Gold-Catalyzed Oxidative Cyclizations on 1,4-Enynes: Evidence for a γ-Substituent Effect on Wagner–Meerwein Rearrangements**

Satish Ghorpade, Ming-Der Su,* and Rai-Shung Liu*

The Wagner-Meerwein rearrangement refers to a 1,2-shift of an alkyl, aryl, and alkenyl group to an adjacent carbocationic center; formation of this carbon-carbon bond has found widespread applications in many Lewis acid or Brønsted acid mediated reactions [Eq. (1)].^[1,2] For this well-known reaction, the 1,2-shift of R^1 versus R^2 is determined primarily by the relative stability of carbocation **B** (or **B**'), as well as the intrinsic properties of the migrating group (Scheme 1).^[1,2] No instance of a y-substituent to stereospecifically direct a 1,2shift of the R group in β -position was reported to date; those carbocations bearing a γ -silvl group are no examples either.^[3a] Although the γ -effect on this arrangement was claimed in an early report,^[3b] the 1,2-shift actually occurred within a benzene skeleton comprising the C_β and C_γ carbon atoms. According to carbocation chemistry,^{[3-5]} we envisage that a metal substituent in the y-position might facilitate an anti activation through hyperconjugation to induce a 1,2-R¹-shift $(\mathbf{C} \rightarrow \mathbf{D})$ in an antiperiplanar conformation (\mathbf{C}) [Eq. (2)].^[3-5] Alternatively, this metal might exert steric interaction to induce a syn activation to enable a 1,2-R²-shift ($\mathbf{C'} \rightarrow \mathbf{D'}$) in a synperiplanar conformation C' [Eq. (3)].^[3,5] The realization of such an unprecedented effect of a metal in y-position relies on the availability of suitable carbocations applicable for a study. Herein, we report our experimental and theoretical work to support an *anti*-activation route [Eq. (2)] for M = $Au^{[6]}$ (path $\mathbf{C} \rightarrow \mathbf{D}$) even in a synperiplanar conformation. This work represents an atypical Wagner-Meerwein rearrangement, because the intrinsic properties of the migrating group $(\mathbf{R}^1, \mathbf{R}^2)$ are no longer decisive.

Shown in Scheme 1 is our strategy to illustrate the γ substituent effect; the key reaction involves a gold-catalyzed oxidative cyclization of 1,4-enyne **3**.^[7,8] The initially formed α oxo gold carbene **E**^[9] is expected to have its olefin π electrons parallel to the positive ⁺Au=C p orbital to achieve a throughspace interaction. We envisage that this spatial arrangement will undergo a facile alkene/carbene coupling^[10] to give 2-oxocyclopent-1-yl cation **F** or **F'**, through either a disrotation or

[*] S. Ghorpade, Prof. Dr. R.-S. Liu Department of Chemistry, National Tsing-Hua University Hsinchu, 30043 (Taiwan, ROC) E-mail: rsliu@mx.nthu.edu.tw Prof. Dr. M.-D. Su Department of Applied Chemistry, National Chiayi University Chiayi, 60004 (Taiwan, ROC) E-mail: midesu@mail.ncyu.edu.tw
[**] We thank National Science Council, Taiwan, for financial support of this work

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/anie.201210313.

Wagner-Meerwein Migration



Metal-directing 1,2-migration (this work)



conrotation route. We employ these special 1,4-enynes, because their bridged cyclopropanes can stabilize carbocation **F** or **F'** with a "bisected" conformation,^[11] in which the ketone group hinders the expansion of the cyclopropane ring.^[12] A cyclopropyl group greatly enhances the electrophilicity of an alkyne in the presence of a gold catalyst.^[12] Our experimental results disclose that only the *cis*-substituent R¹ at the alkene is transferable to give the observed cyclopentanone **F** selectively. Notably, this stereospecificity of the migration is unaffected when varying the R¹ and R² groups to methyl, alkyl, and aryl groups, thereby truly reflecting this significant γ -effect. The object of this work is to clarify if an *anti* or *syn* activation occurs in carbocations with a gold substituent in the γ -position, as in carbocations **F** or **F'**.



Scheme 1. Strategy to study the γ -substituent effect.

Angew. Chem. Int. Ed. 2013, 52, 1-7

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Table 1 shows the oxidative cyclization of 1,4-enyne **1a** by using 8-methylquinoline oxide (3 equiv) as the oxidant in the presence of different catalysts. The feasibility of this reaction

Table 1: Activity screening using various catalysts.

K	1a 5 mol % catalyst 25 °C, solver oxidant (3.0 equiv)) 2a	oxidant]
Entry	Catalyst ^[a]	Solvent	<i>t</i> [h]	Yield [%] ^[b]	
·				1a	2a
1	AuCl₃	DCE	1	-	52
2	$PPh_3AuCl/AgNTf_2$	DCE	2	-	48
3	LAuCl/AgNTf ₂	DCE	0.5	-	82
4	IPrAuCl/AgNTf ₂	DCE	1	-	36
5	LAuCl/AgOTf	DCE	0.5	-	71
6	LAuCl/AgSbF ₆	DCE	0.5	-	66
7	AgNTf ₂	DCE	24	60	-
8	HOTF	CH_2Cl_2	12	76	-
9	LAuCl/AgNTf ₂	CH_2Cl_2	1	-	62
10	LAuCl/AgNTf ₂	CH₃CN	1	-	55

[a] [Substrate] = 0.027 M, L = P(tBu)₂(o-biphenyl). IPr = 1,3-bis(diisopropylphenyl)imidazol-2-ylidene. [b] Product yields are reported after purification from a silica gel column.

is reflected by AuCl₃ (5 mol%) in dichloroethane (DCE, 25°C), which gave the desired oxidative cyclization product 2a in 52% yield (Table 1, entry 1); this process involves a ring expansion of a cyclopentylidene moiety while retaining a cyclopropane ring. We tested further the reaction with cationic gold catalysts; P(tBu)₂(o-biphenyl)AuNTf₂ gave compound **2a** in 82% yield, better than PPh₃AuNTf₂ (48%) and IPrAuNTf₂ (36%) (Table 1, entries 2–4). Other counter anions, such as in LAuOTf and LAuSbF₆ $[L = P(tBu)_2(o$ biphenyl)], gave decreased yields with 71% and 66%, respectively (Table 1, entries 5-6). AgNTf₂ and HOTf alone failed to give the desired product 2a under similar conditions (Table 1, entries 7-8). For LAuNTf₂, the reactions proceeded less efficiently in dichloromethane and CH₃CN, giving cyclopentenone 2a in 62% and 55% yield, respectively (Table 1, entries 9-10).

We tested this oxidative reaction on additional 1,4-enynes **1b-1j** to examine the substrate scope; the reactions were performed with LAuNTf₂ (5 mol%) and 8-methylquinoline oxide (3 equiv) in DCE (25°C). As shown in Table 2, entries 1-3, the reactions are extensible to internal alkyne substrates 1b-1d bearing electron-deficient phenyl substituents ($R^2 = 4-XC_6H_4$, X = F, CN, and NO₂); the resulting cyclopentenone products 2b-2d were obtained in 83-91% yield. The molecular structure of compound 2d was characterized by X-ray diffraction.^[13] We also prepared 1,4-enyne 1e bearing a cyclohexylidene moiety; its Au-catalyzed reaction gave the desired cyclopentenone 2e including a fused sevenmembered ring (Table 2, entry 4). Such oxidative ring expansions were also operable for internal alkynes $1 f (R^2 = Me)$, 1 g $(R^2 = Ph)$, and **1h** $(R^2 = 4-MeCOC_6H_4)$ to give expected products 2 f-2h in (72-78%) yield (Table 2, entries 5-7). The reaction is further extensible to the synthesis of eightTable 2: 1,4-Enynes bearing two equivalent alkenyl substituents.^[a]



[a] [substrate] = 0.027 M, L = P(tBu)₂(o-biphenyl). [b] Product yields are reported after purification from a silica gel column.

membered carbocycle **2i** (71% yield) by using cycloheptylidene derivative **1i**. We tested the reaction on a propylidene substrate **1j** that afforded the vicinal dimethyl cyclopentenone **2j** in 86% yield.

We prepared both *E*- and *Z*-configured 1,4-enynes **3a–f** to assess the migration ability of the alkenyl *cis*- and *trans*substituents (Table 3). With *E*-configured olefins, the reactions proceeded more rapidly than with their corresponding *Z*-isomers, because the former easily attain conformation **E** (see Scheme 1, size: $\mathbb{R}^2 > \mathbb{R}^1$). For 1,4-enyne *E*-**3a**, we observed a 1,2-methyl migration for its resulting product **4a** (Table 3, entry 1), but for its *Z*-isomer **Z**-**3a**, a 1,2-phenyl shift occurred to deliver a distinct regioisomer **4a'** (entry 2). These observations reveal that the *cis*-position is the preferable migration site. As shown in Table 3, entries 3–6, the 1,2-shifts of the *cis*-substituents are again observed for 1,4-enynes *E*-**3b**, *E*-**3c**, *Z*-**3b**, and *Z*-**3c** bearing different electron-rich or

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Table 3: Oxidative cyclization of 1,4-enynes in E- and Z-forms.^[a]

Entry	3	4 (vield [%]) ^[b]	t [h]	Entry	3	4 (vield [%]) ^[b]	t [h]
	Ph	Ph	[,]		Et Ph	Ph Et	['']
1	E-3 a ^[a]	4a (78) Ph	0.5	10	Z-3 e	0 4e' (71) Ph	5
2	Z-3a	0 4a' (81) Ar	2	11	E-3 f	Ö 4f(71) Ph	7
3	E-3b	о 4b (72)	0.5	12	Z-3 f	ő 4 f' (73)	10
4	$\frac{\mathbf{Z} - \mathbf{A} \cdot \mathbf{C} \cdot \mathbf{C}_{6} \cdot \mathbf{I}_{4}}{\mathbf{Z} - \mathbf{A} \cdot \mathbf{C}_{6}}$	4c (79) H Ar	0.5		Ar	Ar	
	Ar	K				N I	
5	Z-3 b Ar = 4-ClC ₆ H ₄	4b ′ (77)	2.5	13	E-3 g Ar = 4-MeOC ₆	4g (76) H ₄	0.5
6	$\frac{Z-3c}{Ar=4-MeOC_6}$	4c' (83) H ₄	1.5		Ar	Ar O	
7	E-3d	4d (62)	1	14	Z-3g Ar=4-OMeC ₆	4g'(43) + 4g(34) H ₄	1.5
8	Z-3d	" 4d' (68) Et ₽h	4	15	E-3 h	4h (67)	8
9	E-3 e	4e (79)	1	16	Z-3 h	4 h ′ (64)	15

[a] [Substrate] = 0.027 μ , 5 mol%, LAuNTf₂ L = P(tBu)₂(o-biphenyl); oxidant (3 equiv), DCE, 25 °C. [b] Product yields are reported after purification by using a silica gel column.

electron-deficient benzenes, giving cyclopentenone derivatives **4b** and **4c** (72% and 79%) through a 1,2-methyl migration and their regioisomers **4b'** and **4c'** (77% and 83%) through a 1,2-phenyl shift. We tested the ring expansions on substrates *E*-3d and *Z*-3d, which conformed to the same migration pattern to give desired products **4d** and **4d'** selectively. Such a site selectivity works well with *E*- and *Z*configured olefins **3e** bearing ethyl and phenyl groups; their corresponding products **4e** and **4e'** were obtained in satisfactory yields (79–71%, Table 3, entries 9,10). This stereospecificity of the migration is applicable to 1,4-enynes *E*-**3f** and *Z*-**3f** bearing two distinct methyl and benzyl groups, delivering desired products **4f** and **4f'** in 71% and 73% yields, respectively (Table 3, entries 11,12). The oxidative cyclization of disubstituted olefin E-3g is compatible with our expectation to give only species 4g in 76% yield (Table 3, entry 13), whereas its Zisomer Z-3g gave a mixture of cyclopentenone species 4g (34%) and 4g' (43%), which were separable by using silica column chromatography (entry 14). We believe that a portion of species 4g in entry 14 was produced from an intrinsic deprotonation in the proposed intermediate F (or F'; Scheme 1, $R^2 = H$). This stereoselective migration pattern also occurs with internal alkyne substrates E-3h and Z-3h, producing desired products 4h and 4h', respectively. The fact that only cissubstituents are transferable for various aryl, methyl, and alkyl substituents strongly indicates the pronounced y-effect of Au to direct a 1,2-shift with stereospecificity.

Table 4 depicts our control experiments to confirm the intermediacy of oxo gold carbenes E. We prepared diazo-containing E-configured olefin *E*-5, and its treatment with gold catalyst (5 mol%) gave only cyclopentenone 4a in 64% yield with a methyl migration (Table 4, entry 1). For its Z-isomer Z-5, we obtained the other regioisomer 4a' in 68% yield with a 1,2phenyl migration (Table 4, entry 2); compound 4a' represents the product from a typical Wagner-Meerwein rearrangement. Again, only cis-substituents are found to migrate. Entries 3-6 (Table 4) illustrate the ligand effects of gold catalysts on the Wagner-Meerwein rearrangement. A large electron-

deficient phosphite ligand as in AuP(OPh)₃NTf₂ (5 mol%) gave the Wagner–Meerwein product **4a'** as the major species (44%) when using *E*-configured olefin *E*-**5** (entry 3); this phosphite ligand gave **4a'** exclusively with *Z*-configured olefin *Z*-**5** (entry 4). In contrast, the small ligand in Au-(PMe₃)NTf₂ gave the methyl migration product **4a** (45%) preferably with *E*-**5** (entry 5). Accordingly, the γ -effect is more prominent for an electron-rich phosphine ligand according to the observed trend: P(*t*Bu)₂(*o*-biphenyl)> PMe₃>P(OPh)₃.

We tested also the migratory cyclizations of diazo species **Z-5** or **E-5** with other metal carbene intermediates (Table 5). $[Rh_2(OAc)_4]$ (0.05 mol%) also showed a 1,2-shift of the

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Yield [%]^[b] Diazo^[a] Entry Ligand(L) t [h] 4a 4a 1 E-5 P(tBu)₂(o-biphenyl) 0.5 64 2 Z-5 P(tBu)₂(o-biphenyl) 1.0 68 P(OPh)₃ 0.5 3 E-5 29 44 P(OPh)₃ 80 4 Z-5 2 5 E-5 PMe₃ 0.5 45 27 6 7.5 PMe 2 78

[a] [substrate]=0.027 м. [b] Product yields are reported after purification by using a silica gel column.

Table 5: Reaction with other metal catalysts.





Entry	Diazo ^[a]	M (mol%)	<i>t</i> [h]	Yield [Yield [%] ^[b]	
				4 a	4 a′	
1	E-5	[Rh ₂ (OAc) ₄] (0.05)	0.5	56	-	
2	Z-5	[Rh ₂ (OAc) ₄] (0.05)	0.5	-	65	
3	E-5	$Cu(OTf)_2$ (1)	2.5	-	77	
4	Z-5	$Cu(OTf)_2$ (1)	3.0	-	79	
5	E-5	$AgSbF_{6}$ (5)	1.0	-	68	
6	Z-5	$AgSbF_{6}$ (5)	2.0	-	71	
7	E-5	$LAgSbF_{6}$ (5)	8.0	16	60	
8	E-5	$LAgNTf_{2}$ (5)	12.0	21	47	

[a] [Substrate] = 0.027 M. L = P(*t*Bu)₂(*o*-biphenyl). [b] Product yields are reported after purification by using a silica gel column.

alkenyl *cis*-substituent to give cyclopentenone derivatives **4a** and **4a'**, respectively, from *E*-**5** and *Z*-**5** diazo species (Table 5, entries 1–2). Notably, the use of both Cu(OTf)₂ (1 mol %) and AgSbF₆ (5 mol %) resulted in a typical Wagner–Meerwein rearrangement to give species **4a'** (68–79%), when using either *E*-**5** or *Z*-**5** olefins species (Table 5, entries 3–6). But electron-rich phosphine-containing silver catalysts, LAgX (X = SbF₆, NTf₂) gave the methyl migration product *E*-**5** in 16% and 21% yields respectively (Table 5, entries 7–8).

The control experiments confirm the intermediacy of α oxo gold carbenes **E** in our working mechanism (Scheme 1), but we are still uncertain about the role of two possible carbocations **F** and **F'** to produce the resulting cyclopentenones **4**. We sought information from density functional theory on the 1,2-shifts of two possible carbocations **F** and **F'**;^[14,15] these calculations were performed using the B3LYP/ LANL2DZ and B97D/LANL2DZ methods, with AuL = P-(*t*Bu)₂PhAu in the gaseous phase. We also used the Onsager model^[16] and the PCM^[17] (polarized continuum model) to consider the solvent effects (in dichloroethane); the results are provided in Figure 1 and Figure S1 in the Supporting Information, respectively; the computational results on the two solvent models gives well agreeable conclusions. Figure 1



Figure 1. Energy profiles for four possible 1,2-migrations. The black line corresponds to the observed path. DFT calculations were performed by using the B3LYP/LAN2DZ method in the gaseous phase (values in []), and the Onsager method was used to consider solvent effects in dichloromethane (values without brackets). Energies are given in kcal mol⁻¹. PR₃ = P(tBu)₂Ph.

presents the results of calculations to assess four possible 1,2shifts on the two carbocations. For carbocation F, a 1,2-phenyl shift has a barrier ($\Delta H^{+}_{(sol)} = +0.62 \text{ kcal mol}^{-1}$) much smaller than that of a methyl shift ($\Delta H^{+}_{(sol)} = +6.9 \text{ kcal mol}^{-1}$). On its diastereomer F', we obtained a small barrier for a methyl migration ($\Delta H^{+}_{(sol)} = +3.6 \text{ kcal mol}^{-1}$), but a large activation energy for a phenyl shift ($\Delta H^{+}_{(sol)} = +8.6 \text{ kcal mol}^{-1}$). These differences $(> 5.0 \text{ kcal mol}^{-1})$ are significant to distinguish the syn and anti activation. These results clearly suggest that a gold substituent in the γ -position in the two cationic intermediates activates a 1,2-shift of the β -anti substituent through hyperconjugation. As a large amount of enthalpic energy ($>30 \text{ kcal mol}^{-1}$) is released for these transpositions, these 1,2-migrations should be irreversible. Accordingly, the migrations with smaller barriers, that is, $F \rightarrow TS-1 \rightarrow G$ and $F' \rightarrow$ **TS-1'** \rightarrow **G'** will become the dominant pathways. The geometries of carbocations H, G and H', G' resemble those of π alkene complexes I, J and I', J', because their energy levels are very close to each other.

We rule out the intermediacy of $\mathbf{F'}$ in Scheme 1, because its corresponding *syn*-activation ($\mathbf{F'} \rightarrow \mathbf{4}$) is inconsistent with our computational results. Our control experiments in Table 4 also support an *anti*-activation route, because the stereospecificity of the migration is more prominent when a small electron-rich ligand, as in PMe₃Au⁺, is used than when a large electron-deficient ligand, as in P(OPh)₃Au⁺, is used; ligand

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size is not a decisive factor. The postulated route $\mathbf{E} \rightarrow \mathbf{F}$ is easily comprehensible, because this disrotation route allows an efficient overlap between two interacting p orbitals in the early stage of rotation [Eq. (4)], whereas the conrotation fails to give an overlap until the late stage of rotation.



To date, there is no example of the Wagner–Meerwein rearrangement where a metal substituent in the γ -position can direct a 1,2-shift of the neighboring group with stereospecificity. To demonstrate this γ -effect, we sought the solution from the gold-catalyzed cyclization of 1,4-enynes 1; in this cyclization only the *cis*-alkenyl substituent is transferable. Our control experiments suggest the intermediacy of α carbonyl gold carbenes **E'**. We performed theoretical calculations to demonstrate a preferable *anti* activation for two possible carbocations **F** and **F'**. Both experimental and theoretical work disclose that a gold substituent in the γ position can direct a 1,2-shift of the *anti*- β -substituent regardless of its intrinsic properties. This discovery provides insight into a new aspect of the Wagner–Meerwein rearrangement.

Received: December 27, 2012 Revised: February 5, 2013 Published online:

Keywords: carbenes · cyclization · gold · homogeneous catalysis · Wagner–Meerwein rearrangement

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Angew. Chem. Int. Ed. 2013, 52, 1-7

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Communications



Rearrangement
S. Ghorpade, M.-D. Su,*
R.-S. Liu* _____

Gold-Catalyzed Oxidative Cyclizations on 1,4-Enynes: Evidence for a γ -Substituent Effect on Wagner–Meerwein Rearrangements



Gold-catalyzed oxidative cyclizations of 1,4-enynes were used to study the γ -effect on the Wagner–Meerwein rearrangement. Both experimental and theoretical work

disclose that a gold substituent in the γ -position can direct a stereospecific 1,2shift of the *anti*- β -substituent regardless of its intrinsic properties.