively, the use of the more electrophilic cationic Au^I catalysts provided (*Z*)-**8a** as the major product (Table 1, entries 2 and



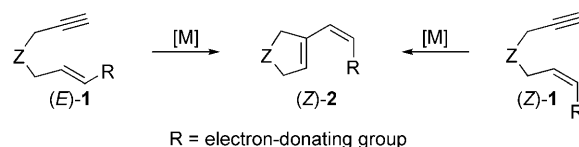
Scheme 1. The three types of skeletal rearrangement of 1,6-enynes and the key reaction intermediates.

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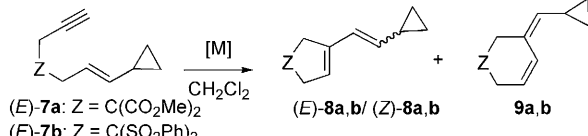
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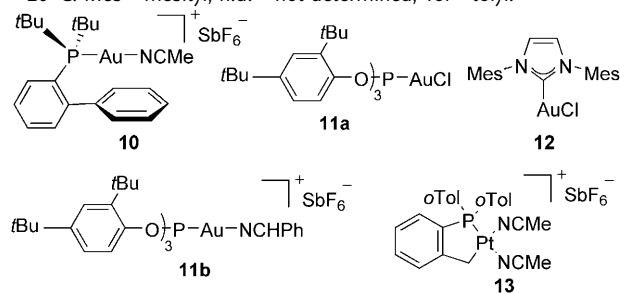


Scheme 2. The *cis*-selective single-cleavage rearrangement of 1,6-enynes (*E*)- and (*Z*)-**1**.

Table 1: Metal-catalyzed skeletal rearrangement of cyclopropylenynes (**E**)-**7a,b**.^[a]


Entry	7	[M]	<i>t</i> [min]	Yield [%]	(<i>Z</i>)- 8 /(<i>E</i>)- 8 / 9
1	(<i>E</i>)- 7a	AuCl	5	95	11:83:6
2	(<i>E</i>)- 7a	[AuCl(PPh ₃)]/AgSbF ₆	5	76	66:7:27
3	(<i>E</i>)- 7a	[AuCl(oTol ₃ P)]/AgSbF ₆	5	98	81:9:10
4	(<i>E</i>)- 7a	10	5	94	34:26:40
5	(<i>E</i>)- 7a	11a /AgSbF ₆	5	93	88:6:6
6 ^[b]	(<i>E</i>)- 7a	11a /AgSbF ₆	5	100	≥ 99:≤ 1:≤ 1
7	(<i>E</i>)- 7a	12 /AgSbF ₆	5	40	65:6:29
8	(<i>E</i>)- 7a	PtCl ₄	240	n.d.	22:76:2
9	(<i>E</i>)- 7a	GaCl ₃	180	n.d.	43:41:16
10	(<i>E</i>)- 7a	InCl ₃	960	n.d.	60:36:4
11	(<i>E</i>)- 7a	AgSbF ₆	240	0	—
12	(<i>E</i>)- 7b	10	5	96	≥ 99:≤ 1:≤ 1

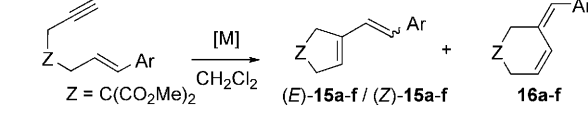
[a] Reaction conditions: catalyst (2 mol %) or AuCl (7 mol %), and PtCl₄ (5 mol %) in CH₂Cl₂, at room temperature. [b] Reaction carried out at −20 °C. Mes = mesityl, n.d. = not determined, Tol = tolyl.



3). This outcome is in contrast to the results reported for the reaction of the ethyl ester analogue of (*E*)-**7a** with an Ir^I catalyst, which gave only the *E* diene.^[4e] The best yields of (*Z*)-**8a** were obtained using [AuCl(oTol₃P)] (Table 1, entry 3) or **11a** (Table 1, entries 5 and 6). Reactions of (*E*)-**7a** with PtCl₄, GaCl₃, or InCl₃ also gave substantial amounts of (*Z*)-**8a**, although these transformations were slower (Table 1, entries 8–10). No reaction was observed with AgSbF₆ (Table 1, entry 11). In contrast to results observed in the reaction of enyne (*E*)-**7a** with catalyst **10**, enyne (*E*)-**7b** reacted very cleanly to exclusively afford (*Z*)-**8b** in excellent yield (Table 1, compare entries 4 and 12). Deuterium labeling experiments confirmed that the *Z* configured products are the result of a single-cleavage skeletal rearrangement.^[27a] In addition, (*E*)-**8a** does not undergo isomerization in the presence of **10** (2 mol %) in CD₂Cl₂.

The formation of *Z* dienes was also observed with substrates (*E*)-**14a–f** bearing electron-rich aryl substituents at the alkene group (Table 2).^[27b] Interestingly, in contrast to the stereospecific reaction of enyne (*E*)-**14g** (Ar = Ph),^[4c,11b,28] the reaction of (*E*)-**14a** also gave (*Z*)-**15a**, along with the expected (*E*)-**15a** (Table 2, entries 1–4). Substrates **14b–f** selectively gave (*Z*)-**15b–f** in good yields with either gold or platinum catalysts (Table 2, entries 5–21).^[29] In general, the best results were obtained with cationic gold catalysts **10** or

Table 2: Metal-catalyzed skeletal rearrangement of enynes (*E*)-**14a–f**.^[a] Boc = *tert*-butoxycarbonyl.



Entry	14	[M]	<i>t</i> [min]	Yield [%]	(<i>Z</i>)- 15 /(<i>E</i>)- 15 / 16
1	(<i>E</i>)- 14a	AuCl	210	50	2:72:26
2	(<i>E</i>)- 14a	10	40	n.d.	4:17:79
3	(<i>E</i>)- 14a	11b	20	100	4:33:63
4	(<i>E</i>)- 14a	PtCl ₄	210	85	11:79:10
5	(<i>E</i>)- 14b	AuCl	240	29	90:10:0
6 ^[b]	(<i>E</i>)- 14b	10	120	70	99:0:1
7	(<i>E</i>)- 14b	11b	20	98	90:5:5
8	(<i>E</i>)- 14b	PtCl ₄	180	80	70:30:0
9	(<i>E</i>)- 14b	13	180	100	88:10:2
10	(<i>E</i>)- 14c	AuCl	360	88	92:5:3
11	(<i>E</i>)- 14c	10	10	88	94:0:6
12	(<i>E</i>)- 14c	11b	960	94	85:3:12
13	(<i>E</i>)- 14c	13	270	100	93:7:0
14	(<i>E</i>)- 14c	PtCl ₄	180	97	60:40:0
15	(<i>E</i>)- 14d	AuCl	180	100	93:7:0
16	(<i>E</i>)- 14d	10	10	83	86:5:9
17	(<i>E</i>)- 14d	11b	15	86	74:9:17
18	(<i>E</i>)- 14d	PtCl ₄	180	100	53:44:17
19	(<i>E</i>)- 14e	10	20	n.d.	75:7:16
20	(<i>E</i>)- 14e	13	90	96	96:4:0
21	(<i>E</i>)- 14f	10	90	89	82:18:0

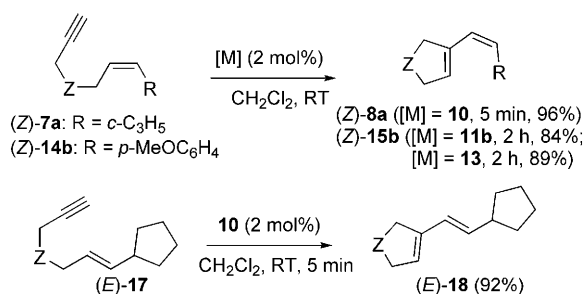
[a] Reaction conditions: catalyst (2 mol %) or AuCl (7 mol %), and PtCl₄ (5 mol %) in CH₂Cl₂, at room temperature. [b] Reaction carried out at −20 °C. n.d. = not determined.

11b, although in the case of enynes (*E*)-**14b–d**, the less electrophilic AuCl also led to (*Z*)-**15b–d** as major isomers (Table 2, entries 5, 10, and 15).

The reaction of (*Z*)-**7a** with catalyst **10** gave (*Z*)-**8a** in 96 % yield (Scheme 3). Only traces of (*E*)-**8a** and **9** were detected in this reaction. Similarly, (*Z*)-**14b** led cleanly to (*Z*)-**15b** (84 %–89 % yield) with catalysts **11b** or **13**. The reaction of (*Z*)-**14b** with catalyst **13** (5 mol %) also led cleanly to (*Z*)-**15b** (89 % yield). In contrast to the *cis*-selective rearrangement observed for (*E*)-**7a** and (*E*)-**7b**, cyclopentyl-substituted enyne (*E*)-**17** was treated with catalyst **10** to exclusively give (*E*)-**18** (92 % yield).

These results for enynes bearing electron-donating groups at the alkene moiety are consistent with the formation of open carbocations that undergo facile bond rotation prior to the rearrangement. According to DFT calculations, for cationic gold intermediates **5a** (R = H) and **5b** (R = Me), carbocation **5''** is the more relevant canonical structure, whereas for **5d** (R = *c*-C₃H₅) and **5e** (R = *p*-MeOC₆H₄) the structure actually resembles that of **5'** (Table 3). In contrast, neutral intermediate **5c** shows a more regular structure resembling **5** with elongated *b* and *c* bonds.

It is interesting to compare the high barrier of rotation around bond *d* of the neutral intermediate **5c** (L = Cl[−]) with that of cationic complex **5d** (Table 3), which correlates



Scheme 3. Gold(I)-catalyzed skeletal rearrangement of enynes (Z)-7a, (Z)-14b, and (E)-17. Z = C(CO₂Me)₂.

qualitatively with the barrier observed in the reaction of (E)-7a with AuCl (preferential retention of the *E* configuration) and cationic Au^I complexes (preferential inversion). These theoretical results support the hypothesis which suggests that cationic intermediates with strongly electron-donating R groups, such as *c*-C₃H₅ and *p*-MeOC₆H₄, are open carbocations 5', which can undergo bond rotation.^[30] The origin of the high selectivity observed for the formation of the *Z* isomers might result from the higher reactivity of the *Z* rotamers of intermediates 5 in the single-cleavage rearrangement. Notably, in all cases, products of endocyclic rearrangement 9a, 9b, and 16a–e were obtained as single stereoisomers, which indicates that these dienes arise from cleavage of bond *b* in intermediates 5 prior to bond rotation.

To support the hypothesis that bond rotation of carbocations 5' causes the lack of stereospecificity in these reactions, we carried out the reaction of (E)-7a, (E)-14b, and (E)-14f with catalyst **10** (Table 4). The alkoxycyclizations proceeded stereospecifically to give adducts 19a–c in good yields when the reactions were carried out in pure MeOH or EtOH (Table 4, entries 1, 2, and 4),^[31] which is in keeping with the general behavior observed by other 1,6-enynes in similar reactions catalyzed by gold^[11a,b] or platinum;^[9] however, when the concentration of the nucleophile was decreased, *anti/syn* mixtures of stereoisomers were obtained (Table 4,

Table 3: Calculated bond distances and barriers of rotation for intermediates 5.^[a] L = ligand.

R	5	L	a [Å]	b [Å]	c [Å]	ΔE [‡] [kcal mol ^{−1}] ^[b]
H ^[c]	5a	PH ₃	1.378	1.742	1.569	–
Me ^[d]	5b	PH ₃	1.372	1.720	1.622	–
<i>c</i> -C ₃ H ₅	5c	Cl [−]	1.401	1.621	1.606	28.1 (14.7)
<i>c</i> -C ₃ H ₅	5d	PH ₃	1.356	1.586	1.987	11.3 (8.8)
<i>p</i> -MeOC ₆ H ₄	5e	PH ₃	1.344	1.578	2.328	8.1 (7.1)

[a] DFT calculations at the B3LYP/6-31G(d) (C,H,P), LANL2DZ (Au) level. Electronic energies corrected with zero point energy (ZPE). [b] Barriers of rotation around the *d* bond. Values in parentheses include the effect of solvent (CH₂Cl₂, PCM). PCM = polarizable continuum model. [c] Reference [11 c]. [d] Reference [15].

Table 4: Gold(I)-catalyzed alkoxycyclization of enynes (E)-7a and (E)-14b,f,g.

Z = C(CO₂Me)₂

19a: R¹ = *c*-C₃H₅, R² = Me
19b: R¹ = *p*-MeOC₆H₄, R² = Me
19c: R¹ = 3-(Boc-Indole), R² = Et
19d: R¹ = Ph, R² = Me

Entry	Enyne	Solvent	t [min]	Product (yield [%])	<i>anti/syn</i>
1	(E)-7a	MeOH	5	19a (86)	100:0
2	(E)-14b	MeOH	60	19b (100)	100:0
3	(E)-14b	CH ₂ Cl ₂ /MeOH ^[a]	60	19b (95)	60:40
4	(E)-14f	EtOH	5	19c (98) ^[b]	100:0
5	(E)-14f	CH ₂ Cl ₂ /EtOH ^[a]	5	19c (82) ^[b]	52:48
6	(E)-14g	CH ₂ Cl ₂ /MeOH ^[a]	60	19d (84) ^[b]	100:0

[a] Reaction conditions: CH₂Cl₂ with MeOH (5 equiv) or EtOH (5 equiv). [b] Traces of skeletal rearrangement products were also observed.

entries 3 and 5). Interestingly, under these reaction conditions, enyne (E)-14g reacted stereospecifically to provide *anti*-19d exclusively^[11b] (Table 4, entry 5). On the other hand, when enynes (E)-20a,b were treated with cationic gold(I) catalysts **10** or **11b** they gave 21a,b as *trans/cis* mixtures of stereoisomers (Table 5), thus indicating that bond rotation of the carbocationic intermediate is faster than attack by the phenyl or *p*-nitrophenyl groups. This result is in contrast with all other examples of [4+2] cycloadditions that are catalyzed by gold for substrates bearing other substituents at the alkene group.^[25]

In summary, the *cis*-selective single-cleavage rearrangement of enynes has revealed an unrecognized aspect of gold intermediates in cycloisomerization and related reactions of enynes. In general, reactions of 1,6-enynes with electrophilic metal catalysts can be interpreted as stereospecific additions of electrophiles (the η²-alkyne-metal complex) to alkenes. For enynes containing alkenes that bear strongly electron-donating substituents these reactions are non-stereospecific, and proceed through open carbocations of the type 5'. Remark-

Table 5: Intramolecular [4+2] cycloaddition of enynes (E)-20a,b.

Z = C(CO₂Me)₂
(E)-20a: X = H
(E)-20b: X = NO₂

Entry	20	[Au]	t	Yield [%]	<i>trans</i> -21/ <i>cis</i> -21
1 ^[a]	(E)-20a	10	6 h	87	82:12
2 ^[b]	(E)-20b	10	8 min	85	67:33
3 ^[a]	(E)-20b	10	1 h	60	72:28
4 ^[b]	(E)-20b	11b	8 min	100	46:54

[a] Reaction conditions: catalyst (2 mol%) in CHCl₃, at room temperature. [b] Reaction conditions: catalyst (3 mol%) in CH₂Cl₂, microwave irradiation, 80 °C.

ably, in this process *cis* dienes are selectively formed when starting from either *cis* or *trans* enynes.

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- [26] Mixtures of stereoisomers were observed in the presence of water in the ring-expansion/Prins cyclization of 1,6-enynes bearing protected cyclopropanol groups at the alkyne moiety. The mixture could be a result of trapping of the intermediates by water, followed by a pinacol-type expansion: E. Jiménez-Núñez, C. K. Clavier, C. Nieto-Oberhuber, A. M. Echavarren, *Angew. Chem.* **2006**, *118*, 5578–5581; *Angew. Chem. Int. Ed.* **2006**, *45*, 5452–5455.
- [27] a) See the Supporting Information for deuterium labeling experiments; b) See the Supporting Information for additional data.
- [28] Reaction of (*E*)-**14g** with catalyst **10** or [Au(MeCN)(PPh₃)]SbF₆ gave a 6–7:1 mixture of **15g/16g**,^[11b] whereas catalyst **11b** gave a 1:3 mixture of these compounds.
- [29] The configuration of the *exo*-rearranged compound obtained from **14b** was originally misassigned as (*E*)-**15b**,^[11b] see the corrigendum: C. Nieto-Oberhuber, M. P. Muñoz, S. López, E. Jiménez-Núñez, C. Nevado, E. Herrero-Gómez, M. Raducan, A. M. Echavarren, *Chem. Eur. J.* **2008**, *14*, 5096.
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- [31] When the reaction of (*E*)-**14b** was carried out with PtCl₄ (5 mol %) in MeOH under microwave irradiation (80°C, 30 min), **19b** was obtained as a 1:1 mixture of diastereomers in quantitative yield. However, under these reaction conditions, the *anti* diastereomer epimerized to provide a 1:1 mixture of diastereomers.