Cycloisomerization Reactions

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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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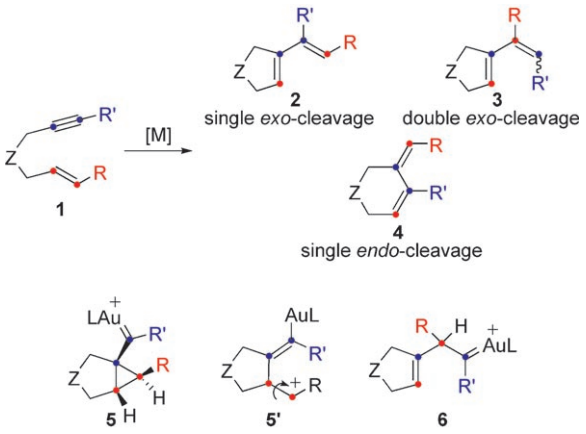
Skeletal rearrangements which are catalyzed by electrophilic metals are the most emblematic transformations of enynes.[1,2] For 1,6-enynes **1** two main types of products, **2** (single *exo*-cleavage) and **3** (double *exo*-cleavage), were initially identified (Scheme 1).[3–10] A third type of product **4** (single *endo*-cleavage) was found when using Au^{I},[11] $InCl_3$,[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 $InCl_3$-catalyzed reactions of substrate in which R′ is an alkyl group.[4f]

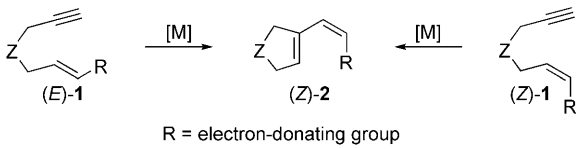


Scheme 1. The three types of skeletal rearrangement of 1,6-enynes and the key reaction intermediates.

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

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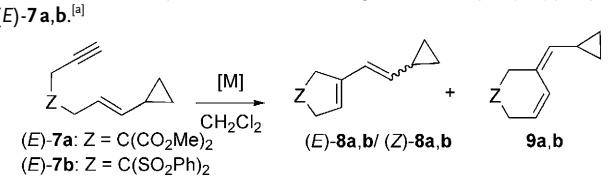
Table 1: Metal-catalyzed skeletal rearrangement of cyclopropylenynes (*E*)-**7a**,**b**.[a]



Entry	**7**	[M]	*t* [min]	Yield [%]	(*Z*)-**8**/(*E*)-**8**/**9**
1	(*E*)-**7a**	AuCl	5	95	11:83:6
2	(*E*)-**7a**	$[AuCl(PPh_3)]/AgSbF_6$	5	76	66:7:27
3	(*E*)-**7a**	$[AuCl(oTol_3P)]/AgSbF_6$	5	98	81:9:10
4	(*E*)-**7a**	**10**	5	94	34:26:40
5	(*E*)-**7a**	**11a**/$AgSbF_6$	5	93	88:6:6
6[b]	(*E*)-**7a**	**11a**/$AgSbF_6$	5	100	≥99:≤1:≤1
7	(*E*)-**7a**	**12**/$AgSbF_6$	5	40	65:6:29
8	(*E*)-**7a**	$PtCl_4$	240	n.d.	22:76:2
9	(*E*)-**7a**	$GaCl_3$	180	n.d.	43:41:16
10	(*E*)-**7a**	$InCl_3$	960	n.d.	60:36:4
11	(*E*)-**7a**	$AgSbF_6$	240	0	–
12	(*E*)-**7b**	**10**	5	96	≥99:≤1:≤1

[a] Reaction conditions: catalyst (2 mol%) or AuCl (7 mol%), and $PtCl_4$ (5 mol%) in CH_2Cl_2, at room temperature. [b] Reaction carried out at −20°C. Mes = mesityl, n.d. = not determined, Tol = tolyl.

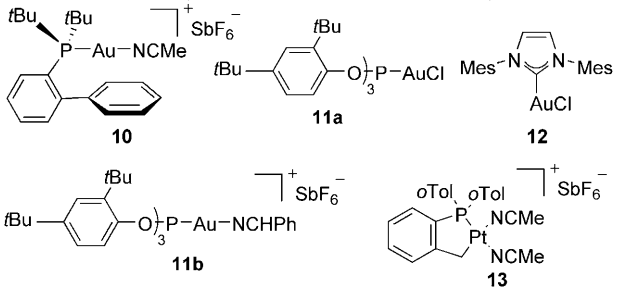
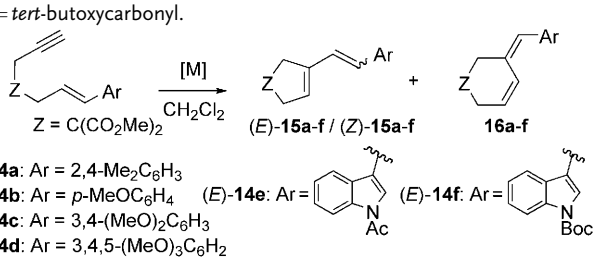


Table 2: Metal-catalyzed skeletal rearrangement of enynes (*E*)-**14a**–**f**.[a] Boc = *tert*-butoxycarbonyl.



Entry	**14**	[M]	*t* [min]	Yield [%]	(*Z*)-**15**/(*E*)-**15**/**16**
1	(*E*)-**14a**	AuCl	210	50	2:72:26
2	(*E*)-**14a**	**10**	40	n.d.	4:17:79
3	(*E*)-**14a**	**11b**	20	100	4:33:63
4	(*E*)-**14a**	$PtCl_4$	210	85	11:79:10
5	(*E*)-**14b**	AuCl	240	29	90:10:0
6[b]	(*E*)-**14b**	**10**	120	70	99:0:1
7	(*E*)-**14b**	**11b**	20	98	90:5:5
8	(*E*)-**14b**	$PtCl_4$	180	80	70:30:0
9	(*E*)-**14b**	**13**	180	100	88:10:2
10	(*E*)-**14c**	AuCl	360	88	92:5:3
11	(*E*)-**14c**	**10**	10	88	94:0:6
12	(*E*)-**14c**	**11b**	960	94	85:3:12
13	(*E*)-**14c**	**13**	270	100	93:7:0
14	(*E*)-**14c**	$PtCl_4$	180	97	60:40:0
15	(*E*)-**14d**	AuCl	180	100	93:7:0
16	(*E*)-**14d**	**10**	10	83	86:5:9
17	(*E*)-**14d**	**11b**	15	86	74:9:17
18	(*E*)-**14d**	$PtCl_4$	180	100	53:44:17
19	(*E*)-**14e**	**10**	20	n.d.	75:7:16
20	(*E*)-**14e**	**13**	90	96	96:4:0
21	(*E*)-**14f**	**10**	90	89	82:18:0

[a] Reaction conditions: catalyst (2 mol%) or AuCl (7 mol%), and $PtCl_4$ (5 mol%) in CH_2Cl_2, at room temperature. [b] Reaction carried out at −20°C. n.d. = not determined.

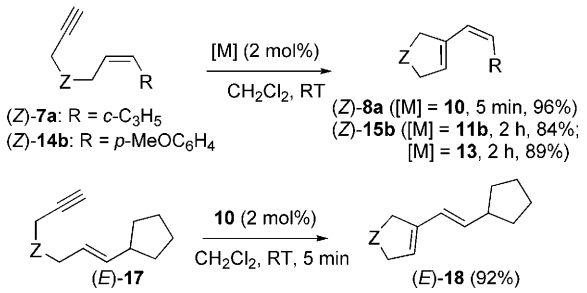
3). This outcome is in contrast to the results reported for the reaction of the ethyl ester analogue of (*E*)-**7a** with an Ir^I catalyst, which gave only the *E* diene.[4e] The best yields of (*Z*)-**8a** were obtained using $[AuCl(oTol_3P)]$ (Table 1, entry 3) or **11a** (Table 1, entries 5 and 6). Reactions of (*E*)-**7a** with $PtCl_4$, $GaCl_3$, or $InCl_3$ also gave substantial amounts of (*Z*)-**8a**, although these transformations were slower (Table 1, entries 8–10). No reaction was observed with $AgSbF_6$ (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 CD_2Cl_2.

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 **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*-C_3H_5) and **5e** (R = *p*-$MeOC_6H_4$) 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



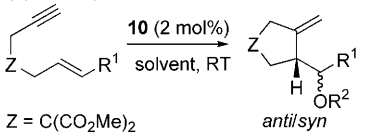
Scheme 3. Gold(I)-catalyzed skeletal rearrangement of enynes (*Z*)-**7a**, (*Z*)-**14b**, and (*E*)-**17**. Z = $C(CO_2Me)_2$.

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*-C_3H_5 and *p*-$MeOC_6H_4$, 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, 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 η^2-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-

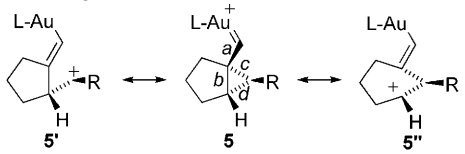
Table 4: Gold(I)-catalyzed alkoxycyclization of enynes (*E*)-**7a** and (*E*)-**14b,f,g**.



Entry	Enyne	Solvent	*t* [min]	Product (yield [%])	*anti*/*syn*
1	(*E*)-**7a**	MeOH	5	**19a** (86)	100:0
2	(*E*)-**14b**	MeOH	60	**19b** (100)	100:0
3	(*E*)-**14b**	CH_2Cl_2/MeOH[a]	60	**19b** (95)	60:40
4	(*E*)-**14f**	EtOH	5	**19c** (98)[b]	100:0
5	(*E*)-**14f**	CH_2Cl_2/EtOH[a]	5	**19c** (82)[b]	52:48
6	(*E*)-**14g**	CH_2Cl_2/MeOH[a]	60	**19d** (84)[b]	100:0

[a] Reaction conditions: CH_2Cl_2 with MeOH (5 equiv) or EtOH (5 equiv). [b] Traces of skeletal rearrangement products were also observed.

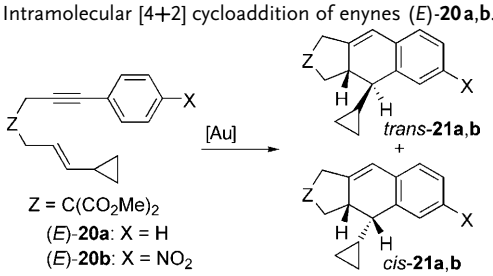
Table 3: Calculated bond distances and barriers of rotation for intermediates **5**.[a] L = ligand.



R	**5**	L	*a* [Å]	*b* [Å]	*c* [Å]	$\Delta E^{\neq}$ [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	–
c-C_3H_5	**5c**	Cl^-	1.401	1.621	1.606	28.1 (14.7)
c-C_3H_5	**5d**	PH_3	1.356	1.586	**1.987**	11.3 (8.8)
p-$MeOC_6H_4$	**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 (CH_2Cl_2, PCM). PCM = polarizable continuum model. [c] Reference [11c]. [d] Reference [15].

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



Entry	**20**	[Au]	*t*	Yield [%]	*trans*-**21**/*cis*-**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 $CHCl_3$, at room temperature. [b] Reaction conditions: catalyst (3 mol%) in CH_2Cl_2, 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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[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 $[Au(MeCN)(PPh_3)]SbF_6$ 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.

[30] Calculated ΔE for the equilibrium between intermediates **5** and their bond *d* rotamers are 1.3 kcal mol^{-1} (**5c**), 0.9 kcal mol^{-1} (**5d**), and 5.8 kcal mol^{-1} (**5e**), and they include the effect of CH_2Cl_2 solvent.

[31] When the reaction of (*E*)-**14b** was carried out with $PtCl_4$ (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.

